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Development of a CFD-PK Nasal Spray Model with *In Vivo* Human Subject Validation

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Introduction

- For regulatory approval of solution-based nasal spray products, U.S. Food and Drug Administration (FDA) guidance recommends multiple *in vitro* tests including:
  - Single actuation content, droplet size distribution by laser diffraction, spray pattern, plume geometry) [1, 2]
- It is currently recommended that suspension nasal spray products use a weight-of-evidence approach for establishing bioequivalence:
  - Based on equivalent *in vitro* performance similar to solution products, equivalent systemic exposure based on pharmacokinetic (PK) studies, and comparative clinical endpoint or pharmacodynamics (PD) studies [2]

Objective

- The objective of this study was to develop a complete nasal transport *in silico* model to correlate drug deposition and plasma concentration for a representative nasal spray product, Nasacort® AQ (triamcinolone acetonide)
  - The transport model was developed by extending the computational fluid dynamics (CFD)-PK approach proposed by Rygg et al. [3]

Methods

- The spray droplet deposition patterns in the nasal airways were predicted using a newly developed 'quasi two-way coupled simulation' approach [4]
  - The initial and boundary conditions of the CFD model were based on *in vitro* measured data for Nasacort® AQ
- For creating the new nasal dissolution, absorption and clearance (DAC) model, a 2D surface representation of the 3D nasal geometry was formed based on the perimeter of the cross-sections and given a thickness consistent with the airway surface liquid (ASL) and epithelial cellular layers

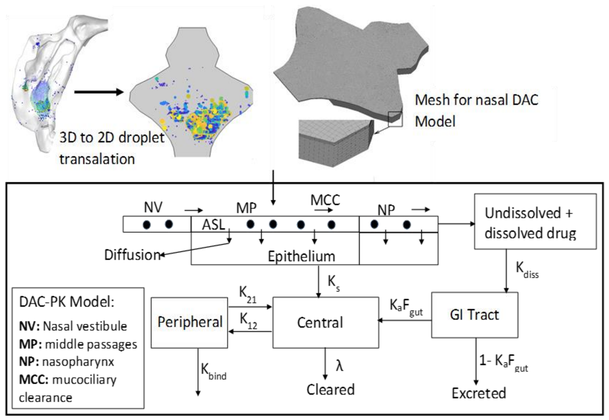

Figure 1. The coupled CFD-DAC-PK approach.

- Figure 1 shows a schematic of the complete coupled CFD-DAC-PK framework
  - Drug dissolution in the ASL region was modeled by the Noyes-Whitney equation
  - Behavior of the dissolved drug in the model was governed by an advection-diffusion equation
  - A mass source was implemented to model mucociliary clearance rate of ~ 6mm/min
  - The diffusion across ASL/epithelium membrane was modeled as:

$$V_{ep}\frac{dC_{ep}}{dt} = PS_{nose}\left(C_{muc}f_{um} - \frac{C_{ep}}{K_{pu}}\right)$$

Methods (continued)

- The PK model rate constants were estimated using IV bolus PK data for triamcinolone acetonide
- The new PK model also accounts for the absorption of the swallowed drug mass using a simple GI tract absorption model
  - Model parameters for oral absorption were estimated from oral dose data
- The nasal systemic absorption constant (K_s) was specified using Gastroplus v9.8 (Simulations Plus, Inc., Lancaster, CA, USA) predicted value
  - The permeability value (in the DAC model) was adjusted to correctly capture the *in vivo* PK values for 110 µg Nasacort® AQ dose
- A new algorithm was developed in MATLAB 2018a for the translation of deposited droplet locations from the 3D CFD model to the ASL layer, which can resolve deposition hotspots (Figure 2)

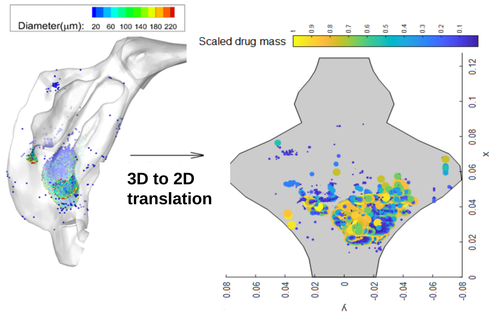

Figure 2. Droplet deposition locations in the 3D model and corresponding translated droplet location in the 2D DAC model using new method.

- Preliminary DAC model was developed by translating a 3D nasal geometry that consisted only the left nasal cavity (one-cavity model)
  - To simulate *in vivo* conditions, an updated DAC model was developed with two symmetric nasal cavities (two-cavity model) as shown in Figure 3

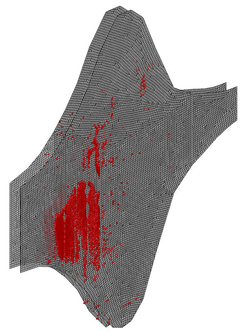

Figure 3. Two-cavity DAC-PK model with injected drug particles.

Results

➢CFD *in vitro* validation

- The CFD predicted anterior and posterior deposition results using the quasi two-way coupled model showed good agreement with the *in vitro* data (Figure 4)
  - Accurate implementation of the *in vitro* positioning data was highly important
  - Nozzle tip diameter was accurately estimated (340 µm) using micro-CT imaging

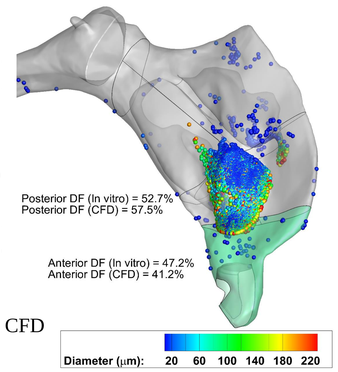

Figure 4. Validation of the 3D nasal CFD model with corresponding *in vitro* deposition results

Results (continued)

➢*In vivo* PK comparison (110 µg)

- One-cavity model showed an inaccurate effect of drug concentration buildup as indicated by delaying drug release and an appearance of the Cmax at a later time
- Two-cavity model simulated the *in vivo* conditions more realistically (i.e., one spray to each nostril) and, therefore, better predicted the Tmax value

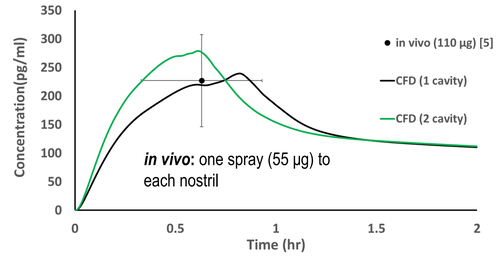

Figure 5. Comparison of different modeling approaches with *in vivo* data for 110 µg Nasacort AQ dose.

➢*In vivo* PK comparison (220 µg)

- 220 µg dose with the one-cavity model was modeled by injecting droplet mass corresponding to four sprays, which changed the dissolution and absorption physics and gave poor agreement with the *in vivo* data
- The two-cavity model showed better agreement with the *in vivo* data
- Additional one-cavity approaches were also found to give adequate results:
  - By doubling the mucus dose post-dissolution or by doubling the absorbed dose
  - Both of these approaches showed reasonable agreement with the *in vivo* data

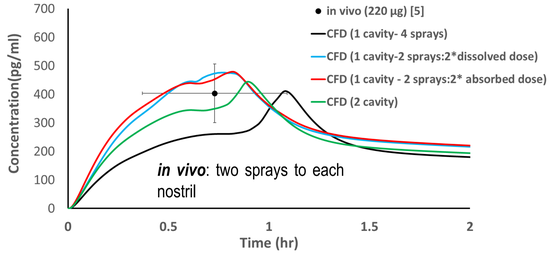

Figure 6. Comparison of different modeling approaches with *in vivo* data for 220 µg Nasacort AQ dose.

Conclusions

- The two-cavity model, which was developed by mirroring the one-cavity model to mimic in vivo physiological and drug delivery conditions, showed very good agreement with the *in vivo* data
- The CFD-DAC in silico tool presented here may, in the future, help with establishing bioequivalence and guide the design of new nasal spray products

References

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