Effect of Polydispersity on PBPK Model Simulations of Intranasal Corticosteroid Sprays

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Introduction

- Intranasal corticosteroid sprays are used to treat symptoms associated with rhinitis.
- Active pharmaceutical ingredient (API) particle size in suspension nasal sprays is a key attribute affecting the dissolution rate, absorption through the nasal epithelium, local tissue concentrations, and systemic bioavailability.
- Recent studies using Raman spectrometry have shown that API particle sizes in suspension nasal spray formulations are polydisperse and range in size from 1-15 µm [1, 2].
- API polydispersity should be accounted for in modeling efforts relating corticosteroid drug properties to absorption and bioavailability characteristics.

Approach

- A physiologically-based pharmacokinetic (PBPK) model was previously developed using Matlab R2017a (Mathworks, Natick, MA, USA) to simulate absorption and bioavailability of aqueous suspension corticosteroid nasal sprays (Fig. 1) [3].
- Key elements of the existing PBPK model include nasal spray deposition estimates, dissolution, diffusion through nasal epithelium, mucociliary clearance, absorption in the gastrointestinal tract, glucocorticoid receptor binding, plasma protein binding, and metabolism.
- Nasal spray deposition estimates in anatomical regions of the nose were obtained from computational fluid dynamics (CFD) models (Fig. 2) [4].
- Droplet size, API particle size bin data, and nasal deposition predictions were used to estimate numbers of deposited particles in size bin.
- Model simulations were conducted for fluticasone propionate and budesonide.
- Comparisons using size bin data or lognormal distributions and effects of geometric standard deviation (GSD) were examined.

Simulation Results

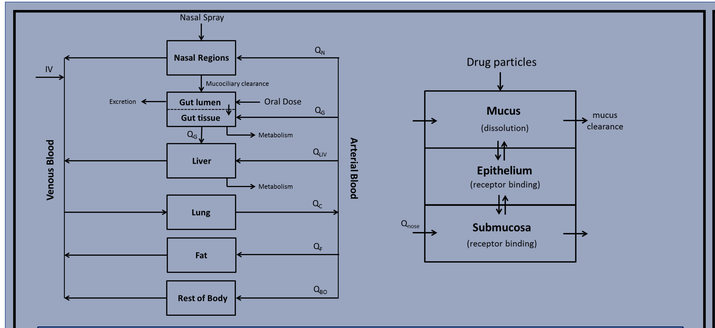


Figure 1: The PBPK model included key elements to simulate absorption and bioavailability of nasal sprays (left), including a detailed multi-layer description of the anatomical regions of the nose (right).

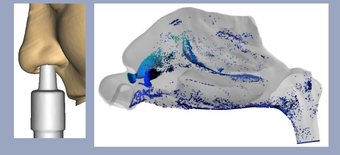
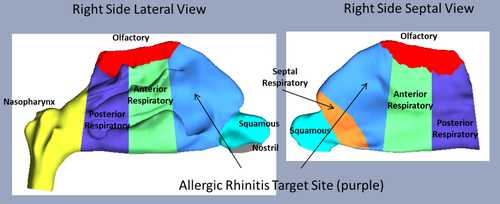


Figure 2: A nasal CFD model was used to simulate corticosteroid nasal spray deposition (top) and define anatomical regions of interest (bottom).



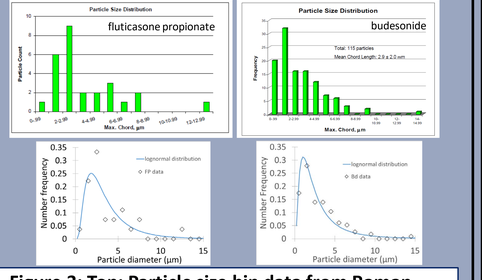


Figure 3: Top: Particle size bin data from Raman spectrometry studies [5]; bottom: lognormal distributions representing the size bin data.

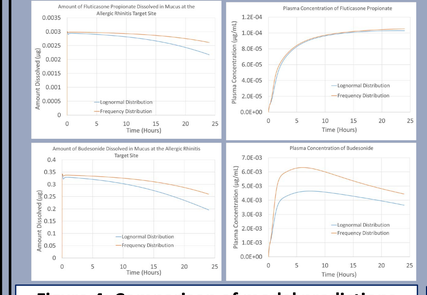


Figure 4: Comparison of model predictions using size bin data or lognormal distributions.

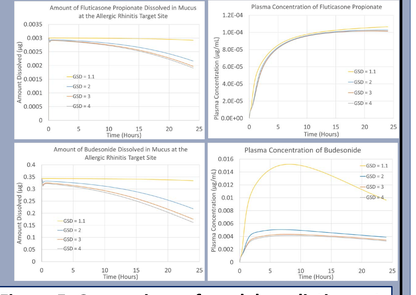


Figure 5: Comparison of model predictions at various GSD values.

Conclusions

- A previously developed PBPK model for nasal corticosteroid sprays was modified to accept API size bin data or lognormal distribution parameters.
- Model predictions showed greater differences in plasma and nasal tissue concentrations for budesonide than fluticasone propionate for size bin data versus lognormal distributions.
- Model predictions showed significant differences in nasal and plasma concentrations as a function of GSD for budesonide.
- Effects of particle size were more pronounced for the more soluble budesonide (solubility = 16 µg/ml) compared to fluticasone propionate (solubility = 0.14 µg/ml).

References

1. Doub WH et al. (2007). Raman chemical imaging for ingredient-specific particle size characterization of aqueous suspension nasal spray formulations: a progress report. Pharm Res 24(5):934-945.
2. Farias G et al. (2017). Investigating orthogonal in vitro analytical approaches to demonstrate the bioequivalence of nasal suspension formulations. J Aerosol Med Pulm Drug Deliv 31(2): A30-A31.
3. Schroeter J, Kimbell J, Walenga R, Babiskin A, Delvadia R. A CFD-PBPK model to simulate nasal absorption and systemic bioavailability of intranasal fluticasone propionate. J Aerosol Med Pulm Drug Deliv 30(3): 13-14.
4. Kimbell JS et al. (2015). Simulating nasal spray deposition: effects of spray nozzle presence in the nasal vestibule. J Aerosol Med Pulm Drug Deliv 28(3):A41.
5. Nelson MP et al. (2008). An ingredient-specific method for particle size characterization of corticosteroid nasal sprays. ExcipientFest Presentation.

Acknowledgments

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