Artificial dispersing aids and carriers for Dry Powder Inhalation formulations - Proof of Principle -

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Introduction

Fundamental influences of shape, size, mass and surface involved in the process of cohesion and adhesion of API particles and, for delivery of interactive powder blends, the detachment from the **DPI** carrier during the inhalation manoeuvre can be investigated by the use of Additive Manufacturing techniques. With these technologies, uniform carrier particles and auxiliary implements of different geometries, sizes and materials can be produced. In this Proof of Principle, several different prototypes were printed using **Fused Deposition Modelling (FDM)** to obtain uniform structures that can be used as levitating **Dispersing Aids (DA)** in DPI formulations. Subsequently, **aerodynamic assessments** with the NGI were carried out to determine the general influence of different DA design approaches and their respective ability to increase the **Fine Particle Fraction (FPF)** caused by enhanced dispersion. Fundamentally new applications could be derived in the future with this approach. When technical limitations such as accuracy, reproducibility and scalability are overcome, it will also be possible to **print carrier particles** with uniform morphology on a µm scale.

Proof of Principle

- **3D-printed** particles as **dispersing aids** in DPI formulations
- Improvement of dispersion in a **capsule-based device**
- **Aerodynamic assessment** of a model **interactive mixture**: lactose + 2 % SBS
- Investigation of conceivable relationship between **shape, size and dispersion**
- **Additive manufacturing** as a future approach for **3D-printed carrier particles**?

Methods

Additive manufacturing

Printing of dispersing aids with Fused Deposition Modelling (FDM): "layer-by-layer"; thermoplastic polymer filament is heated above its glass transition temperature and extruded through a nozzle.

- 3D-design: SketchUp® (Trimble Inc., USA) and open source databases
- Slicing: Cura® (Version 3.6, Ultimaker B.V., The Netherlands)
- Printing: Ultimaker® 3+ with PLA and PVA (Ultimaker B.V., The Netherlands)

Aerodynamic assessment

Interactive Blend (2 % SBS): Picomix ® (Hosokawa, Germany; 500 rpm, 2 x 60 sec)

- Acceptance criteria for homogeneity: recovery 100 % ± 5 % and RSD < 5 %

Uniformity of Delivered Dose (DD) and Aerodynamic Particle Size Distribution (APSD)

- According to Ph.Eur. 9; HPLC-analytics for drug quantification (Waters Corp., USA)

Data evaluation of Fine Particle Dose (FPD) and Fine Particle Fraction (FPF)

- Copley Inhaler Testing Data Analysis Software 3.0 (Copley Scientific Ltd., UK)

Results

Printed dispersing agents

Geometries, such as rolling-knot(1), cube(2), icosahedron(3), octahedron(4) and triangular prism(5) were printed with regards to applicability as DAs in a capsule-based inhaler. Since FDM is technically not suitable for printing parts with intricate details, a compromise between applicability and feasibility determined the printing size range. During printing, the filament extruded through the heated nozzle cools at different rates, depending on the geometry. This causes internal stress, leading to deformation, warping or shrinkage and thus to a rough and corrugated surface.

Influence of dispersing aids on delivered dose

To determine the influence of the artificial DAs on the total delivered dose from a model device, the emitted doses with and without DA inserted into a device were investigated (Figure 1).

- Model device: Twister® (capsule opening feature, relatively large chamber)
- Device retention of approximately 30.0 % appears to be high
- API does not adhere to the auxiliary implement (max. 0.38 % of total amount)

Test of dose uniformity: no major differences in either the total delivered dose (DD) or the device retention (DR) between dispersing aids compared to blank (DD = 249.74 µg ± 18.41 µg; DR = 30.89 % ± 5.28 % SD).

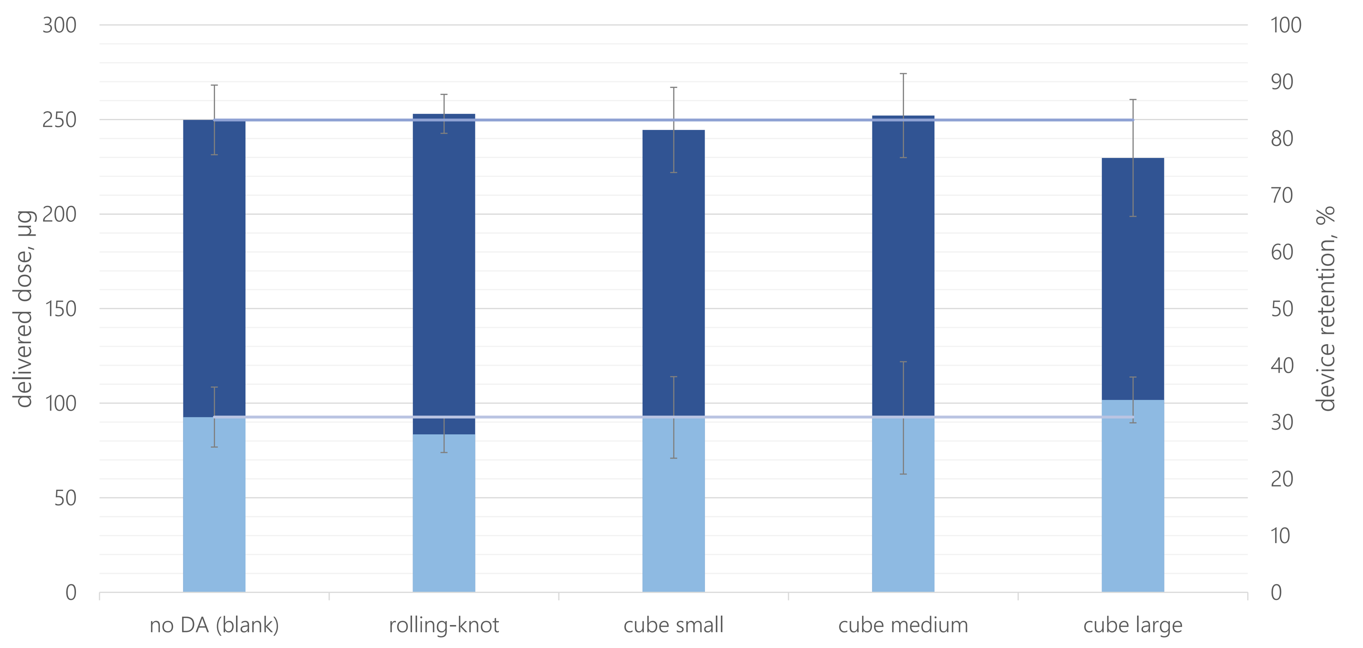

Figure 1: Comparison of the delivered dose according to Ph. Eur. (dark blue) and device retention (light blue) using various dispersing agents in a capsule-based Twister® device (n = 10; error bars = standard deviation). Each capsule was filled with 20 mg of the formulation.

Influence of DAs on deposition profile in aerodynamic assessments

Aerodynamic assessment with the Next Generation Pharmaceutical Impactor (NGI) was carried out to examine the effect of the DA on the APSD.

Although no significant difference in the total emitted dose had been observed by DUSA experiments, a meaningful deviation in the deposition profile was detected (Table 1). It is striking that the use of dispersing aids affected the performance of the interactive blend to some extent, namely a shift of API deposition towards stages with smaller aerodynamic cut-offs resulting in a smaller calculated MMAD.

Name	FPD [µg]	SD [µg]	FPF < 5 µm	SD [%]	FPF < 3 µm	SD [%]	FPF < 2 µm	SD [%]	MMAD [µm]	SD [µm]
blank (no DA)	59.7	6.23	21.7 %	2.66	18.9 %	2.63	13.2 %	2.24	1.84	0.139
rolling-knot	71.3	4.97	23.9 %	0.94	21.0 %	0.67	15.1 %	0.25	1.75	0.032
cube small	67.9	5.27	23.0 %	1.22	20.7 %	1.13	15.0 %	0.79	1.72	0.002
cube medium	66.1	1.45	22.3 %	0.18	19.7 %	0.11	14.3 %	0.07	1.75	0.016
cube large	65.9	4.77	22.8 %	1.33	20.3 %	1.36	14.9 %	0.92	1.72	0.029

Table 1: Different dispersing aids and their resulting FPD and FPF in comparison with no DA inserted in the device (n = 3).

To determine whether it was merely a matter of the insert itself or if the geometry also plays a role in the aerodynamic performance, a number of other printed aids were tested (Figure 2). By comparing the data of the Twister® device with or without inserted aids, an influence of the geometry on the performance can be assumed. It can be seen, that with decreasing size of the geometries, in particular of icosahedra(3) and triangular prisms(5), the FPF increased.

Although being a trend only, it seems as if higher FPFs could principally be achieved with relatively smaller DAs.

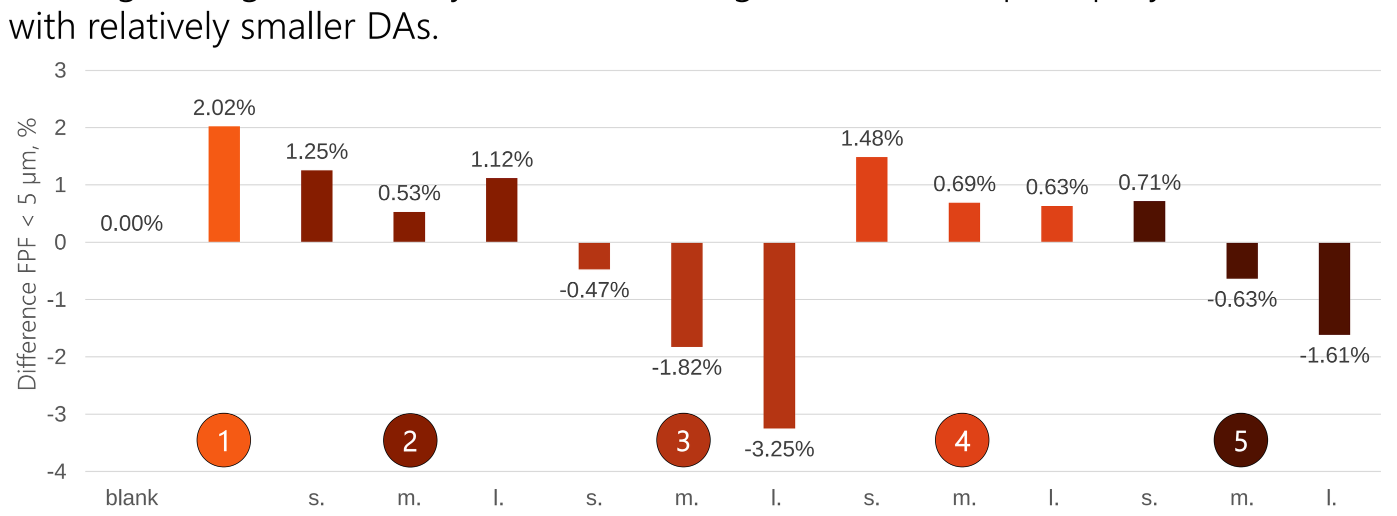

Figure 2: Comparison of FPF < 5 µm obtained by NGI deposition profiles (n = 3) utilising various dispersing aids compared to blank (0; equals baseline at 0 %). The Geometries investigated included the rolling-knot(1), cube(2), icosahedron(3), octahedron(4) and triangular prism(5), each in small (s.), medium (m.) and large (l.).

In a Nutshell

- Dispersing aids were printed using an additive manufacturing method (FDM)
- No major differences in either the total delivered dose or the device retention (DUSA)
- Shift of deposition profile (NGI) results in higher FPFs and smaller MMADs
- Geometry influences APSD performance: decreasing size → higher FPF
- Additive manufacturing: better understanding of influence of shape & size on dispersion behaviour

Conclusion

It has been shown that the use of **artificial implements** can potentially be a strategy for external energy input to aerosolise a powder bed. The assumption arises from the observation that the use of relatively large **dispersing aids** led to a slight shift of the API deposition towards stages with smaller aerodynamic cut-offs. **From the obtained data an assumed trend between size, and thus the surface area to volume ratio, and fine particle fraction could be derived.** For an evidence-based statement on such a correlation, further efforts are needed to characterise the dispersing behaviour and to improve the precision of printing techniques in order to miniaturise the implements. Other 3D-printing techniques with higher accuracy could address these deficits. Moreover, the manufacture of **uniform, tailored particles in the µm range** can lead to new perspectives in aerosol sciences.

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