On the Importance of Liquid Motion in Nasal Spray Delivery

Arun V Kolanjiyil[1], Laleh Golshahi[1] and Worth Longest[1,2]
[1]Department of Mechanical and Nuclear Engineering, Virginia Commonwealth University, Richmond, VA
[2]Department of Pharmaceutics, Virginia Commonwealth University, Richmond, VA

Introduction

- Nasal sprays are a popular choice for intranasal delivery of locally-acting drugs such as corticosteroids, antihistamines, and anticholinergics
  - Advantages include non-invasive administration, fast onset of action, and avoidance of first-pass metabolism
- During nasal spray pump actuation, a liquid formulation is forced through an orifice, which atomizes the liquid into droplets
- Nasal sprays carry significant momentum due to large spray droplet size and high spray velocity, which can strongly influence spray-wall interaction dynamics during droplet impaction on the wall [1]
- Additionally, droplets deposited on the nasal surface have been reported to form thin liquid films that move along the nasal surface [1]

Objective

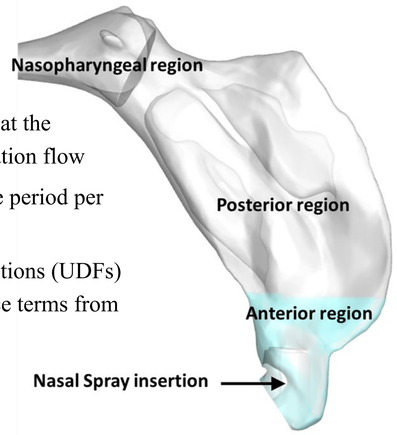
- Spray-wall interaction and post-deposition liquid motion can be dominant factors determining nasal spray drug delivery to specific nasal regions, as noticed in in-house experiments and shown in a recent *in vitro* study [1-2]
- Hence, a new spray-wall interaction (SWI) and post-deposition liquid motion (PDLM) model was developed by expanding an existing computational fluid dynamics (CFD) model of nasal spray droplet transport and deposition [1]
- **Objective**: to understand spray-wall interaction and accompanying surface liquid layer dynamics that occur during experimental nasal spray testing within rapid prototyped models of nasal anatomy
- Effects of mucus and mucociliary clearance (*in vivo* conditions over longer time scales) on drug transport are not considered in this study of shorter-term spray-wall interaction dynamics

Methods

- Newly developed SWI-PDLM model + two-way coupled spray transport simulations
- Two representative nasal sprays: Flonase® and Flonase® Sensimist™
- Representative nasal airway model: Medium Adult deposition model analogous to rapid prototyped *in vitro* model
- Initial and boundary conditions of the models as well as properties of the formulations were based on in-house *in vitro* experiments and measurements
  - Polydisperse droplet size distributions, cone angles, spray droplet mass flow rates and turbulent spray velocity profile
  - Formulation viscosity (shear thinning-thixotropic) and surface tension
  - Liquid adhesion effects (contact angle on 3D printed material surface)
  - Surface roughness effects of the 3D printed material

Methods – continued

- Medium Adult deposition nasal model

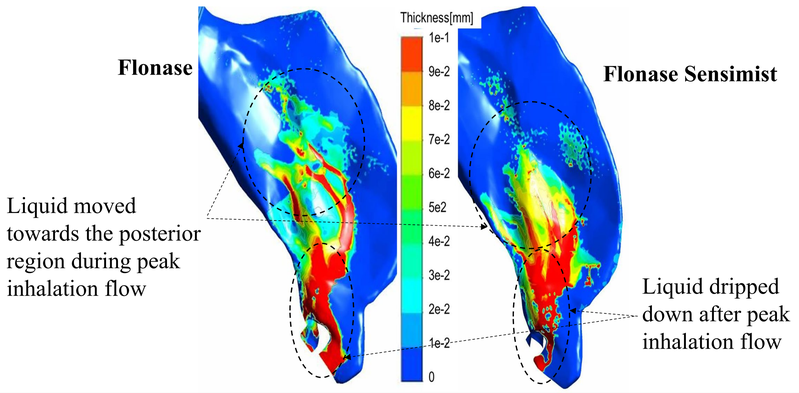


- Sprays were actuated into the nasal cavity at the beginning of "gently sniffing" nasal inhalation flow
- Two spray actuation cycles with ~2 s cycle period per actuation (4 s total simulations)
- In-house ANSYS Fluent user-defined functions (UDFs) were used to transfer the momentum source terms from simplified models to the nasal domain
- UDFs were also used to [1]
  - Implement two-way coupling effects
  - Identify droplet impingement conditions and specify the droplet spray-wall interaction model
  - Specify the droplet rebound conditions
  - Define variable time step size for the flow solver
  - Model viscosity (shear thinning-thixotropic) and multi-spray liquid fractions
  - Validated with and without SWI-PDLM model by comparing the liquid mass in the anterior and the posterior regions of the nasal cavity with *in vitro* measurements

Results

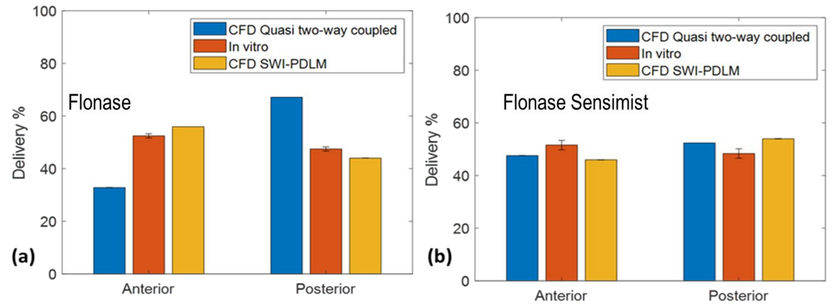
- SWI model captured the complex spray-wall interaction and PDLM model captured the liquid layer formation and movement
- Inhalation flow resulted in liquid motion towards the posterior part of the nasal cavity
- Once the inhalation flow subsided, the liquid film moved along the surface in the direction of the gravitational vector (dripping down) and tended to accumulate in regions of the nasal surface with inward curvatures

Liquid film thickness at time = 4.0 s (See on-demand slides for additional details)



Results – continued

- Comparison of simulated spray deposition predictions with *in vitro* measurements



- Flonase liquid motion on the nasal surface was more prominent, while for Flonase Sensimist spray-wall interaction and liquid motion were competing forces that largely cancelled each other
- Differences in liquid motion between the two products could be attributed to higher spray liquid mass (~2-fold higher), formulation properties (viscosity, surface tension, contact angle), differences in angle of impaction, and spray cone angle
- Flonase spray deposition prediction by the SWI-PDLM model showed closer agreement with the *in vitro* measurements compared to the quasi two-way coupled model alone (highlighting importance of post-deposition liquid motion)
- Flonase Sensimist predictions were similar for both the quasi two-way coupled model and the SWI-PDLM model (which included the quasi two-way coupled model result as a starting point)

Conclusions

- SWI-PDLM model results showed the physical mechanisms of how spray impaction and subsequent liquid film motion affect the drug deposition when using *in vitro* nasal airway geometries
- **Both sprays showed substantial spray-wall interaction and post-deposition liquid motion**
- Hence, the need for spray-wall interaction and post-deposition liquid motion modeling is **complex** and likely **dependent on a number of factors** including the spray formulation, spray pump shot weight, number of shots, nasal geometry, positioning of the spay nozzle within the nose, surface properties of the *in vitro* model or *in vivo* airway surface, and point of initial spray-wall contact

References

1. Kolanjiyil, AV.,..Golshahi L. & Longest PW. . Importance of Spray-Wall Interaction and Post-Deposition Liquid Motion in the Transport and Delivery of Pharmaceutical Nasal Sprays. 2022, Pharmaceutics (under review).
2. Sosnowski TR.,.., Dobrowolska K.: Impact of physicochemical properties of nasal spray products on drug deposition and transport in the pediatric nasal cavity model. Int. J. Pharm.2020, 574: 118911.

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