Dissolution of Orally Inhaled Drugs using DissolvIt®: Influence of a Newly Designed Pre-Separator for Particle Collection

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Introduction

- **Inhalation dosage forms present unique problems** when developing a **dissolution test** due to their physicochemical properties and the physiological environment in which they should release their content.

DissolvIt® was developed as a dissolution model which simulates the physiological conditions in the lung and mimics the pharmacokinetic data of inhaled particles[1]. It is used in combination with the PreciseInhale® exposure platform[2] to collect the aerosolized powder on glass coverslips by simulating human breath with an automated system.

- Moreover, only the **respirable fraction** of the dry powder (1-5 µm) should be considered in a dissolution test.

PreciseInhale® is equipped with an induction port (IP) simulating the patient's throat, however it does not completely separates the non-respirable fraction, leading to coarse particle collection, and thus presence in the dissolution experiment.

In this work a newly designed pre-separator (PS) was employed during particle collection as an extra impaction stage for coarse particles, aiming to investigate the **influence of the particle size of the collected powder on the DissolvIt® dissolution/absorption profiles.**

Materials and Methods

Powder characterization and collection on coverslips

1. PreciseInhale® (Figure 1) was employed to aerosolize and collect the commercial powders on coverslips, to be tested in the Dissolv*It*® apparatus (Figure 2).

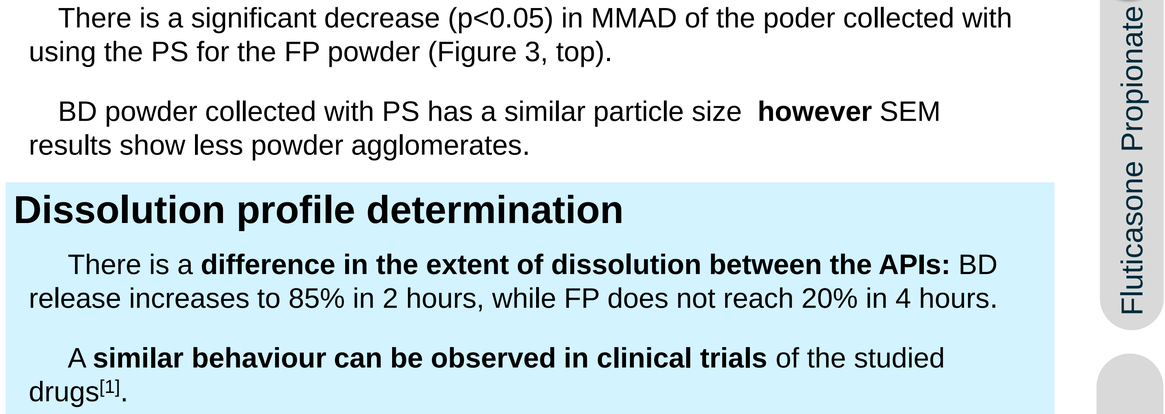

Figure 1 – Experimental set-up.

2. The number of actuations per API and set-up was selected to achieve similar deposited doses.

Table 1 – Amount of API deposited on the collecting glasses with the PreciseInhale®.

Set up	Inhaler	API	Deposited dose (ng/glass)	Number of actuations
Without PS	Flixotide Diskus	Fluticasone Propionate (FP)	651±293	1
With PS			618±144	5
Without PS	Pulmicort Flexhaler	Budesonide (BD)	587±51	7
With PS			739±62	3

Aerosol characterization

The aerodynamic particle size of the powder was determined by Marple cascade impactor, coupled to the coating chamber during exposure at an airflow of 2 L/min.

The powder deposited in the coverslips was also analysed by SEM.

Dissolution profile determination with DissolvIt®

N=3

Dissolution takes place in the **dissolution chamber,** from the coverslip glass to the pumped perfusate through a 50 µm-thick layer of mucus simulant and a polycarbonate membrane (0.03 µm pores).

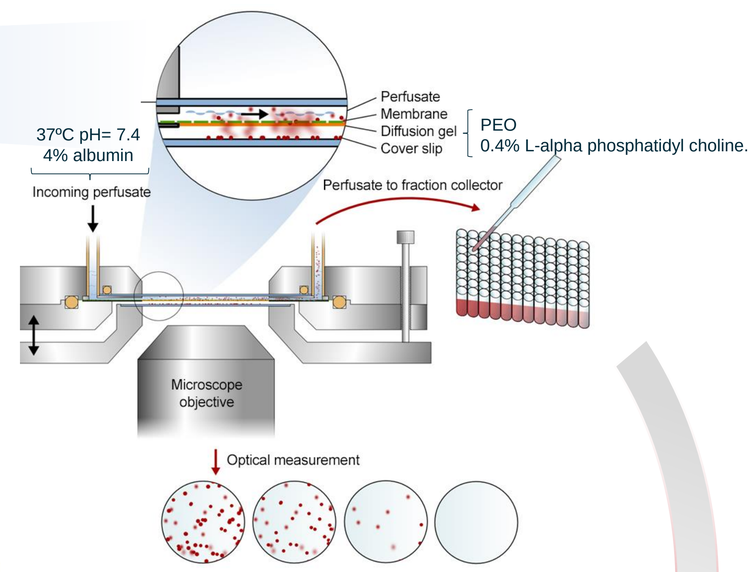

Figure 2 – DissolvIt® schematized, reprinted from [1];

Eq.1: similarity factor

$$f_2 = 50 \times \left\{ \left[1 + \frac{1}{n} \sum_{j=1}^{n} |R_j - T_j|^2 \right]^{-0.5} \right\}$$

Results and Discussion

Powder characterization and collection on coverslips

There is a significant decrease ($p<0.05$) in MMAD of the poder collected with using the PS for the FP powder (Figure 3, top).

BD powder collected with PS has a similar particle size **however** SEM results show less powder agglomerates.

Dissolution profile determination

There is a **difference in the extent of dissolution between the APIs:** BD release increases to 85% in 2 hours, while FP does not reach 20% in 4 hours.

A **similar behaviour can be observed in clinical trials** of the studied drugs[1].

PS effect

FP collected with and without PS shows a **similar profile**, BD profiles show a difference (f_2=0.38<0.50). **Without PS:**

→ **Slower dissolution**, which may be explained by the presence of larger agglomerates of particles on the glass coverslips visible to the naked eye, and therefore a reduced dissolution area (according to Fick's law)

→ **Half maximum concentration** of the dissolution profile

→ Longer half-life time, however, the time of maximum concentration was not influenced.

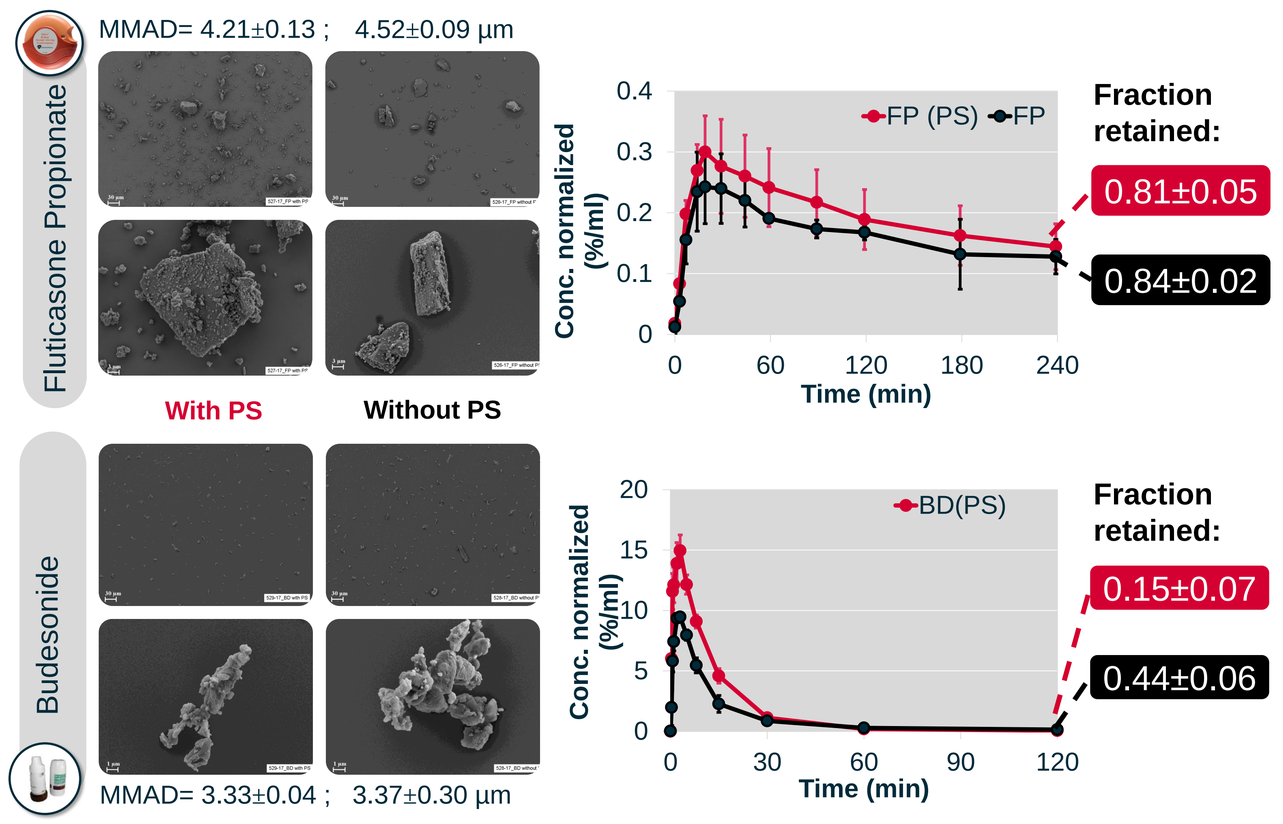

Figure 3 – Left: SEM images from collected particles according to Table 1; Right: dissolution profile in the DissolvIt® apparatus, powder collection with (red) and without (black) the PS. n=3

Conclusion

- The PS proved to have an influence on the powder aerodynamic profile and the API load collected on the coverslips.
- The dissolution results were not significantly different for Flixotide (FP), but for Pulmicort (BD) the **powder collected using the PS showed a higher dissolution rate**, possibly due to the deposition of smaller agglomerates, pointing to the importance of particle deagglomeration on API dissolution behaviour.
- **Future work** includes testing the inhalers with higher flow-rates and a new pre-separator appropriately designed for said flow-rates, to increase powder de-agglomeration and to better mimic the deposition of a fine particle fraction of an API in the real lung.

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] Gerde P, Ewing P, Låstbom L, Ryrfeldt Å, Waher J, Lidén G. A novel method to aerosolize powder for short inhalation exposures at high concentrations: isolated rat lungs exposed to respirable diesel soot. Inhalation toxicology. 2004 Jan 1;16(1):45-52.