A MULTISCALE MODELING APPROACH TO OPTIMIZE PULMONARY DRUG DELIVERY

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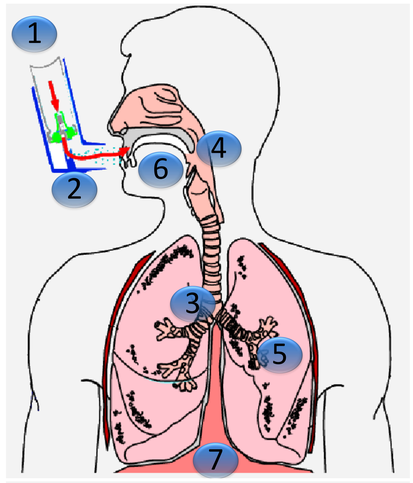
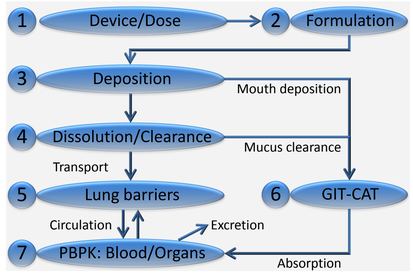
Can we efficiently use computational tools to capture the experimentally challenging mechanistic insights of pulmonary drug delivery processes?

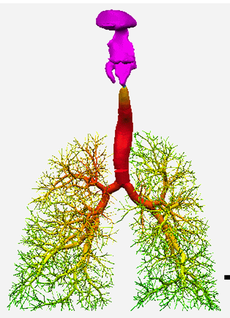
INTRODUCTION

- **Pulmonary drug delivery** via oral inhalation is being increasingly used for both treatment of lung diseases and for delivering drugs to the systemic circulation.
- Efficacy and safety of such orally inhaled drugs is **dependent on deposition and absorption** of drugs in targeted regions of the lung.
- However, analyzing inhaled pulmonary drug disposition is **experimentally challenging** as it involves complex mechanisms, such as regional drug deposition, dissolution, transport in lung barriers and mucociliary clearance.
- Here, using multiscale computational tools, **our goal** is to:
  - Develop, evaluate, and improve physiologically-based absorption and pharmacokinetic models of pulmonary (inhaled) drugs; and
  - Support the development of generic oral inhaled drug products (OIDPs).

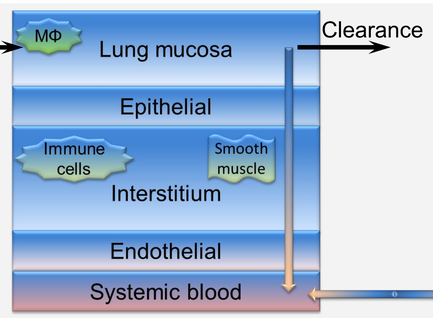




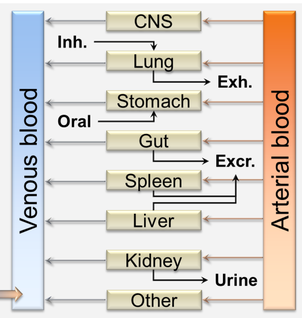
MULTISCALE COMPUTATIONAL METHODOLOGY



CFD models of inhalation



Compartmental models of translocation to blood

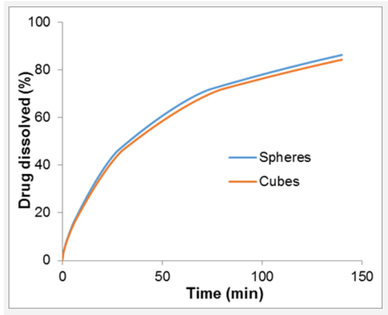


PBPK models of major organs

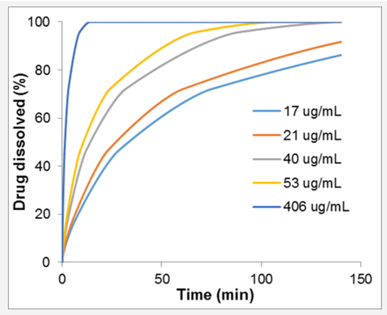
- The framework employed Typical Path Lung (TPL) & Computational Fluid Dynamics (CFD) models to calculate **lung depositions**. Results presented here are based on TPL models.
- To evaluate **dissolution** we employed Noyes-Whitney type equation in any compartment based on dose, solubility, diffusivity, size, and mono/poly-dispersability of the selected drug.
- Experimental data-based **mucociliary transport** equation is used to account for the loss of dissolved drug when mucous moves from upper lung 'airways-to-mouth-to-gut'.
- The **lung-barrier transport/absorption** model from Yu *et al*. is used to predict drug retention/transport across lung tissue from 'epithelial-to-blood'
- Finally, whole-body human physiology-based pharmacokinetic model (PBPK) is used to connect pulmonary blood to gut (CAT) model to predict **lung and blood PK** of the drug.

SELECTED COMPUTATIONAL PK RESULTS

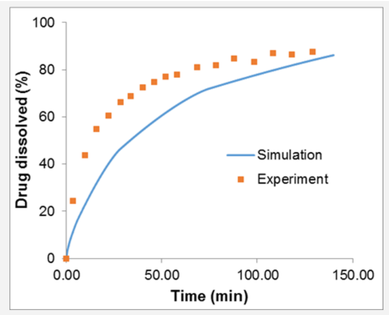
- The **predicted formulation effects** of pulmonary drugs on drug particle dissolution for poly-dispersed budesonide (dose = 200 µg; Solubility = 17 µg/ml; Diffusion coefficient = 6.2e-6 cm^2/min; Dissolution vol. = 1 L) is shown below:



Effect of drug shape (Faster for spheres)

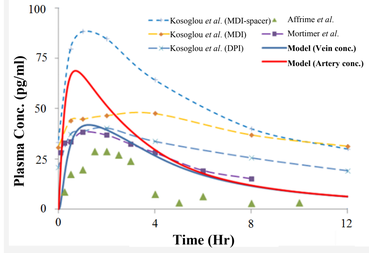


Effect of solubility (Faster dissolution=higher

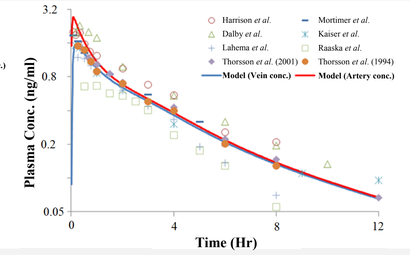


Experimental validation (May *et al*., 2014)

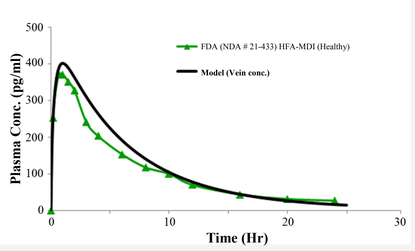
- The **predicted inhaled PK** values for momentasone furoate (MF), budesonide and fluticasone propionate (FP) simulations is shown below:



MF plasma concentration after 400 µg inhalation dose



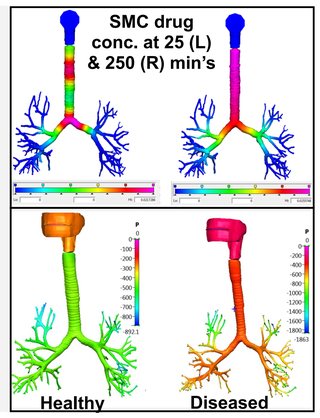
Budesonide plasma concentration after 1000 µg inhalation dose



FP plasma concentration after 1760 µg inhalation dose

FUTURE AND CONCLUSION

- Our comprehensive multiscale modeling approach can be efficiently used to predict OIDPs PK profiles at multiple lung sites (e.g., in smooth muscle cells [SMC] as shown in figure on right).
- Our approach can be successfully applied in: Dose optimization, effect of drug's physiochemical properties (logP, MMAD, etc.), and ultimately device design and generic drug formulations, if relevant information is available for modeling input.
- Attempts to model and compare the drug delivery in disease (reduced diameter) vs. healthy lungs as shown in figure on right.



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ACKNOWLEDGEMENT:

The authors gratefully acknowledge the funding & research support from the U.S. Food and Drug Administration (**FDA**) under award number 1U01FD005214-01 (2015-17).

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