A novel strategy to examine dry powder biorelevant dissolution in lung simulated mucus

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Introduction

The therapeutic efficacy of inhaled drugs is limited by their rapid clearance in the lungs and a short residence time, which can imply frequent dosing (and thus lower patient compliance). The development of controlled release formulations (CRF) can be a strategy to maintain drug levels and improve therapeutic outcomes[1].

Hence, a biorelevant dissolution method is necessary capable of (1) assessing the dissolution and permeation of the API which deposits in the lung, and (2) recording particle dissolution to understand what controls it. Moreover, only the respirable fraction of the dry powder (1-5 µm) should be considered in a dissolution test.

DissolvIt® was developed as a dissolution model which simulates the physiological conditions in the lung and mimics the pharmacokinetic data of inhaled particles[2]. It is used in combination with the PreciseInhale® exposure platform to collect the aerosolized powder on glass coverslips by simulating human breath with an automated system [3].

The main goal of the present work is to assess how two commercial dry powder inhalers (DPI) behave in the presented dissolution system, and evaluate its suitability to assess CRF performance.

Particle collection

Table 1 – Amount of API deposited on the collecting glasses with the PreciseInhale®, n=3.

Inhaler	API	Deposited dose (ng/glass)	# actuations
Flixotide Diskus	Fluticasone Propionate	618±144	5
Pulmicort Flexhaler	Budesonide	739±62	3

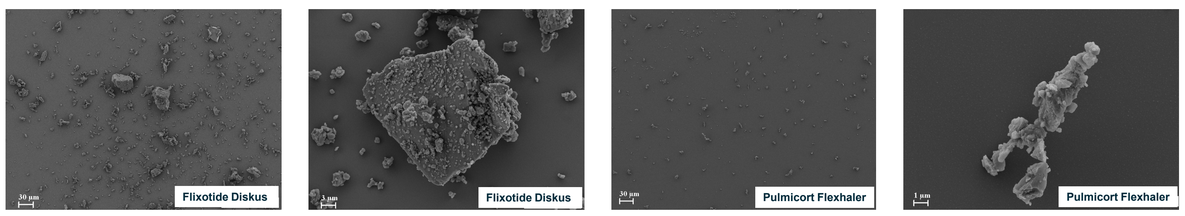

Figure 3 – SEM images from collected particles according to Table 1.

Dissolution

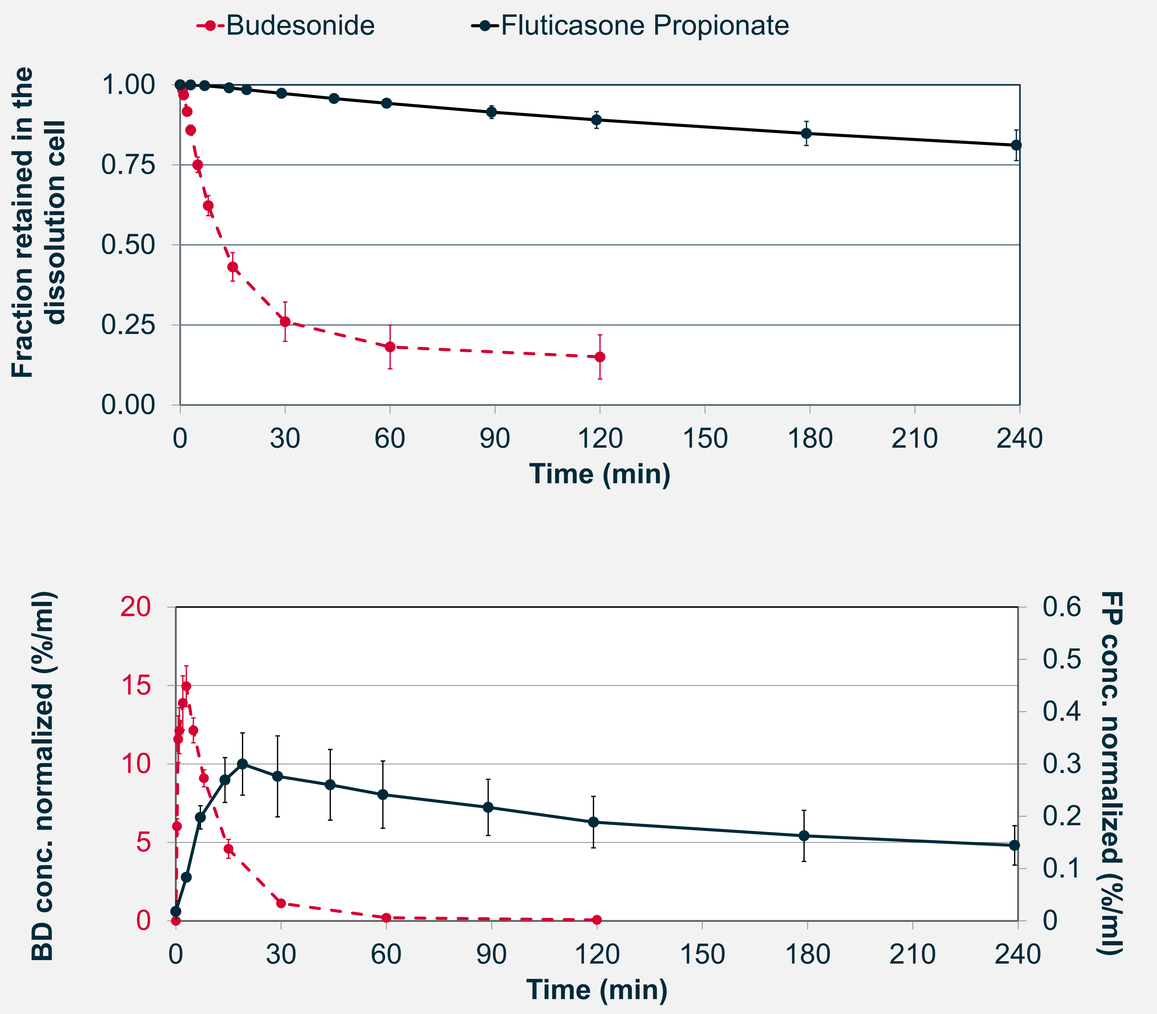

Figure 4 – Top: fractional retention of API in dissolution chamber as a function of time; bottom: dissolution profile in the DissolvIt® apparatus (n=3). FP – fluticasone propionate; BD – budesonide.

Experimental methodology and results

Experimental set-up

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

2. The number of actuations per API and set-up was selected to achieve similar deposited doses (Table 1).

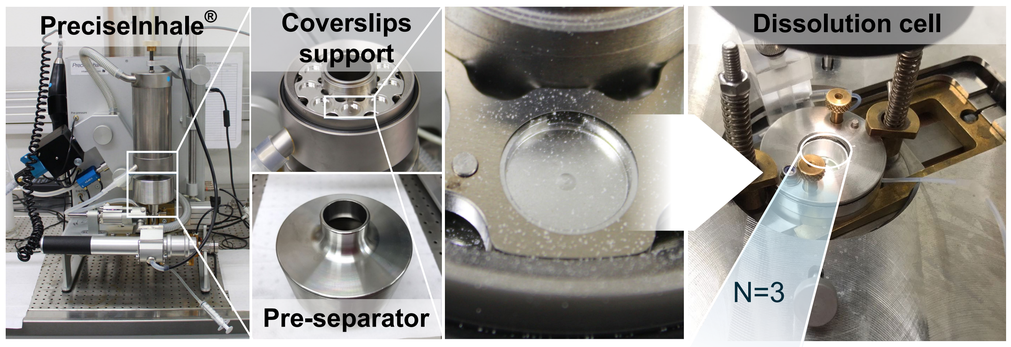

Figure 1 – Experimental set-up.

Dissolution profile determination with DissolvIt®

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).

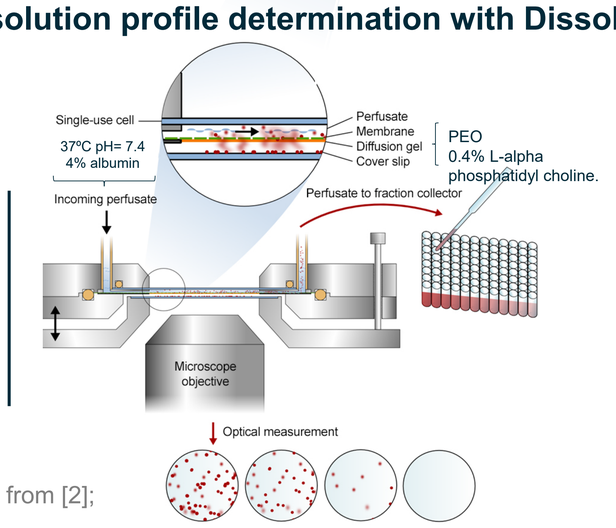

Figure 2 – DissolvIt® schematized, reprinted from [2];

Fluticasone Propionate

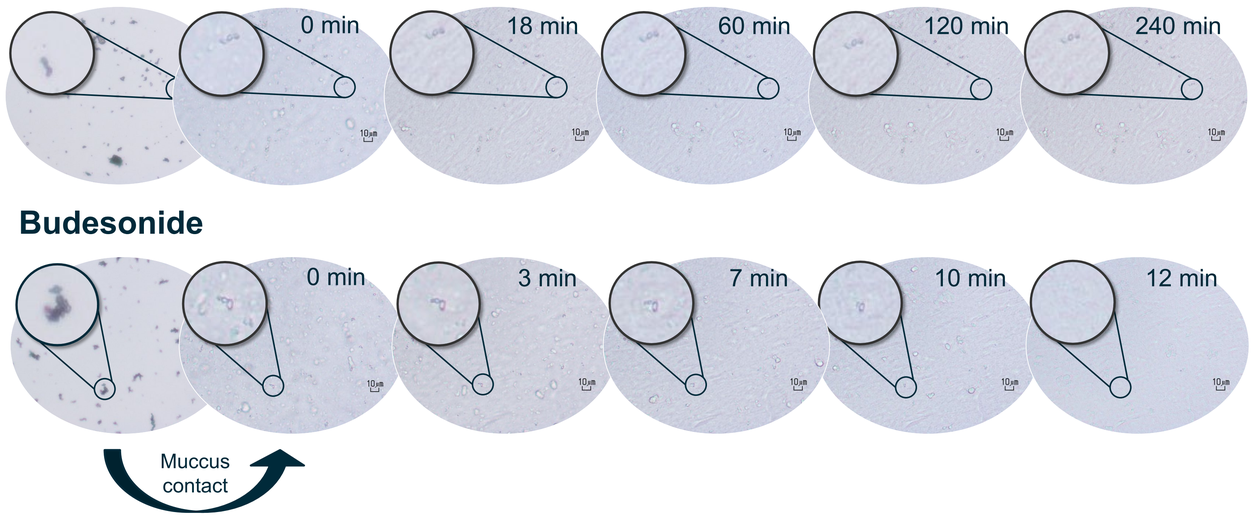

Figure 5 - Snapshots of the mucus while the dissolution is taking place, for budesonide (top) and fluticasone (bottom). The first snapshot from each group shows the powder previous to mucus contact.

Discussion and conclusions

- Particles in mucus (Figure 5) and dissolution/diffusion profiles (Figure 4) show the dissolution behavior of the two DPIs, containing lactose and drug particles.
- Most of the powder on the coverslip disappears after contacting the mucus - lactose particles. This is confirmed by the dissolution profiles, which do not show a drug concentration peak in the first minute.
- **The system can differentiate the dissolution of the different components of a formulation, by crossing information**.
- Moreover, the particles of the budesonide DPI completely disappear after 12 min, while the fluticasone's are still present after 4 hours. This is in accordance with the dissolution profiles.
- **In conclusion, the system can differentiate the dissolution formulations with different solubilities.**

[1] C. Loira-Pastoriza, J. Todoroff, and R. Vanbever Adv. Drug Deliv. Rev. 2014. vol. 75, pp. 81–91. [2] P. Gerde et al. Assay Drug Dev. Technol. 2017. vol. 15, no. 2, pp. 77–88. [3] B. Noriega, M. Malmlöf, M. L. Corvo, P. Gerde, and E. Costa, Respiratory Drug Delivery. 2018.