A Semi-physiological Approach for Evaluating the Sensitivity of Pharmacokinetics to Detect Differences in Regional Lung Deposition of Orally-inhaled Drug Products (OIDPs)

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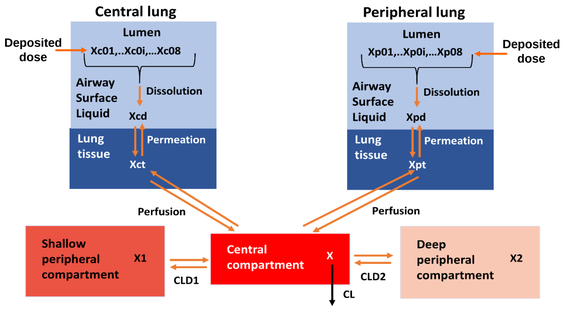
Introduction

- Unlike oral drugs, the bioequivalence (BE) assessment of OIDPs is challenging
- As plasma is downstream to the sites of action in the lung, FDA currently recommends the aggregate weight of evidence (AWE) approach
- The AWE includes the *in vitro*, pharmacokinetic (PK) and clinical endpoint studies, in addition to formulation sameness and device similarity
- Clinical endpoint studies are difficult to pass due to flat dose-response curves and pronounced variability (alternatives are needed)
- Alternative approaches need to answer the following three questions:
  - Is the available pulmonary dose equivalent?
  - Is the mean pulmonary residence time equivalent?
  - Is the regional lung deposition equivalent?
- **A previous PK study suggested a biphasic absorption profile for the three lipophilic fluticasone propionate (FP) dry powder inhaler (DPI) formulations indicating that PK might be able to detect differences in the regional lung deposition (central to peripheral or CP ratio) of slowly dissolving formulations with negligible oral absorption**
- **This study evaluated whether the above observations can be explained by physiological differences of the central and peripheral lung**

Methods

- Previously, the PK of three FP DPI formulations (A, B and C) was assessed in a randomized, double-blind, four-way crossover PK study (formulation C was repeated) in 24 healthy subjects
- The *in vitro* aerodynamic particle size distribution (APSD) of the FP formulations was characterized by next generation impactor (NGI), lung dose by anatomical throat replicas and dissolution rate by Transwell® cell experiments
- Earlier, the population PK (PopPK) analysis identified two absorption processes:

  a) a slow process presumably from central lung b) a fast process presumably from peripheral lung
- A semi-physiological PK model (model diagram and parameters below) was developed to link PopPK biphasic absorption profiles with relevant physiological attributes (dissolution and regional deposition characteristics)



Input parameter/process	Source
Deposited dose	PopPK estimates
Particle size distribution	Preludium software (in vitro APSD and inhalation maneuver)
Dissolution (Nernst-Brunner equation, NB)	**In vivo FP saturation solubility in airway surface liquid (ASL):** a) Peripheral lung: Fitted to PopPK absorption profile b) Central lung: Identical to peripheral lung ASL solubility
Permeation (Fick's law)	**Permeability across the lung tissue:** a) Peripheral lung: Ex vivo isolated perfused rat lung permeability b) Central lung: Fitted to PopPK absorption profile
Perfusion	**Blood flow per unit tissue volume:** Peripheral lung: 2400 1/h; Central lung: 730 1/h
Systemic parameters	PopPK estimates
Other lung physiological parameters (surface area, volume) and drug-related FP parameters taken from literature	

- The parameter estimation was performed for formulation C using 'deSolve' and 'minpack.lm' packages in R software
- The model was validated by simulating the PK profiles of formulations A and B
- **The contribution of dissolution rate and regional deposition differences to the observed difference in the dose-adjusted Cmax between formulations was determined by integrating *in vitro* dissolution rate into the PK model**

Results

❖ *In vitro* data

Formulation	*MMAD (GSD), µm	Mean dissolution time (MDT, h)	Relative surface area	Relative ex-throat dose
A	4.5 (1.9)	15.4	0.46	1.00
B	3.8 (2.0)	13.3	0.65	1.32
C	3.7 (2.1)	10.3	1.00	1.21

*MMAD (GSD): Median Mass Aerodynamic Diameter (Geometric Standard Deviation)

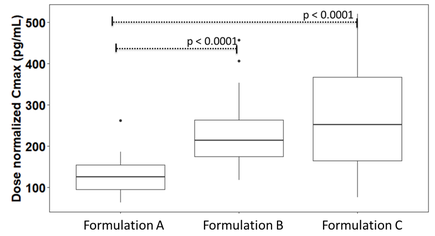
Formulations A showed larger MMAD, slower dissolution rate and lower in vitro lung dose compared to the other two formulations B and C.

❖ Pharmacokinetic study

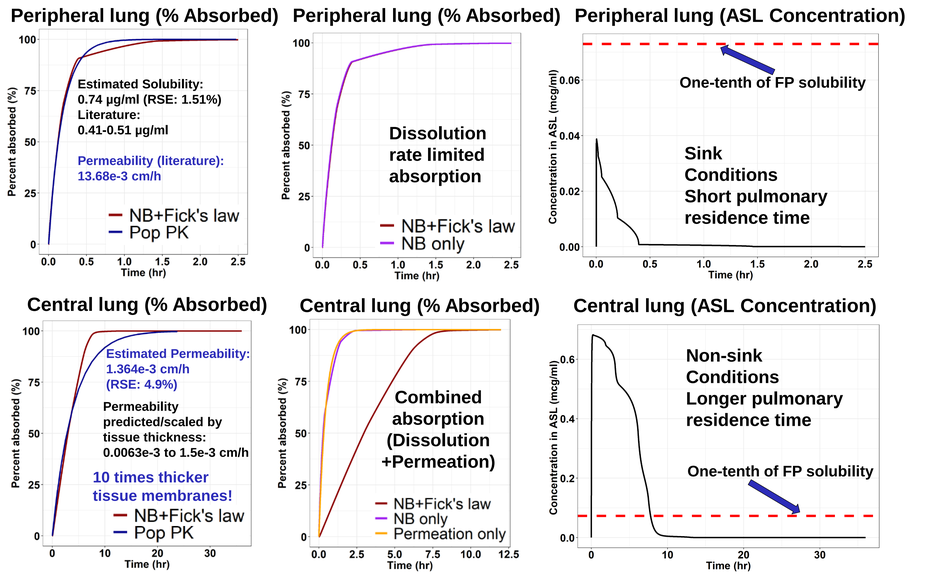
Dose adjusted Cmax of formulation A (largest MMAD) was significantly lower, which can be explained by:

a) Potentially higher central to peripheral deposition compared to formulations B and C, and/or

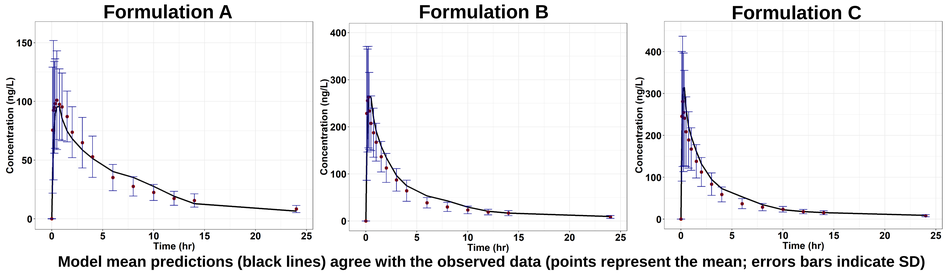
b) Slower dissolution



❖ Physiologically based absorption profiles of formulation C

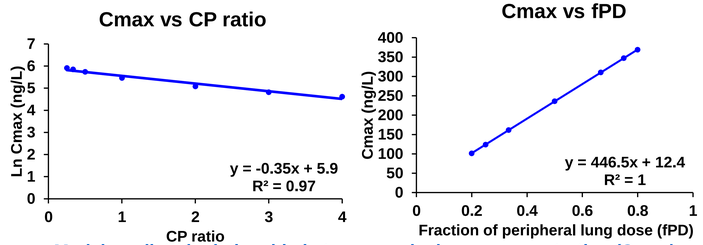


❖ Physiologically based PK profiles of the three FP DPI formulations



Model mean predictions (black lines) agree with the observed data (points represent the mean; errors bars indicate SD)

PK Cmax is sensitive to CP ratio

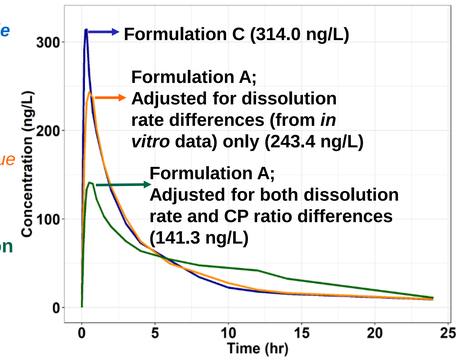


Model predicted relationship between peak plasma concentration (Cmax) and regional lung deposition

Dose-adjusted PK profile simulations:

40% of the observed difference in the dose-adjusted Cmax between formulations A and C is due to dissolution rate differences

The regional deposition (CP ratio) explained 60% of the observed difference in dose-adjusted Cmax



Conclusions

- **The observed biphasic absorption profile of FP is consistent with the physiology of central lung and peripheral lung**
- **PK (especially peak plasma concentration i.e. Cmax) is sensitive to the regional deposition differences of the FP formulations**
- **PK may provide supportive information on the pulmonary fate of poorly soluble OIDPs without the need for conducting clinical endpoint studies**

References

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2. Eriksson J, Thorn H, Sjogren E, Holmsten L, Rubin K, Lennernas H. *Mol Pharm. 2019; 16(7): 3053-3064*.

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