How Spray Metric Variability Impacts the Initial Deposition of Nasal Sprays

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Nasal Drug Delivery using Sprays

- 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, avoidance of first-pass metabolism and good patient compliance
- During nasal spray pump actuation, a liquid formulation is forced through an orifice, which atomizes the liquid into droplets
- Drug delivery efficiency is dependent on the device, formulation, patient related factors such as pump insertion and inhalation conditions, and nasal geometry
    - Variable usage conditions can lead to variability in the amount of the drug delivered to specific nasal regions
    - The nose can be divided into anterior and posterior regions, with the posterior nasal cavity being the primary target for nasal spray deposition and action

Objective

- *In vitro spray metrics* are currently recommended by the U.S. FDA as a means to compare the bioequivalence of a generic nasal spray under review for approval with a reference listed product
- It is currently not clear which *in vitro spray metrics* have the strongest correlation with regional nasal deposition
- Quantitative relations are desired between the currently recommended *in vitro spray metrics* and droplet deposition in the posterior nasal cavity
    - For example: What is the impact of a 5-degree change in nasal spray cone angle on posterior nasal deposition
- In this study, the effects of variability in two spray metrics, spray cone angle and spray velocity, were analyzed using validated computational fluid dynamics (CFD) simulations of Flonase® Sensimist™ in an average adult nasal airway model
        - Plume geometry including spray cone angle is a currently recommended spray metric for bioequivalence analysis by the U.S. FDA[1]
        - Spray velocity is not currently recommended, but is hypothesized to impact posterior nasal deposition

[1] US FDA. Draft guidance for industry: Bioavailability and bioequivalence studies for nasal aerosols and nasal sprays for local action. US Food and Drug Administration, 2003. Washington, DC.

Methods

- Effects of variability were investigated by varying one spray metric at a time, while keeping the other metrics constant and calculating the posterior nasal deposition with CFD
- CFD simulations were performed using a quasi two-way coupled Lagrangian model[1]
  - Mesh and solver settings followed our best practices and recommendations [1]
  - Initial and boundary conditions for the CFD model were based on measurements from in-house *in vitro* experiments[2,3]
- Base case spray metric values - cone angle of 35^0 and spray velocity of 14.4 m/s
- Five cases for each spray metric were considered
- Variability of each spray metric was within measured ranges for nasal sprays

[1] Kolanjiyil, Arun V, S Hosseini, A Alfaifi, M Hindle, L Golshahi, and PW Longest. 2021. "Importance of cloud motion and two-way momentum coupling in the transport of pharmaceutical nasal sprays." *Journal of Aerosol Science* (available online).

[2] Manniello MD, Hosseini S, Ali A, Esmaeili AR, Kolanjiyil AV, Walenga R, Babiskin A, Sandell D, Mohammadi R, Schuman T, Hindle M, Golshahi L: *In vitro* evaluation of regional nasal drug delivery using multiple anatomical nasal replicas of adult human subjects and two nasal sprays. *International Journal of Pharmaceutics* 2020, 593: 120103.

[3] Hosseini S, Wei X, Wilkins Jr JV, Fergusson CP, Mohammadi R, Vorona G, Golshahi L: I*n vitro* measurement of regional nasal drug delivery with Flonase,® Flonase® Sensimist,™ and MAD Nasal™ in anatomically correct nasal airway replicas of pediatric and adult human subjects. *Journal of Aerosol Medicine and Pulmonary Drug Delivery* 2019, 32: 374–385.

Methods contd.

- Spray cone angles considered

In vitro metric	Case I	Case II	Case III	Case IV	Case V
Spray cone angle	55^0	45^0	35^0	25^0	15^0

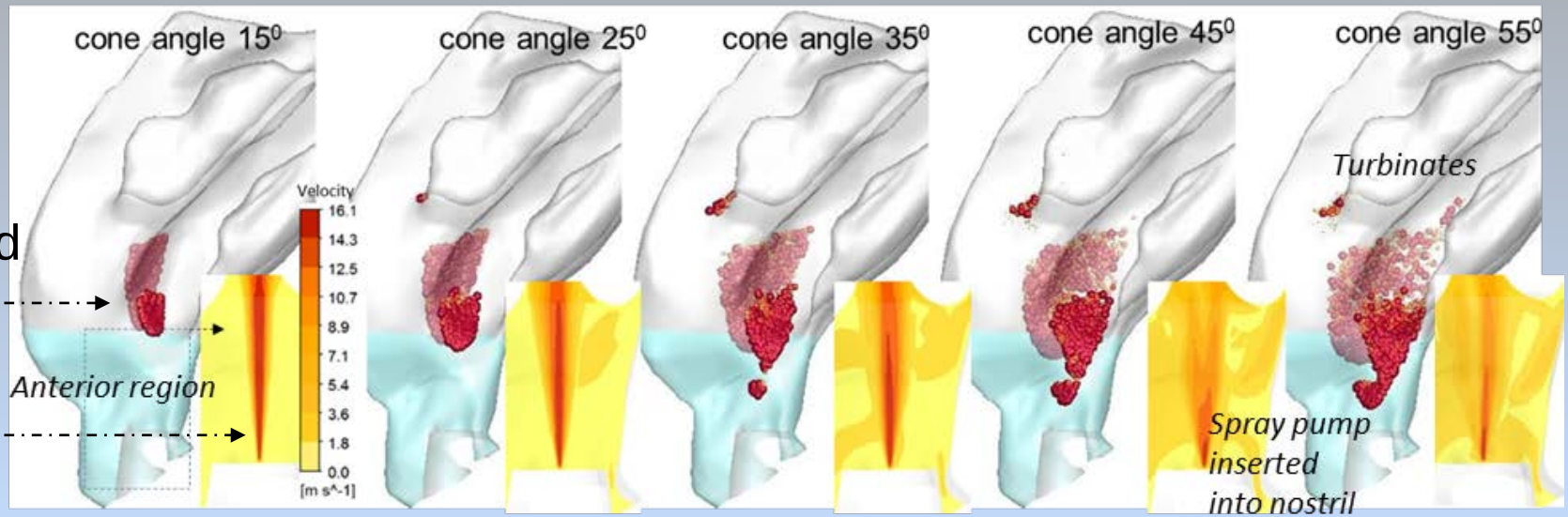
- Spray velocities considered

In vitro metric	Case I	Case II	Case III	Case IV	Case V
Spray average velocity	17.4 m/s	15.9 m/s	14.4 m/s	12.9 m/s	11.4 m/s

- New parameter - relative difference in the posterior delivery (RD_PD) was calculated as the difference between PD for the test case and PD for the base case and then normalized by the PD for the base case (Case III)
- RD_PD was plotted as a function of relative difference in the *in vitro* metric (compared with the base case) and a linear curve was fitted to capture the trend
    - High slope of the RD_PD trend line indicates high sensitivity to the *in vitro* test metric, and zero slope (horizontal line) indicates no sensitivity

Results and Discussion

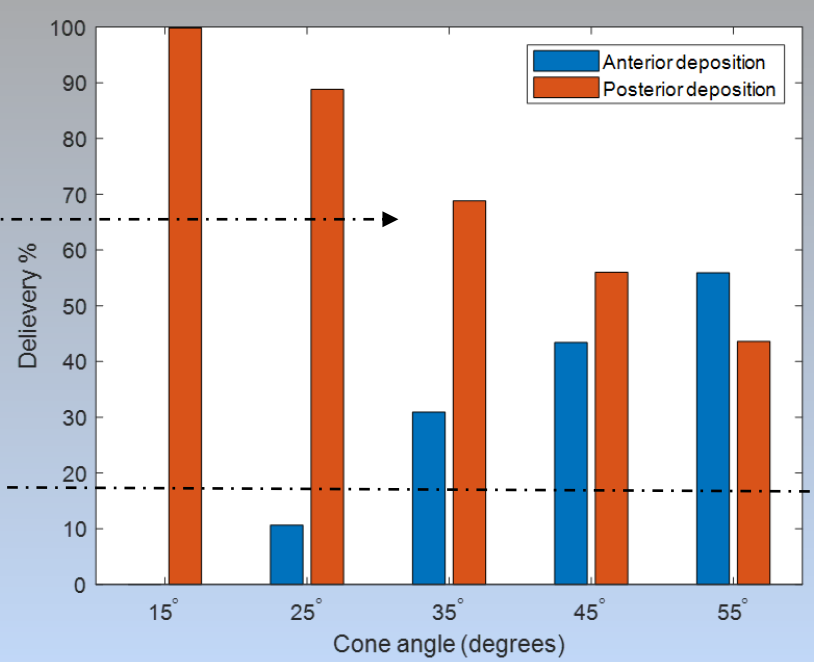
- Variability in spray cone angle

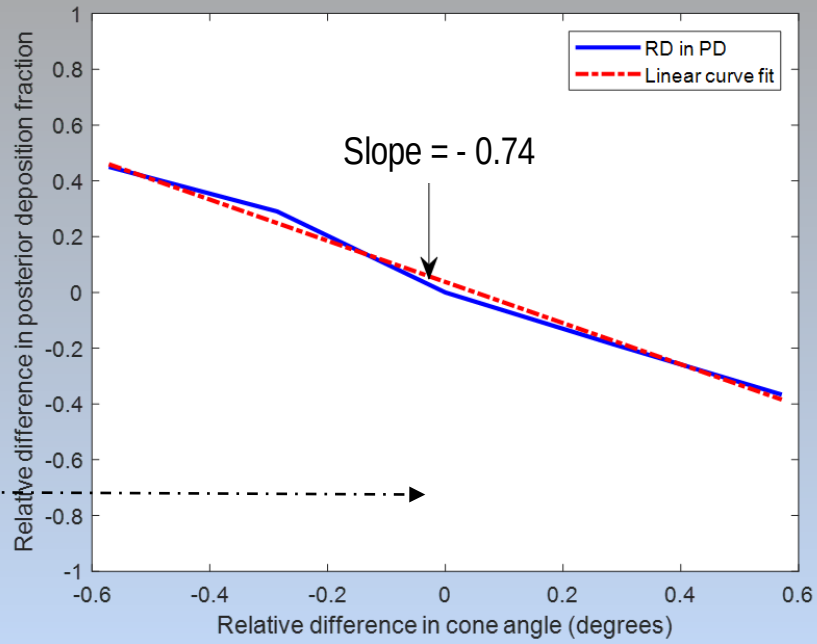


- Increase in cone angle led to higher dispersion of deposition along the direction of the projected spray plume
- Width of the momentum-jet showed a positive correlation with the cone angle, while peak momentum-jet velocity showed a negative correlation
- With increasing cone angle, momentum from the spray droplets was transferred to a larger spray volume and, hence, the momentum was distributed more evenly leading to lower peak velocity

Percentage delivery of spray to the anterior and posterior sections

RD_PD



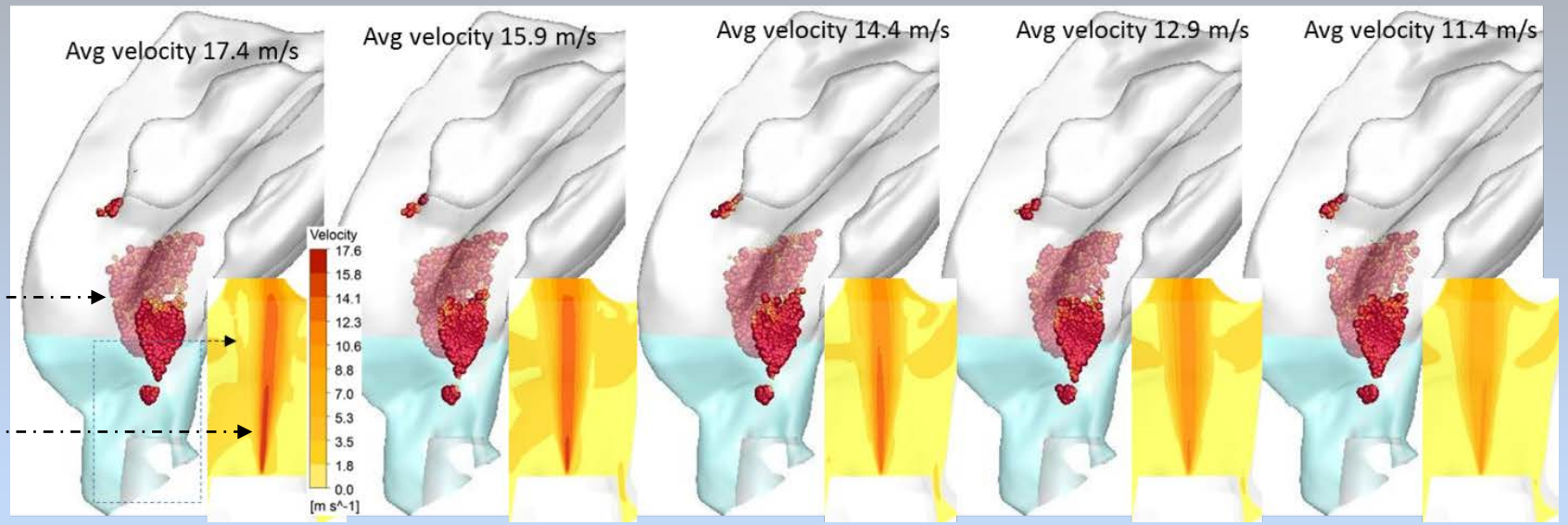


- With the increase in cone angle the anterior deposition increases, while the posterior deposition decreases
- RD_PD vs. relative difference in the cone angle captures the influence of variability in spray cone angle on posterior deposition
- Considering the large slope (-0.74) for the RD_PD trend line, the variability in spray cone angle largely influences the nasal spray delivery profile

➢ Variability in spray velocity

Locations of the deposited spray droplets

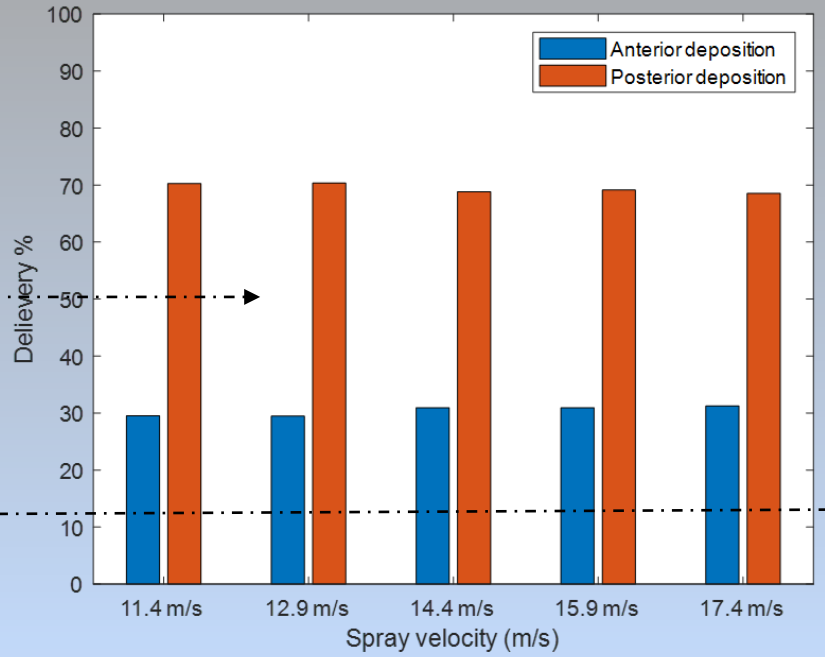
Momentum-jet

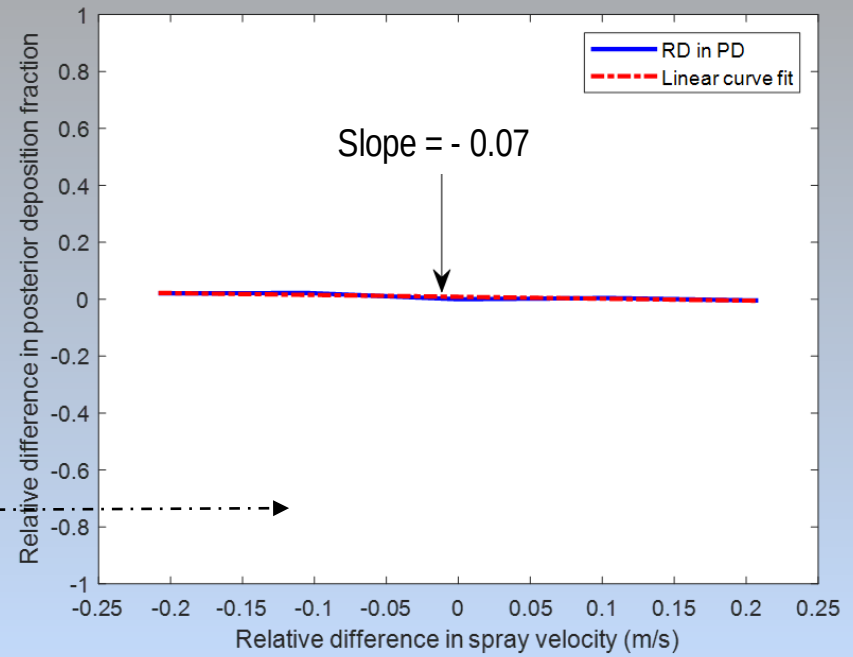


- Droplet locations were similar for each spray velocity case
- With the increase in spray droplet velocity, the velocity magnitude of the momentum-jet also increased

Percentage delivery of spray to the anterior and posterior sections

RD_PD





- Anterior deposition and posterior deposition did not vary noticeably with the spray velocity cases considered
- Small slope (-0.07) of the RD_PD trend line indicates that variability in spray velocity does not largely influence the nasal delivery profile

Conclusion

- This study indicated that posterior nasal deposition in the average deposition adult nasal airway model is sensitive to spray cone angle and not largely sensitive to spray velocity, within the metric ranges tested
- Considering the large influence of the spray cone angle on the posterior nasal spray delivery, it can be expected that the changes in the spray cone angle can directly impact the clinical efficacy of a nasal spray product
  - Based on the correlation observed, a 10% relative difference in spray cone angle will produce a 7.4% change in posterior nasal deposition
  - Quantitative relations identified may be impacted by nasal spray insertion conditions including depth and angle; however, we expect that the qualitative trends identified will remain unchanged under normal use conditions
- It is to be noted that the spray cone angle is a U.S. FDA recommended *in vitro* test metric, while spray velocity is not
- Further analysis using different sprays, nasal airway models with different insertion conditions are required to complement the findings of this study

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Thank you