Towards a standardised dissolution methodology for orally inhaled drug products

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Key message

In response to recent frameworks emphasising the importance of dissolution for certain classes of inhaled medicines, we have taken learnings from the literature to configure a preliminary dissolution method that combines simplicity, biorelevance and predictivity. Although this proved non-discriminatory for different dosage strengths of Advair Diskus, this contributes to the iterative development of systems with the potential to become standardised dissolution procedures for orally inhaled drug products (OIDPs).

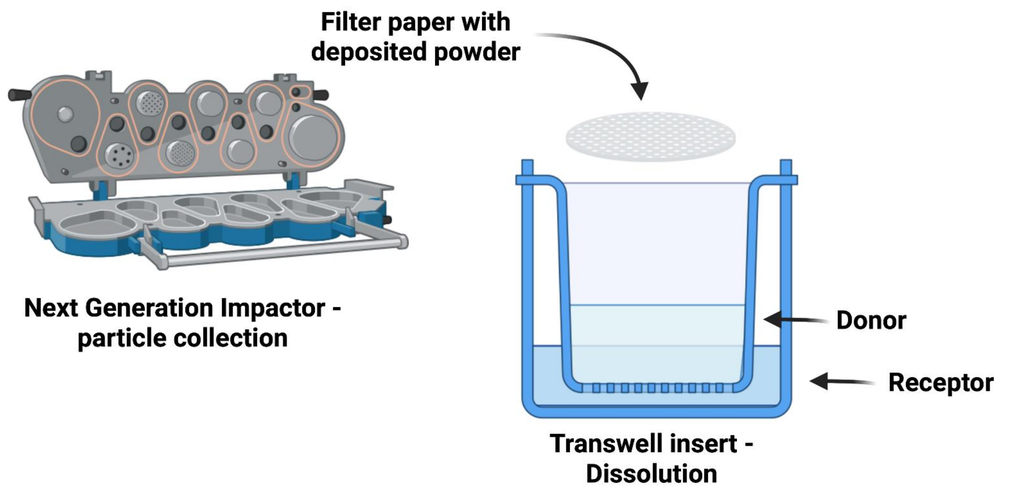
Introduction

The current interest in the dissolution of inhaled drug dosage forms reflects a growing appreciation that understanding inhalation biopharmaceutics is key to exploiting the full potential of inhalation for delivery of drugs to the lungs. OIDPs containing the corticosteroid fluticasone propionate (FP), e.g., Advair Diskus, fall into the category of products for which dissolution may play a significant role in product performance.

The aim of this study was to use Advair Diskus as a 'test product' and utilise learnings from the scientific literature to develop a discriminatory *in vitro* aerosol deposition and dissolution system for OIDPs.

Materials and Methods

Respirable fractions of Advair Diskus dosage strengths, salmeterol xinafoate 50 µg with FP 100, 250 or 500 µg, were collected using a Next Generation Impactor (NGI) at a 60 L/min flow and transferred to a Transwell® chamber in which dissolution conditions were selected based on simplicity, previously published literature and biorelevance. The dissolution was performed under non-sink conditions and the medium was phosphate-buffered saline (PBS) containing the surfactant, sodium lauryl sulphate (SDS).



Results and Discussion

We configured a dissolution system according to key parameters demonstrated by reported *in vitro* dissolution studies to be important for the evaluation of aerosols from OIDPs (Table 1).

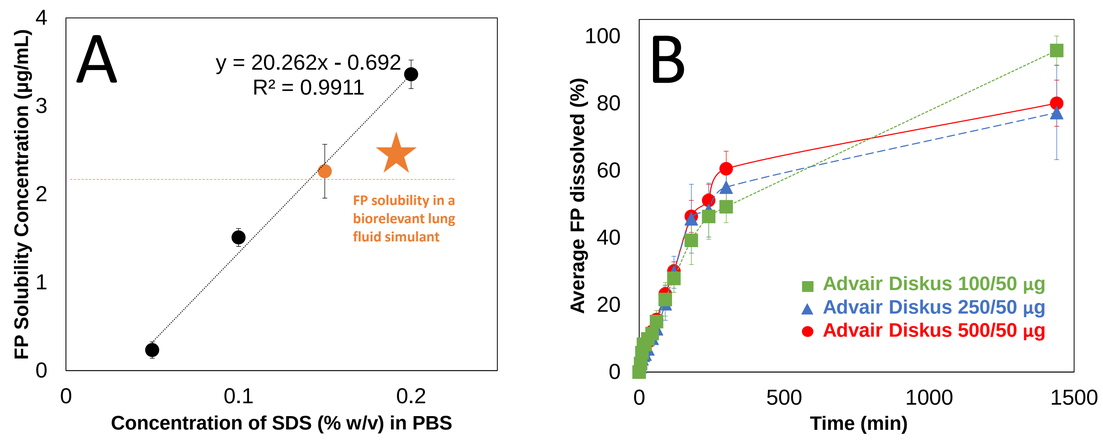
Table 1: Key features of the *in vitro* dissolution system developed for orally inhaled drug products.

Specification	Explanation for selection
Dissolution system and aerosol collection	• Transwell® is a well-studied, widely available system that can be configured for biorelevance. • NGI to collect mass from a single stage (stage three; 2.82 - 4.46 m) to sample an aerosol size fraction that would deposit in the airways.
Dissolution medium composition and volume	• Composition (PBS buffer with 0.15 % w/v SDS) selected as a solution in which FP has equivalent solubility in lung lining fluid (2.0 ug/mL) . • Dissolution volumes based on the requirement for hydrodynamic balance, Equation (1).

Aerosol fraction collection:

The amount of powder collected on stage three filter paper in the NGI, was determined gravimetrically for each Advair Diskus dose strength (100, 250 and 500 µg FP) with the number of actuations adjusted to keep the emitted dose of FP equivalent. The FP mass collected on the 24 mm filter paper was consistent at approximately 10 µg.

Figure 1: A) Solubility of FP in PBS at different concentrations of SDS and B) Dissolution of FP (% dissolved vs. time) for three strengths of Advair Diskus. Data represent mean ± sd, n=6.



Dissolution medium selection:

The solubility of FP increased with increasing surfactant concentration (Figure 1A). To ensure that the solubility of FP in the dissolution medium was biorelevant, we determined the concentration of SDS in PBS in which FP had a solubility equivalent to the reported level of 2.0 µg/mL in a simulated lung lining fluid.[1] The concentration of SDS was approximated to 0.15 % w/v for the purpose of this study.

Dissolution medium volume:

The volume of dissolution medium was adjusted based on the solubility and the mass deposited of FP. A volume of 5.0 mL was utilised for dissolution of ~10 µg FP. Equation (1) was used to specify the receptor and donor volumes, while achieving hydrodynamic balance between the two compartments in the Transwell system.[2]

$$Vr = \left(\left(\frac{Vd+Vf}{0.47}\right) \times 0.35\right) + 0.86 + Wv$$

Equation (1)
Derived by E. Amini et al. (2021).[2]

The receptor volume (Vr) was 2.74 mL, the donor volume (Vd) was 2.27 mL with Vf being the filter paper volume (0.118 mL) and Wv being the required wetting volume (0.100 mL).

Transwell dissolution optimisation:

The dissolution profiles were opposite to previous literature and did not demonstrate discrimination across dosage strengths (Figure 1B). Clinical data and mechanistic modelling suggests that dissolution of FP in the lungs varies according to Advair Diskus dosage strength [3], with the lowest dosage strength having the fastest dissolution kinetics for FP, followed by the medium and then the highest.

Potential reasons for our findings:

1. Use of non-sink conditions
2. Factors related to the dissolution medium and/or dissolution apparatus
3. Collection of a single stage aerosol fraction from the NGI

Conclusions

- The Transwell® dissolution system can be configured with a dissolution medium that provides FP solubility equivalent to the estimated solubility of FP in the lungs.
- The dissolution of Advair Diskus strengths (100, 250 µg, and 500 µg FP) were not discriminative compared to previously published literature potentially due to the aerosol collection method and use of non-sink vs sink conditions.

The next steps are the further development of the dissolution system before using *in silico* modelling to understand the biorelevance and ability to predict *in vivo* pharmacokinetics.

References

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2. Amini E, et al. Int J Pharm. 2021;13:1-21.
3. Bäckman P, et al. RDD Online. 2020;1:113-122.

Disclosures

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