Exploring the Relationship Between the In Vitro Properties and the Pharmacokinetic Parameters of Advair Diskus

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INTRODUCTION

- Advair Diskus, as a combination of fluticasone propionate (FP) and salmeterol xinafoate (SX) dry powder inhaler, is an important treatment for asthma and chronic obstructive pulmonary disease (COPD).
- Batch-to-batch variability has been reported for Advair Diskus.
- This work explored the relationship between the in vitro properties of Advair Diskus and its pharmacokinetics (PK) parameters, with the intent to better understand where batch variability may be informative for batch selection.

METHOD

- Sixty healthy subjects administered two batches each of reference (R) and test (T) products of Advair Diskus (100/50 µg inhalation: denoted as R_1, R_2, T_1, T_2) in a crossover study was leveraged.
- The aerodynamic particle size distribution parameters of the four batches were measured by cascade impaction, including total emitted dose percentage, mass median aerodynamic diameter, geometric standard deviation, and fine-particle fraction (FPF).
- PK properties of these four batches were leveraged from previous work, including total exposure (AUC_{inf}) and maximum concentration (C_{max}) in plasma.

RESULTS

- A positive relationship between FP AUC_{inf} and the FPF with aerodynamic diameter less than 1 µm (FPF < 1 µm) was found (Figure 1).
- Other FPF parameters (FPF < 3 µm, FPF < 5 µm) also demonstrated positive correlation within-formulation (Figure 1, Supplemental Figure S1).
- Similar trends were noted for SX (Figure 2, Supplemental Figure S3). A positive relationship between SX AUC_{inf} and the FPF with aerodynamic diameter less than 2 µm (FPF < 2 µm) was identified.
- The relationship between C_{max} and the in vitro properties displays more uncertainty in terms of in vitro to in vivo relationship (Supplemental Figures S2, S4).

Fine particle fraction **positively correlated** to drug total exposure among batches for inhalation power products.

Proposed mechanism:

More fine particle
↓
More peripheral lung deposition
↓
Less mucociliary clearance
↓
More systemic exposure
↓
Higher drug total exposure in plasma

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Relationship between all the in vitro parameters and AUC_{inf}, C_{max} are in the supplemental material (scan the barcode).

RESULTS

Figure 1. FP AUC_{inf} and fine particle fraction with particle size < 1 um, < 3 um (FPF < 1 um, FPF < 3 um) relationship

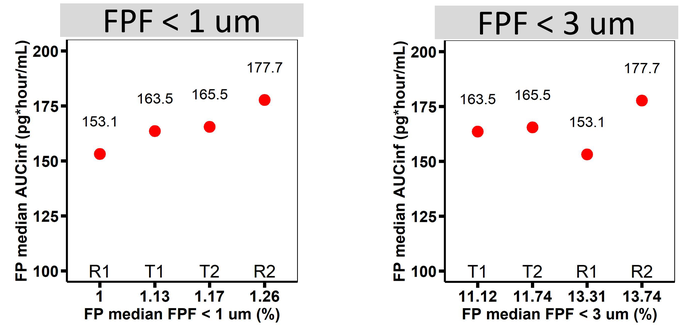
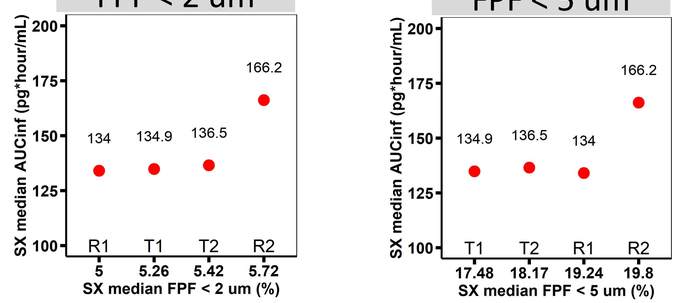


Figure 2. SX AUC_{inf} and fine particle fraction with particle size < 2 um, < 5 um (FPF < 2 um, FPF < 5 um) relationship



DISCUSSION & CONCLUSION

- FPF has the potential to be used qualitatively in batch selection for PK BE study.
- For example, R1 is the batch that has closer FPF properties to T1, which should be preferred over R2 in a BE study to compare with T1.
- The proposed mechanism is that finer particle might result in higher peripheral lung deposition, less mucociliary clearance and consequently more systemic absorption (middle diagram).

ACKNOWLEDGEMENT & DISCLAIMER

This project is funded by the grant from FDA (No. 75F40119C10068). This poster reflects the views of the authors and should not be construed to represent FDA's views or policies.