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™. Micronized salbutamol sulphate powder and aerosol-processed fine powders of mannitol (a model excipient) and salbutamol sulphate coated with L-leucine were used. In the aerosol process L-leucine forms rough and crystalline surface layer of a few nanometers via physical vapor deposition. The aerosolization performances were studied with an Inhalation Simulator using a fast inhalation profile with the pressure drop of 4.7 kPa and the flow rate of 44 l/min. The L-leucine coated powders show relatively high emission efficiency from the capsules, 57-72 %, the low coefficient of variation in the emission, 10-30 %, and excellent fine particle doses (<5.50 µm), 48-61 %. This study showed the feasibility of Twister™ inhaler for the delivery of fine powders in small quantities with the aid of coarse carrier particles conventionally used in dry powder inhalers.

INTRODUCTION

In 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, but also electrostatic and capillary interactions between particles. The particles within a respirable size range of 1–3 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 respiration, are developed. A recently demonstrated gas-phase coating method enables to fabricate a rough coating layer of from a few to hundreds of nanometers via the physical vapour deposition of L-leucine of the surface of aerosol particles. This coating markedly enhanced the aerosolization properties of fine powders by a lowered adhesion force between the particles. Here we report the DPI delivery characteristics of carrier-free fine powders using a novel capsule inhaler Twister™, see **Fig. 1**.

Figure 1. Twister™ device, made by Aptar, is a new simple, easy-to-use, and robust dry powder inhaler. Its low number of components, transparency and simplicity make it ideal for the fast growing markets. Twister™ is a versatile inhaler and can be used with various API combinations. In the studies below we looked to tackle the key assessment factors when considering developing a DPI.

EXPERIMENTAL

Drug powders with rough L-leucine coating

Particles containing β-agonist bronchodilator salbutamol sulphate or excipient material 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 (D50 = 0.7 µm at 90 L/min). Size distributions of the produced particles were determined with an electrical low-pressure impactor (ELPI; Dekati Ltd.) directly from the gas-phase at the reactor downstream. The particles were imaged with a scanning electron microscope (FE-SEM; Leo DSM982 Gemini, LEO Electron Microscopy Inc.). Powder composition was determined by proton nuclear magnetic resonance (^{1}H-NMR) spectrometry (400 MHz Bruker Avance DPX400, D_2O).

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 by 10 times (10 HPMC capsules) with the powder loading of 3.8 – 4.6 mg. Powder entrainments from Twister™ inhaler (Aptar Pharma) were monitored with opposingly deposited IR-probes at the exit of the inhaler mouthpiece.

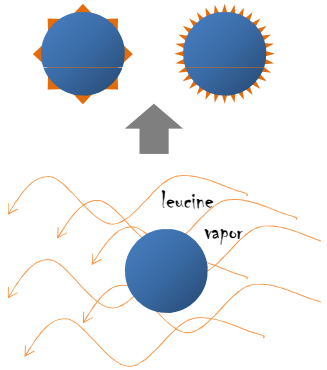

Figure 2. Continuous aerosol process to produce fine powders with a leucine coating of tunable roughness.

Powder emissions, emitted dose (ED_{OUT}), were measured gravimetrically after each inhalation. The efficiency of the emission (ED_{EFF}) was estimated by the ratio of ED / Loaded Dose. Inhalation profile was fast to reach a steady flow of 44 l/min with 4.7 kPa within 2 s. The flow rate and pressure drop were kept for 4.5 s and then 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 11.05 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) are crystalline and the L-leucine coated salbutamol sulphate (S97L03) is amorphous. In the samples S97L03 and M91L09 L-leucine vapour deposits on the surface of spherical particle upon cooling. While depositing L-leucine crystallizes forming nanosized crystals pointing outwards from the particle surface. Micronized drug particles non-uniform and elongated with facets.

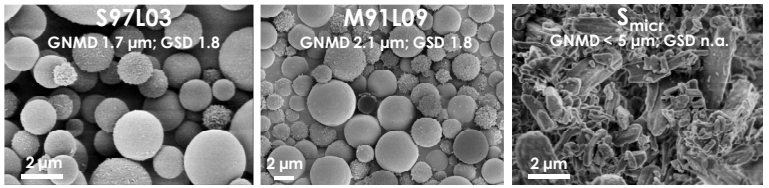

Figure 3. SEM images of the L-leucine coated encapsulated aerosol particles composed of salbutamol sulphate (S97L03) or mannitol (M91L09) and micronized salbutamol sulphate particles (S_{micr}). S = salbutamol sulphate; M = mannitol; L = L-leucine; GNMD = geometric number mean diameter; GSD = geometric standard deviation. Micronized salbutamol sulphate (S_{micr}) is a gift from Camprex. The company provides the estimation on particle size to be < 5 µm.

A rapid powder entrainment is likely to be beneficial for drug delivery to the lungs since it provides a high initial particle concentration. **Figure 4** shows representative powder emissions from Twister™. The entrainments of all the tested fine powders from Twister™ were rapid and took less than 2 s. However, the entrainments of S97L03 and M91L09 were instantaneous whereas that of S_{micr} took place in a burst-like manner. The latter is due to very 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.

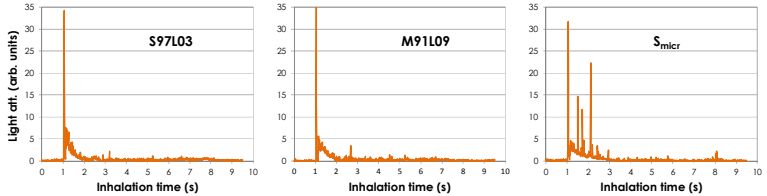

Figure 4. Inhaler entrainments of the fine powders recorded as IR light attenuations upon a fast inhalation with 44 l/min and pressure drop 4.7 kPa.

FINE POWDER AEROSOLIZATION

Table 1 summarizes the aerosolization results. The emissions of the L-leucine coated powders were around 20 % higher than that of S_{micr}. Moreover, the efficiencies of the emissions which was measured by emitted dose/loaded dose were relatively high in all cases but more pronounced with S97L03 and M91L09. However, the coefficient variations, which were representing dose repeatability, were good with all the powders but M91L09 showed to be the most repeatable. Fine particle fractions less than 5.50 µm, $FPF_{<5.50\ \mu m}$ (stages 0.04 – 5.50 µm) as compared to the emitted doses were very good even up to 60 %. Calculated alveoli delivery doses of the materials based on the $FPD_{<5.50\ \mu m}$ were 1.72 mg of salbutamol sulphate with S97L03, 1.48 mg of mannitol with M91L09, and 1.10 mg of salbutamol sulphate with S_{micr} powders.

Table 1. Aerosolization results of the powders conducted by the Inhalation Simulator (44 l/min; 4.7 kPa). ED = averaged emitted dose from the inhaler; ED_{EFF} = efficiency of the emission; CV_{ED} = coefficient variation of the emission; $FPD_{<11.05\mu m}$; $FPD_{<5.50\ \mu m}$; MMAD = mass medium aerosol diameter; GSD = geometric standard deviation.

Sample	ED (mg/dose)	ED_{EFF} (%)	CV_{ED} (%)	$FPF_{<5.5\ \mu m}$ (% of ED_{OUT})	MMAD (µm)	GSD
S97L03	2.9	72	24	61	1.7	1.8
M91L09	2.8	64	10	58	3.4	1.7
Smicr	2.3	57	30	48	2.5	1.5

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 powder sets, the spherical particles coated with the rough layer of L-leucine nanocrystals performed better aerosolization properties than micronized drug powder. Moreover, the emptying 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 60 %. All in all, the fine powders can be delivered efficiently from Twister™ inhaler without any coarse carrier particles.