Aerodynamic performance and imaging characterization of DPI formulations

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Introduction

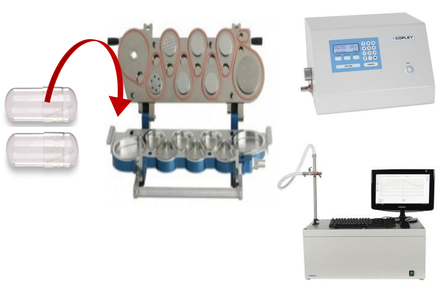
The efficacy of inhaled drugs is associated with the total amount of drug deposited in the lungs, or in a specific lung region. This deposition is strongly dependent of the aerodynamic particle size distribution (aPSD) and specific patient conditions such as age and associated respiratory diseases. [1] A better understanding of aPSD and drug deposition relationships has many benefits, not only during process development but also for formulation screening in early development stages. Nowadays regulatory authorities have been demanding proof of the product's quality by *in vitro* and *in vivo* performance characteristics such as consistent dose delivery throughout shelf-life and consistency of doses in between inhalers.[2] *In vitro in vivo* correlations (IVIVCs) may be extremely complex due to the different variables among different patients. The fact that dry powder inhalers (DPIs) actuation mode depends on patient's inspiration, breathing simulators (BRS) are highly interesting to study IVIVC. Raman spectroscopy and chemical imaging are starting to be employed on the characterization of pharmaceutical aerosols for pulmonary delivery, especially on dry powder inhalation aerosol delivery systems [3] , due to the possibility to investigate the components distribution within a formulation and to characterize homogeneity of pharmaceutical samples.[4]

In this work, three foprmulations with different API loads were tested for aPSD by NGI using a TPK *versus* a BRS setup. Confocal Raman imaging was used to evaluate aggregation state and chemical species in the different NGI stages.

Materials & Methods

Powder collection

- Carrier-based formulations of micronized API blended with a mixture of coarse and fine lactose
- Three formulations: 3.75% (w/w); 2.5% (w/w) and 0.25% (w/w) of API
- Size #3 HPMC Swedish Orange capsules with a net fill weight of 20 mg/capsule
- Plastiape® model RS51 device with a resistance of 100 L/min at 4 kPa



- Two different flow controllers were used:
- Critical flow controller model (TPK) (quadratic profile)
- BRS using a USP Throat (healthy patient breathing profile)

API Quantitation by UHPLC

API quantitation by UHPLC:

UV absorbance detector (Waters): 254 nm

Column: Phenyl-hexyl based

Mobile phase: Mixture of aqueous and organic components in a 75:25 (v/v) proportion; Flow rate: 1.0 ml/min; Injection volume: 10 µL

Raman Analysis

Confocal Raman Microscope Alpha 300 RA (WITec).

Laser wavelength: 532 nm

Laser intensity: Between 10 and 40 mW

Integration time: 0.1 to 1 second

Results

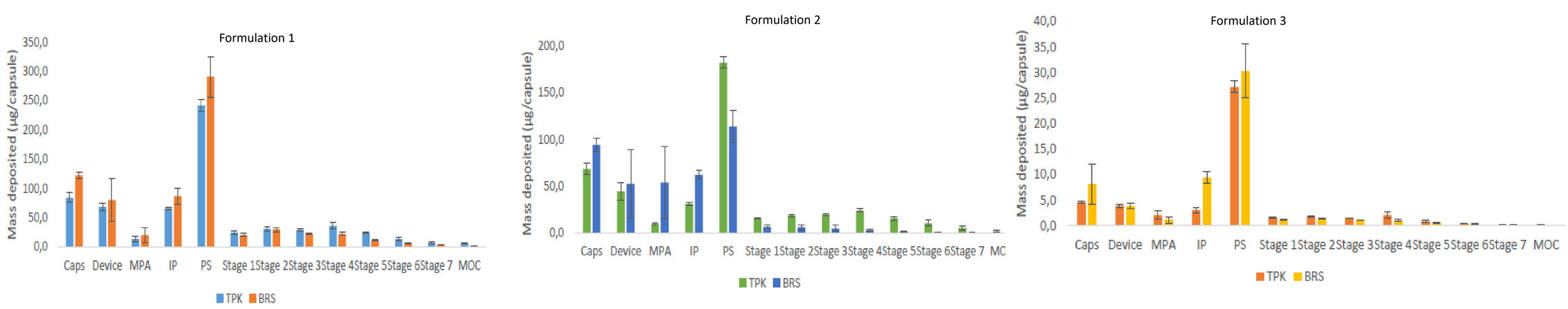


Figure 1: Comparison of deposition profiles obtained using a TPK and a BRS

Table 1: Comparison of the aerodynamic properties between different formulations (using TPK and BRS)

	Formulation 1 (LC%: 3.75%)		Formulation 2 (LC%: 2.5%)		Formulation 3 (LC%: 0.25%)	
Flow controller	TPK	BRS	TPK	BRS	TPK	BRS
ED (µg/Capsule)	490.5	514.6	335.6	255.8	40.9	46.7
FPD (µg/Capsule)	135.9	59.9	90.8	10.3	6.4	2.9
FPF_{ED} (%)	27.7	11.7	27.1	4.0	15.6	6.2
MMAD (µm)	2.2	4.9	2.1	6.4	2.6	5.1
GSD	2.7	2.6	2.7	2.8	2.3	2.8

Lower values for BRS

Target value 2 – 3 μm

For all formulations, the FPF by BRS is lower when compared to TPK. However, no correlation with API load was found

For common respiratory diseases, the goal in formulation screening is to have a higher deposition in the lower stages, commonly detected by a high FPF

For all formulations, the amount of drug deposited in the upper stages is higher in the BRS setup

API distribution

TPK set-up: Quadratic profile; flow rate 100 L/min

BRS set-up: Healthy patient breathing profile; flow rate 36 L/min

The smaller flow rate (BRS) reflects less energy in the system than the one present in a higher flow rate (TPK), thus leading to a poorer disaggregation and aerosolization of the dry powder

Is component interaction (API:API, API:lactose, lactose:lactose) interfering with aerosolization?

✓ **Confocal Raman Microscopy evaluated the particles distribution and chemical species of the DPI co-deposit through all cascade impactor stages**

✓ **In the first stages (figure 2a)) the Raman signal comes not only from the irradiated API particle but also from lactose particles, which indicates the existence of aggregates and corroborates the aPSD results.**

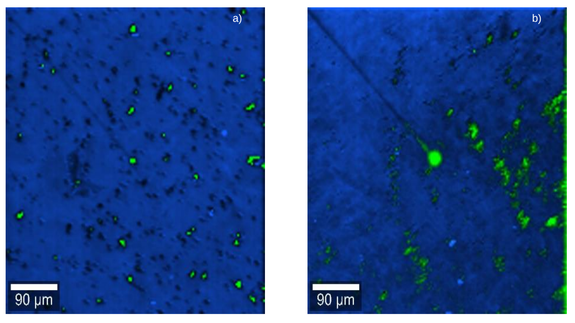


Figure 2: Chemical maps obtained by confocal Raman for Stage 2 (a) and for Stage 4 (b) of BRS set-up. API represented by green dots.

Is there aggregation of particles, in BRS, preventing a suitable aerosolization?

Conclusions

- The poorer aerosolization of particles obtained in the BRS set-up can be attributed to the formation of API:lactose cohesive interactions that aren't broken with a more biorelevant respiratory profile – understanding the degree of component interaction is thus key in finding a suitable aerosolization behavior. This can be achieved by the application of techniques such as inverse gas chromatography (IGC).
- For the formulations studied, the different API load doesn't correlate to the FPF fraction obtained; this is particularly relevant for the BRS setup. These results point to the importance of understanding if there is a sweet spot regarding API:lactose cohesive forces in promoting the aerosolization of the API;
- The integrated approach of BRS and Raman showed to be an important tool for aerodynamic performance characterization and related mechanism understanding.
- By correlating component interaction, chemical distribution and aerodynamic performance, a more effective design and selection of new inhalation products will be achieved.

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