Biorelevant Dissolution Testing of Orally Inhaled Drugs: Adding a Newly Designed Pre-Separator to PreciseInhale®

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INTRODUCTION

Dissolution testing can be a way of discriminating between different formulations; still, currently there are no standard apparatus or procedures available for inhaled products.

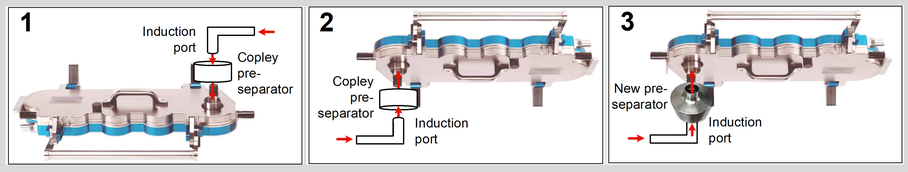
Gerde *et al.* [1] developed an *in vitro* model that simulates the dissolution and absorption of drugs from inhaled aerosols - Dissolv*It*®. Prior to dissolution testing, products are aerosolized and collected on coverslips using the PreciseInhale® aerosol generator. However this collecting equipment lacks an impaction stage for coarse particle and agglomerates – a pre-separator - , thereby decreasing the biorelevance of the succeeding dissolution test.

The aim of this work is to optimize the particle collection procedure for dissolution testing by including an extra impaction stage for excluding coarse particles in the PreciseInhale.

PRE-SEPARATOR BENCHMARKING

The newly designed pre-separator (PS) was benchmarked using Copley's next generation impactor PS.

The flow direction of the PreciseInhale® generator is opposite to the NGI. Hence, to test the new PS, **three configurations were considered**:



1 - standard NGI set-up (15 ml of solvent in the PS)
2 - upside down NGI set-up using a PS and IP from Copley (without solvent)
3 - upside down set up with the new PS and IP (with a solvent reservoir at the bottom)

To access the PS performance, 2 different inhalers, Plastiape RS01 (PL) and PowdAir (PW), were used, actuating ten capsules each, containing a lactose ternary mixture with a drug load of 32.7 µg (n=3).

PARTICLE COLLECTION USING PRECISEINHALE

Flixotide Diskus 250 µg of fluticasone propionate, containing coarse lactose particles

Pulmicort Flexhaler 180 µg of budesonide without coarse particles

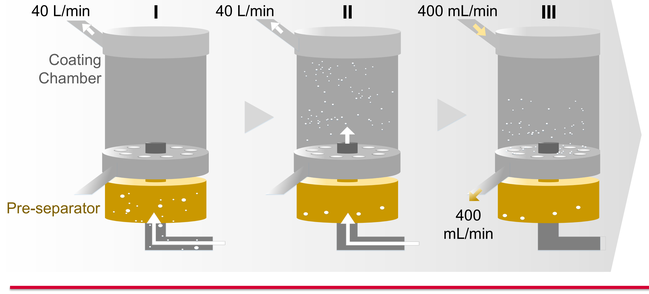
Two commercial products were used. The number of actuations (Nact) were defined to obtain a deposited dose (DD) within 600-700 ng/glass (Table 1).

The inhalers were actuated according to Figure 2.

Table 1 – Schematic of PreciseInhale actuation and glass holding.

Set up	Inhaler	DD (ng/glass)	Nact
Without PS	Flixotide	651±293	1
With PS	Diskus	618±144	5
Without PS	Pulmicort	587±51	7
With PS	Flexhaler	739±62	3

Figure 2 – Schematic of PreciseInhale actuation and glass holding.



- Aerodynamic particle size distribution (APSD) by Marple Cascade Impactor
- Optical microscopy after deposition
- SEM analysis after deposition
- Dissolution testing using Dissolv*It* apparatus

REFERENCES: [1] Gerde P, Malmlöf M, Havsborn L, Sjöberg CO, Ewing P, Eirefelt S, Ekelund K. Dissolv It: An *In Vitro* Method for Simulating the Dissolution and Absorption of Inhaled Dry Powder Drugs in the Lungs. ASSAY and Drug Development Technologies. 2017 Mar 1;15(2):77-88. [2] Noriega B, Malmlöf M, Costa E, Corvo ML, Gerde P and Maia FM Dissolution of Orally Inhaled Drugs using DissolvIt®: Influence of a Newly Designed Pre-Separator for Particle Collection. In Drug Delivery to the Lungs 28. The Aerosol Society. Bristol, UK: 2017: page 190.

RESULTS & DISCUSSION

Pre-separator Benchmarking

The two inhalers showed different performances - PowdAir (PW) had a higher emitted dose but also a higher retention in the PS, which was observed when using both PS's, indicating a comparable performance.

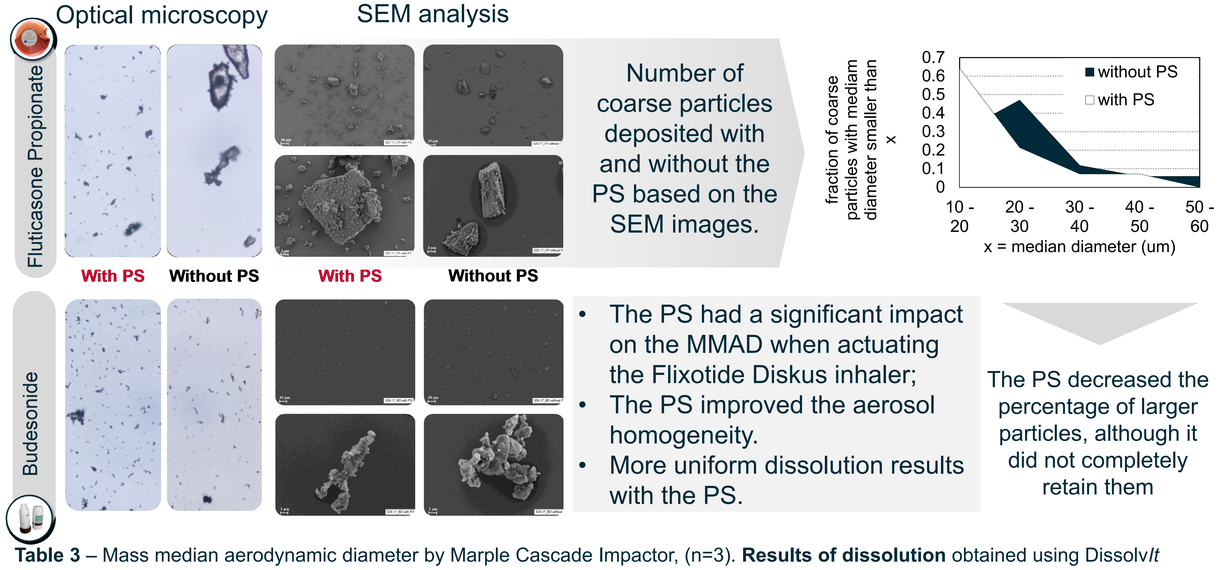
A decrease in recovery was observed when actuating the NGI upside down, probably due to particle deposition on the nozzle plates, from which the API could not be recovered.

Table 2 – Aerodynamic profile of Plastiape (PL) and PowdAir (PA), by NGI standard set-up (STD), upside-down (UD) and with the new pre-separator and induction port (PS+IP) (NEW)

	PL STD	PL UD	PL NEW	PW STD	PW UD*	PW NEW
Emitted dose (µg)	13.8±0.5	12.2±0.9	12.1±1.1	20.2±0.3	19.1	19.3±2.6
PS+IP (µg)	6.5±0.1	5.7±0.7	6.6±0.3	11.4±0.1	11.2	12.6±2.9
Fine Particle Dose (µg)	4.2±0.3	4.3±0.4	4.3±0.6	5.2±0.1	4.8	4.1±0.6
Total recovery (%)	82.2±5.3	79.2±8.7	78.0±3.1	86.5±1.7	71.3	75.4±15.7

* based on one replicate

Particle Collection Using PreciseInhale



- The PS had a significant impact on the MMAD when actuating the Flixotide Diskus inhaler;
- The PS improved the aerosol homogeneity.
- More uniform dissolution results with the PS.

The PS decreased the percentage of larger particles, although it did not completely retain them

Table 3 – Mass median aerodynamic diameter by Marple Cascade Impactor, (n=3). **Results of dissolution** obtained using Dissolv*It* apparatus. t_{max} – time of maximum concentration; C_{max} – maximum concentration. Adapted from [2].

	APSD (µm)		Dissolution	
Inhaler	**With PS**	**Without PS**	**With PS**	**Without PS**
Flixotide Diskus	4.21 ± 0.13	4.52 ± 0.09	t_{max}=19±0 min C_{max}=1.8±0.1 ng/ml	t_{max}=36±21 min C_{max}=1.5±0.3 ng/ml
Pulmicort Flexhaler	3.33 ± 0.04	3.37 ± 0.30	t_{max}=3±0 min C_{max}=110±5 ng/ml	t_{max}=3±0 min C_{max}=55±3 ng/ml

CONCLUSIONS

The PS exhibited a similar retention and fine particle dose when compared to a commercially available, for the two inhalers tested, suggesting a similar action. Used in the PreciseInhale showed an influence on the APS for an aerosol containing coarse particles; also allowed a more even deposition for the two products tested.

The dissolution rate increased with the use of the PS, possibly due to the decrease of the particle size of the collected aerosol and to a better dispersion, increasing the available surface area for dissolution. The newly designed PS for the PreciseInhale can be a candidate to be adopted for the collection of a more biorelevant fraction of different dry powder formulations.