Investigation of Pharmacokinetic Sensitivity to Lung Deposition of Locally-Acting Orally Inhaled Drug Products

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Introduction

Dry powder inhalers (DPIs), a subset of orally inhaled drug products (OIDPs), are complex drug-device combination products widely used as portable delivery systems to treat pulmonary disorders such as asthma and chronic obstructive pulmonary disease (COPD). Currently, only one generic DPI is available on the U.S. market, due, in part, to challenges related to establishing equivalence for regulatory approval of generic locally-acting drugs.

The current thinking for demonstrating bioequivalence (BE) of OIDPs is based on using an aggregate weight-of-evidence approach, which consists of recommendations for equivalence of (i) *in vitro* drug delivery performance, (ii) *in vivo* systemic exposure, and (iii) *in vivo* drug delivery to the local sites of action in the lungs, in addition to qualitative and quantitative formulation sameness (same inactive ingredients within 95-105% of that of the reference product concentration) and device similarity.[1] The main challenge is establishing equivalence of drug delivery to the lungs; specifically, equivalence in the amount, residence time, and regional deposition of drug in the lungs.

Since there is limited understanding of how pharmacokinetics (PK) relates to drug concentrations in the lungs, and uncertainties with *in vitro* correlations to lung deposition and clinical efficacy, comparative pharmacodynamic (or clinical endpoint) BE studies are currently recommended to demonstrate equivalence at the sites of action. Hypothetically, PK studies can provide insights on the fate of drug in the lungs when the oral bioavailability of the drug is negligible (e.g., fluticasone propionate)[2] or prevented through charcoal co-treatment. Under such conditions, the area under the concentration-time curve (AUC) may indicate the dose available to the airways, while the peak concentration (C_{max}) may be sensitive to the local deposition pattern (e.g., faster absorption (i.e., higher C_{max}) suggests more peripheral deposition).[3]

This study evaluated the potential application of PK studies in assessing differences in local delivery of DPI formulations engineered to differ in central to peripheral lung deposition.

Methods

Preparation of DPI formulations: The same batch of micronized fluticasone propionate (FP) and coarse lactose particles were used to prepare three DPI formulations (A, B, C) to target a similar fine particle dose (FPD), but differ in mass median aerodynamic diameters (MMAD) to achieve different regional (i.e., central to peripheral) deposition in the lungs; the amount and grade of lactose fines (different median volumetric particle size, D_{50}) were varied. The following final formulation compositions were studied:

Component, %w/w	*Formulation A*	*Formulation B*	*Formulation C*
Fluticasone propionate (FP, D_{50} = 2.1 µm)	*0.8*	*0.8*	*0.8*
Sieved lactose (SV003, D_{50} = 63.6 µm)	*79.4*	*89.3*	*96.7*
Milled lactose (LH201, D_{50} = 20-25 µm)	*19.8*	*-*	*-*
Milled lactose (LH230, D_{50} < 10 µm)	*-*	*9.9*	*-*
Micro-fine lactose (LH300, D_{50} < 5 µm)	*-*	*-*	*2.5*

***In vitro* characterization:** The formulations were filled into size 3 HPMC capsules to contain 100 µg FP in 12.4 mg of lactose and evaluated with the capsule-based Plastiape Monohaler 8® DPI device.

Aerodynamic particle size distribution (APSD) was evaluated using the Next Generation Impactor (NGI) with USP induction port and pre-separator at a flow rate of 60 L/min. FPD < 3 and 5 µm were interpolated from cumulative aerosol size distributions using a Weibull function.

Realistic aerosol characterization was performed with various medium-sized anatomical mouth-throat (MT) models [Virginia Commonwealth University (VCU), Oropharyngeal Consortium (OPC), and Alberta Idealized Throat] and a realistic inhalation profile (Figure 1) to determine the *in vitro* total lung (ex-MT) dose for each formulation. The ex-MT dose was used for dose normalization during PK analysis to adjust for differences in the *in vivo* total lung dose.

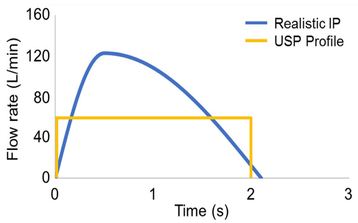


Figure 1: Comparison of realistic IP (50th percentile of the IPs likely to be produced by healthy subjects) with USP profile. IP = inhalation profile

Realistic: PIFR = 122.7 L/min; inhalation volume = 2.7 L; inhalation time = 2.1 s; average flow rate = 77 L/min. USP: Flow rate of 60 L/min for 2 s.

In vitro dissolution studies were performed using the UniDose apparatus[4] for sample collection (whole impactor-sized mass at 60 L/min) and a USP Apparatus V (paddle-over-disk) modified to house a 47 mm filter.

Pharmacokinetic study: A randomized, double-blind, single-dose, four-way crossover PK study (formulation C was replicated to assess intra-subject variability) was performed in 24 healthy, adult volunteers.

Subjects inhaled from 5 capsules (500 µg FP); two inhalations per capsule were performed to ensure complete dose delivery.

Blood samples were obtained pre-dose and up to 24 hours after the last inhalation. Non-compartmental PK analysis was performed using Phoenix WinNonlin software. C_{max}, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}inf}$ (AUC_{inf} was extrapolated) were dose normalized based on *in vitro* ex-MT determinations. ANOVA performed for statistical comparisons on log-scale with SAS software; pair-wise treatment comparisons using Bonferroni-adjusted p-values at a 5% significance level.

Results

Particle size distribution

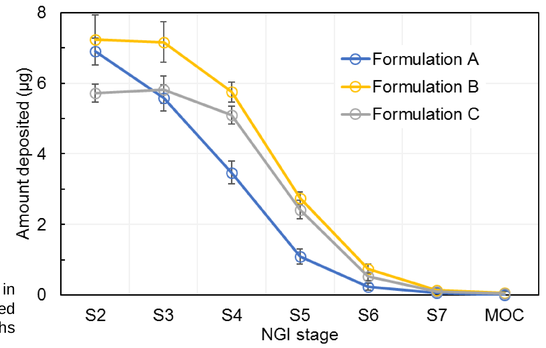


Figure 2: Impactor-sized mass deposition profiles for DPI formulations actuated into the NGI with a flow rate of 60 L/min. Circles represent mean [DPI formulations stored under long-term conditions (25°C/60%RH) for 12 months (n=3) and 20 months (n=3)] ± SD.

The total amount of drug deposited on stages 2 and 3 were similar across the formulations, while the mass deposited on stage 4 to micro-orifice collector (MOC) was lower for formulation A compared to formulations B and C (Refer to Table 1).

Table 1: Characteristics of DPI formulations differing in lactose fines. Values are mean [DPI formulations stored under long-term conditions (25°C/60%RH) for 12 months (n=3) and 20 months (n=3)] ± SD.

Parameter	Formulation A	Formulation B	Formulation C
Mass Median Aerodynamic Diameter (MMAD), µm	4.5 ± 0.1	3.8 ± 0.1	3.7 ± 0.0
Geometric Standard Deviation (GSD)	1.9 ± 0.0	2.0 ± 0.1	2.1 ± 0.0
Fine Particle Dose (FPD) < 5 µm, µg	12.2 ± 1.0	18.7 ± 0.9	15.8 ± 0.9
Fine Particle Dose (FPD) < 3 µm, µg	5.3 ± 0.7	10.0 ± 0.5	8.6 ± 0.6
Impactor-Sized Mass (ISM), µg			
Stage 2 to MOC (< 8.1 µm)	17.3 ± 1.2	23.8 ± 1.3	19.6 ± 1.1
Stages 2 and 3 (2.8 -8.1 µm)	12.5 ± 0.7	14.4 ± 1.2	11.5 ± 0.6
Stage 4 to MOC (< 2.8 µm)	4.8 ± 0.6	9.4 ± 0.4	8.2 ± 0.5
Normalization Factor (derived from ex-MT dose determinations)	1.00	1.32	1.21

Particle A (highest ratio of fine to coarse carrier particles, 20:80, with the largest D_{50} fines) had a larger MMAD compared to formulations B and C.

Formulation A had a lower FPD and lower ISM compared to formulations B and C.

FPD and ISM values varied across formulations, thus, a normalization factor (average of the various MT models relative to formulation A) was derived.

Pharmacokinetic study

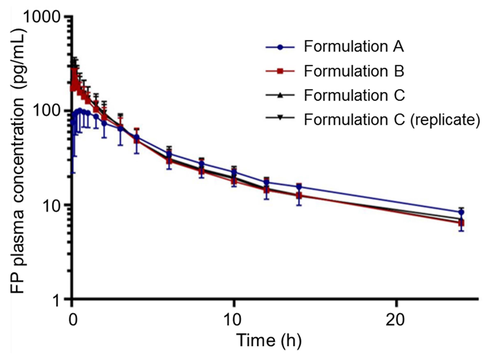
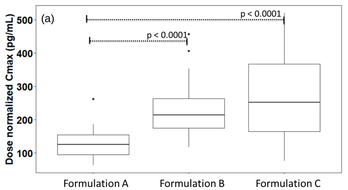


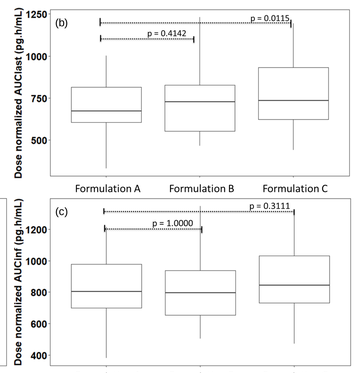
Figure 4: Plasma concentrations of fluticasone propionate for formulations A, B and C following dose normalization based on ex-MT determinations. Symbols represent mean (n=24 subjects) ± SD.

Formulations B and C (similar MMAD) revealed similar PK profiles, indicating BE.

C_{max} of formulation A (largest MMAD) was lower indicating potentially higher central to peripheral deposition compared to formulations B and C, but could also theoretically be due to slower dissolution.

Figure 5: Boxplot comparisons of key PK parameters: C_{max} (a), $AUC_{0\text{-}last}$ (b), and $AUC_{0\text{-}inf}$ (c). * Significantly different ($p<0.05$) from the estimate for formulation A.





C_{max} of formulation A was significantly lower (a).

$AUC_{0\text{-}last}$ of formulation A was significantly lower than formulation C (b); a weak indication that deposition of formulation A is more central.

No significant differences were observed for $AUC_{0\text{-}inf}$ (c).

In vitro dissolution

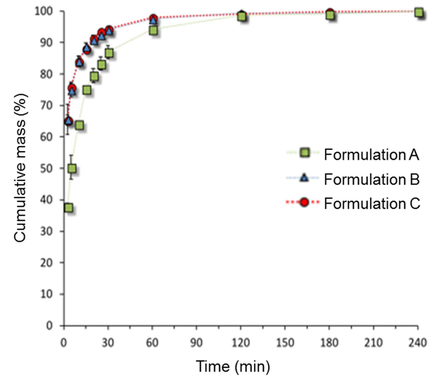


Figure 3: Dissolution profiles of DPI formulations of aerosolized impactor-sized mass dose. Symbols represent mean (n=3) ± SD.

Formulations B and C (similar MMAD) revealed similar in vitro dissolution profiles.

Formulation A was observed to have a slower dissolution rate (indicating that the characteristics of formulation A were different) compared to formulations B and C, but reached the same percent cumulative mass as formulations B and C (120-240 min), which may be correlated to the observed slower C_{max}.

Conclusions

- Varying the amount and grade of lactose fines in FP DPIs, which impacted the MMADs (formulations B and C had comparable MMADs, which was different from formulation A), altered the *in vitro* APSD and dissolution performance, and *in vivo* PK parameters.
- *In vitro* evaluation of the DPI formulations with comparable MMADs were shown to have similar dissolution profiles and total ex-MT dose, while the formulation with a larger MMAD (formulation A) was shown to have a slower dissolution rate and lower total ex-MT dose.
- The DPI formulations with comparable MMADs revealed similar PK profiles. C_{max} was shown to be sensitive to differences in DPI formulation attributes – formulation A (larger MMAD) revealed a significantly lower C_{max}. In addition, formulation C (smallest MMAD) was shown to have a significantly higher $AUC_{0\text{-}last}$ compared to formulation A, indicating a weak trend that PK may help differentiate total and central to peripheral lung deposition.
- PK may provide supportive information on pulmonary performance characteristics of orally inhaled drugs (the available dose, the pulmonary residence time, and the regional deposition of drugs in the lungs). This could help generic drug development and BE evaluation of poorly soluble OIDPs.

References

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