Simulation lung dissolution – fast-tracking DPI development

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Introduction

Biorelevant collection and dissolution methods are a specially “hot topic” for orally inhaled drug products (OIDPs) aiming at supporting the regulatory context and providing a predictive tool in formulation development (as is the case for other dosage forms). Several dissolution systems for orally inhaled drugs have been proposed, with different sample collection strategies, dissolution set-ups, and ultimate goals (formulation differentiation versus bioequivalence tool).

This work present steps towards the development/ optimization of a biorelevant actuation-, collection- and dissolution system for inhaled drugs. The strategy was then used for the differentiation of various DPI formulations containing two different solubility APIs; Fluticasone Propionate (FP) and Salmeterol Xinafoate (SX).

Experimental methods

The manufacturing of the micronized APIs and carrierbased formulations are summarized in Table 1.

Table 1. Summary of micronized APIs and carrier-based formulations (containing 1% w/w of micronized API) used for the collection and dissolution studies.

Formulation	Micronization technology	Mixing technology	Coarse lactose (%)	Fine lactose (%)
FPJ blend	Jet Milling	High shear	94	5
FPW blend	Wet Polishing	Low shear	89	10
FP JM	Jet milling	-	-	-
FP WP	Wet Polishing	-	-	-
SXJ blend	Jet Milling	High shear	84	15
SXW blend	Wet Polishing	High shear	84	15
SX JM	Jet milling	-	-	-
SX WP	Wet Polishing	-	-	-

The composite formulation containing 20% w/w L-leucine and 79% w/w trehalose was manufactured using a laboratory scale spray drier from Buchi.

PreciseInhale was used for aerosol generation- and collection together with a tailored pre-separator to further increase the biorelevance of the aerosol deposition procedure. Dissolv*It,* with its biorelevant design simulating some critical lung physiological conditions, was then used for dissolution- and absorption testing. The deposited dose range on test coverslips was also optimized.

Future perspectives

The presented strategy using PreciseInhale and Dissolv*It* to detect small differences in formulation manufacturing will be further tested and validated on other APIs such as fluticasone furoate, vilanterol and umeclidinium. The set-up will also be used for additional development of generic drugs.

Results and discussion

Dose collection

The of the PreciseInhale aerosol generation set-up seems to increase dissolution/absorption rate of the test substances (Figure 1). Most likely this depends on effect of finer particles (Figure 1 B and D compared to A and C). The pre-separator splits, before the deposition chamber, the coarser particles and agglomerates that deposit in the head airways, leading to the collection of a more relevant fraction of finer particles for testing. This fact ensures a more are biorelevant method to analyse the particles.

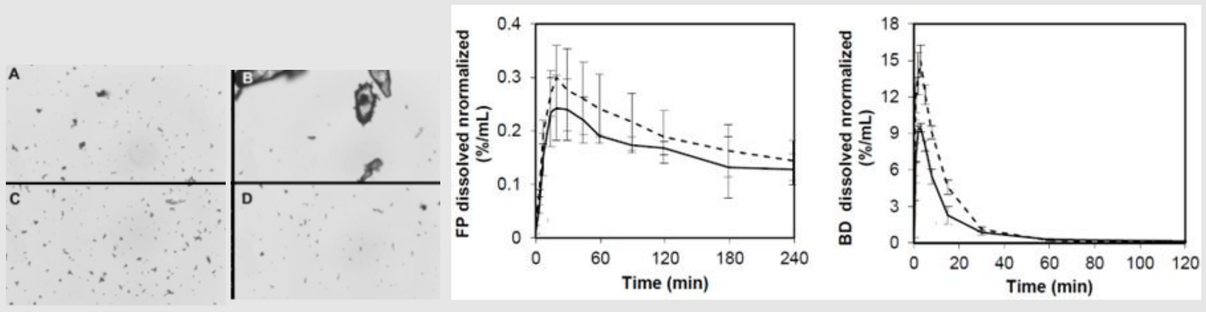

Figure 1. Deposition pattern on coverslips of the Flixotide Diskus without (A) and with (B) the pre-separator, and Pulmicort Flexaher without (C) and with the PS (D), after actuation using the PreciseInhale. Dissolution profiles of the products with (dash line) and without (full line) the pre-separator. Data presented as a % of total DS in coverslip.

Dissolv*It* dose range

It was shown that the deposited dose affects the dissolution/absorption. The range of optimal doses was defined (0.7 – 1.0 µg/glass) to prevent impact of the collected dose on the obtained results when comparing different formulations.

Application to formulation comparison

It is shown that Dissolv*It* detects differences in dissolution properties for formulations of the same APIs (Figure 2).

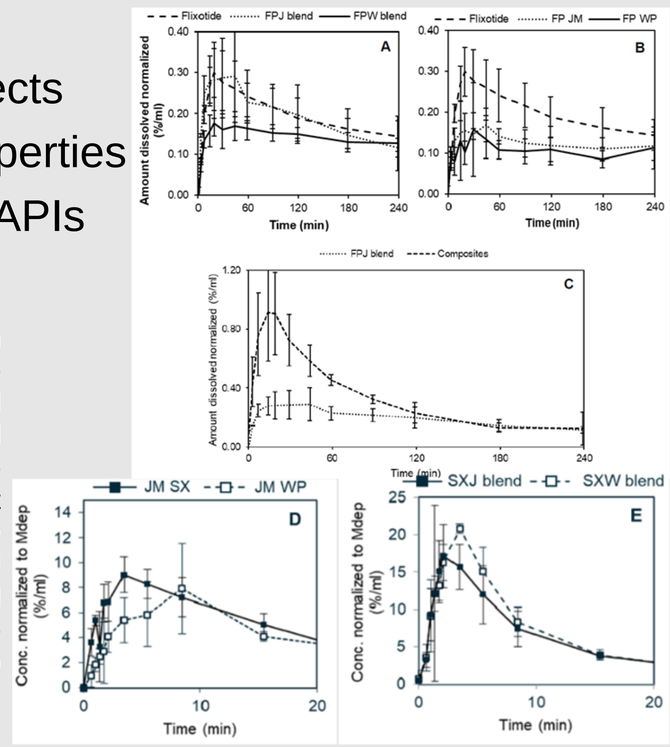

Figure 2. Dissolution profiles for formulation comparison obtained using Dissolv*It*®. A-Carrier-based formulations with jet milled fluticasone (FPJ blend), wet polished fluticasone (FPW blend), commercial carrier-based product; B-jet milled (FP JM), wet polished (FP WP) fluticasone and the commercial; C-Composite formulation and FPJ blend formulation; D-Jet milled (SX JM) and wet polished (SX WP) salmeterol; E - carrier-based formulations with jet milled (SXJ blend) and wet polished (SXW blend) salmeterol. Data presented as a % of total DS in coverslip.

Conclusion

The biorelevant collection- and dissolution system comprised of PreciseInhale and Dissolv*It*, were optimized and tested for differentiation of DPI formulations. The methodology as per developed is capable of differentiating particle engineering technologies and formulation composition in carrier-based and composite approaches, which can be essential for fast-tracking DPI development of both new molecules and generics.