ESTIMATING SIZE-SPECIFIC NUMBERS OF ACTIVE PHARMACEUTICAL INGREDIENT PARTICLES IN THE REGIONAL DEPOSITION OF A NASAL SPRAY

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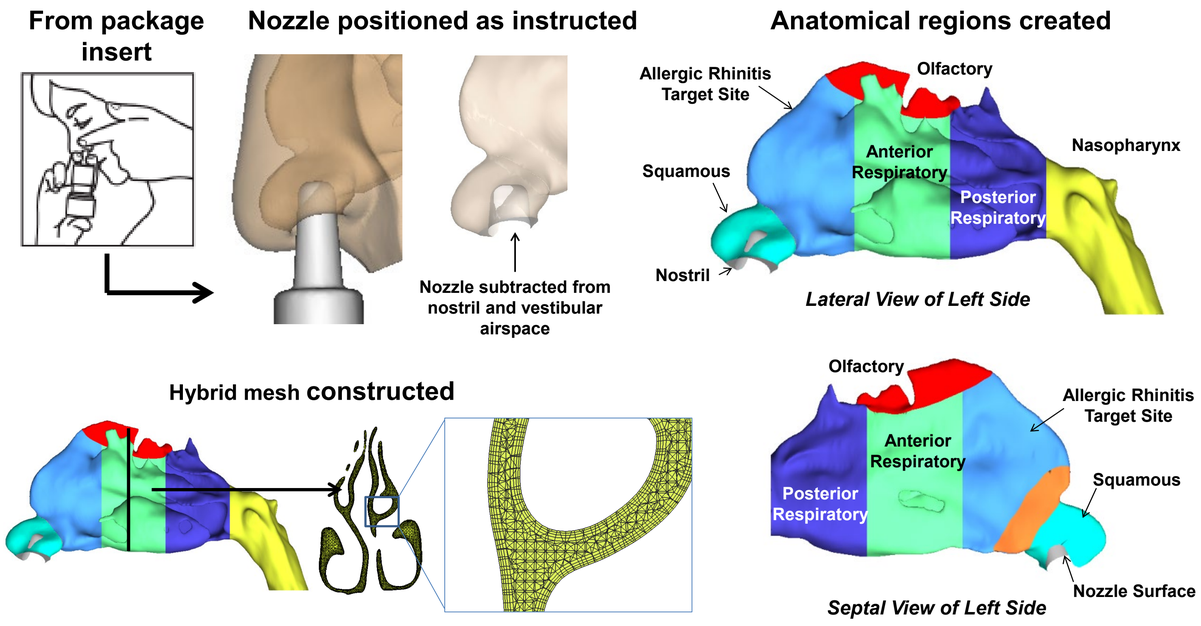
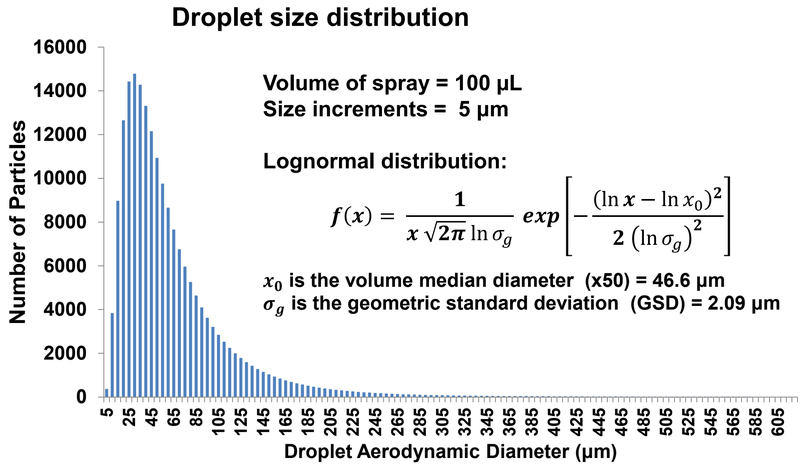
INTRODUCTION

- Regional deposition of sprayed corticosteroid droplets are needed to quantify nasal drug delivery
- Computational fluid dynamics (CFD) → simulate sprayed particle transport in three-dimensional (3D) nasal reconstructions
- Most nasal sprays contain active pharmaceutical ingredient (API) particle suspensions in liquid vehicles
- API particle size may affect mucosal dissolution, absorption, and transport rates
- A method is needed to estimate the number and size of API particles in nasal spray deposits to determine API dose and systemic uptake

3D Model Construction

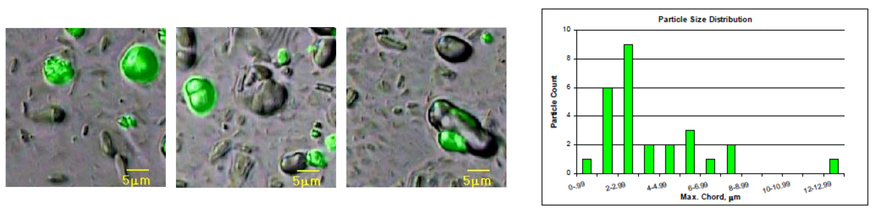


Spray Simulation



METHODS

- Subject: 26 year old male, 6'0", 69.4 kg, with allergic rhinitis, unknown smoking history, history of fluticasone propionate (FP) nasal spray use, otherwise normal
- 3D reconstruction created from CT scan (0.7-mm resolution) using 3D Slicer
- 3D spray nozzle reconstruction positioned in nasal vestibule according to instructions from package insert [1], subtracted from airspace using ICEM-CFD™ v15.0 (ANSYS, Inc., Canonsburg, PA)
- Anatomical regions of interest created for post-processing using ICEM-CFD™
- Hybrid computational mesh of nasal airspace constructed using ICEM-CFD™ [2]
- Steady-state inspiratory resting airflow simulated using Fluent™ v14.5 (ANSYS)
  - Instructions for use → "Breathe gently inwards through the nostril"
  - Pressure drop obtained for airflow at twice estimated minute volume [3] with nostrils open
  - Right nostril closed, pressure at left nostril and outlet set to 0 and -18.7 Pa, respectively, air velocity set to 0 at airway walls ("no-slip" condition) → airflow rate of 6.4 L/min
- Droplet transport simulated [4], regional deposited mass computed using Fluent™
  - Mean adult actuation force of 56.9 N (N, Newtons) [5]
  - Droplet size distribution and spray speed measured for 100mg FP spray [6]
  - Spray cone angle = 70° [7]
  - Using solid-cone injections in Fluent's™ Discrete Phase Model; averaging 5 repeated runs
- Size-specific numbers of API particles computed in regional spray mass
  - Regional API mass assumed proportional to regional spray mass (50 μg FP per spray)
  - Example API particle size distribution from Raman chemical imaging [8]
    - FP density (1.32 g/cm^3) → "frequency mass fraction" for each size bin



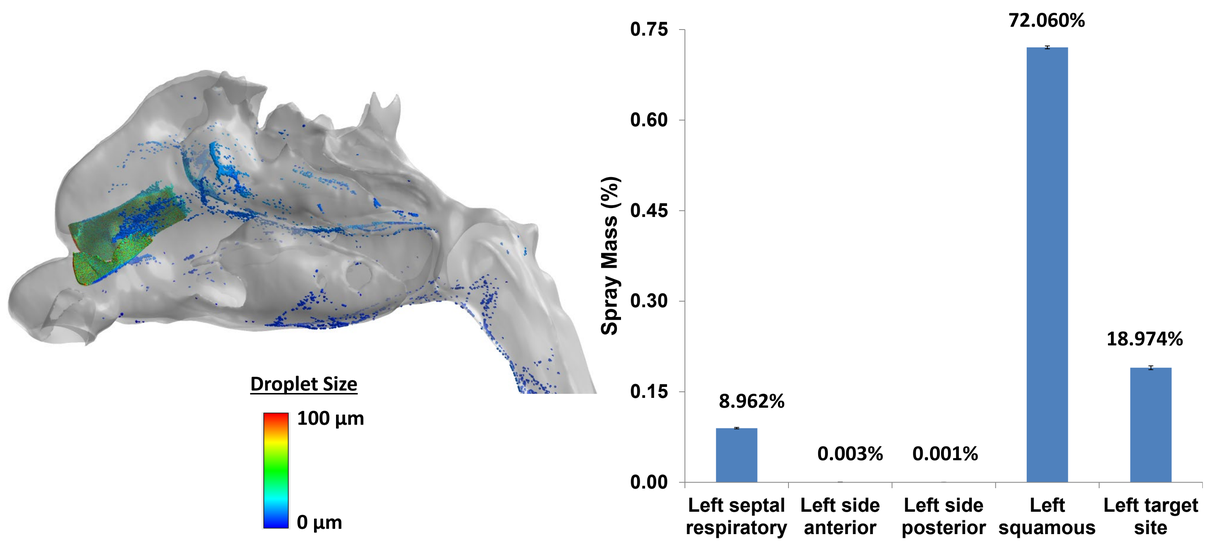
- Frequency mass fractions applied to regional deposited API mass, spherical volume used to estimate numbers of particles per API size bin in each region

Estimation of API Particle Numbers

Max Chord (μm)	Mid-Chord (μm)	Frequency [Nelson]	Frequency Mass (μg)	Freq. Mass Fraction
0-0.99	0.5	1	8.639E-08	3.125E-05
1-1.99	1.5	6	1.400E-05	5.063E-03
2-2.99	2.5	9	9.719E-05	3.516E-02
3-3.99	3.5	2	5.927E-05	2.144E-02
4-4.99	4.5	2	1.260E-04	4.557E-02
5-5.99	5.5	3	3.450E-04	1.248E-01
6-6.99	6.5	1	1.898E-04	6.866E-02
7-7.99	7.5	2	5.832E-04	2.110E-01
8-8.99	8.5	0	0.000E+00	0.000E+00
9-9.99	9.5	0	0.000E+00	0.000E+00
10-10.99	10.5	0	0.000E+00	0.000E+00
11-11.99	11.5	0	0.000E+00	0.000E+00
12-12.99	12.5	1	1.350E-03	4.883E-01

RESULTS

Regional Spray Mass Deposition



Estimated Regional API Particle Numbers

	Left septal respiratory	Left side anterior	Left side posterior	Left squamous	Left target site
Spray dep. fraction	8.962%	0.003%	0.001%	72.060%	18.974%
μg API	4.48E+00	1.54E-03	4.45E-04	3.60E+01	9.49E+00
Particle Size (μm)	Numbers of Particles				
0.5	1621	1	0	13034	3432
1.5	9726	3	1	78203	20591
2.5	14589	5	1	117304	30887
3.5	3242	1	0	26068	6864
4.5	3242	1	0	26068	6864
5.5	4863	2	0	39101	10296
6.5	1621	1	0	13034	3432
7.5	3242	1	0	26068	6864
8.5	0	0	0	0	0
9.5	0	0	0	0	0
10.5	0	0	0	0	0
11.5	0	0	0	0	0
12.5	1621	1	0	13034	3432

CONCLUSIONS

- A method is presented for estimating size-specific API particle numbers deposited throughout the nasal cavity via spray transport.
- The method estimates that 50 μg of FP in one spray actuation is represented by nearly 500,000 FP particles in nearly 200,000 spray droplets

FUTURE DIRECTIONS

- Obtain additional measurements of particle size distribution (PSD) for FP in nasal sprays
- Estimate FP PSD measurement variation
- Couple deposition predictions with a physiologically-based pharmacokinetic model to predict bioequivalent doses from alternate medication routes

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