In Silico and Experimental Methods to Support Generic Nasal Drug Product (NDP) Development

RDD 2021

May 7, 2021

Ross Walenga, Ph.D.
Chemical Engineer
Division of Quantitative Methods and Modeling, Office of Research and Standards, Office of Generic Drugs
CDER | U.S. FDA

Generic Drug User Fee Amendments (GDUFA)

- Passed in July 2012 in the U.S., to speed access to safe and effective generic drugs to the public, reauthorized in 2017
- Requires user fees to supplement costs of reviewing generic drug applications and provides additional resources, including support for **regulatory science research**
- User fee program which directly supports regulatory science research activities
  - www.fda.gov/gdufaregscience

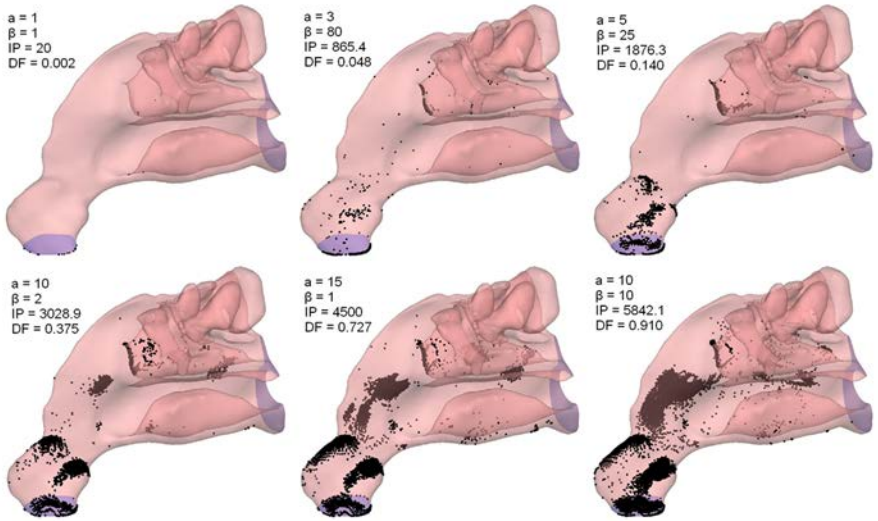
Slide adapted from Dr. Kimberly Witzmann

GDUFA Funded Research for Nasal Drug Products (NDPs)

- Eight external grants and contracts (six ongoing)
- Variety of academic and consulting experts
- Includes in vivo, in vitro, and in silico research
- Focus of this presentation is on in silico approaches and in vitro nasal models
  - Influence of device and formulation differences on regional deposition and absorption
  - Prediction of olfactory region absorption for blood-brain-barrier (BBB) delivery

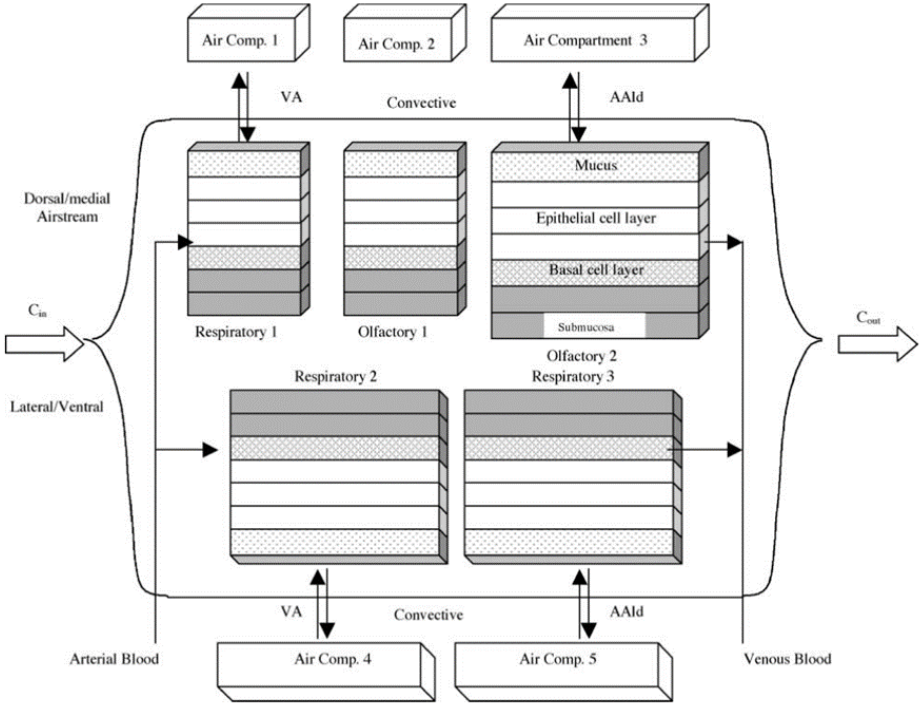
Computational Fluid Dynamics (CFD) Modeling of NDPs

- Predict influence of device and formulation parameters
  - Particle size distribution, spray angle, spray velocity
  - Regional deposition
    - Intersubject variability
  - Pharmacokinetic (PK) profile
    - Combined with physiologically-based pharmacokinetic (PBPK) modeling



Fiber deposition in nasal cavity, where a is the fiber radius in μm, β is the fiber aspect ratio, IP is the impaction parameter, and DF is the deposition fraction. (Fig. 13 from Dastan et al.[1])

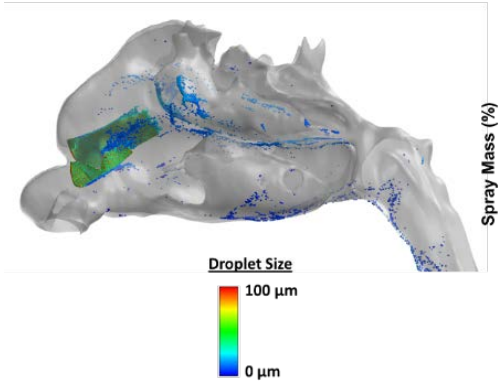
PBPK Modeling of NDPs



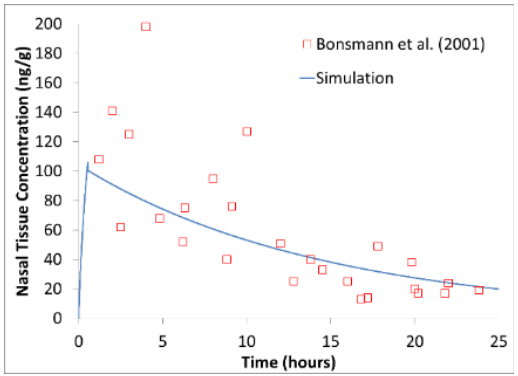
Nasal PBPK model structure as shown in Fig. 2 of Andersen et al.[2]

- Compartmental model
- Prediction of local and systemic PK
  - Dissolution in mucus layer
  - Absorption through nasal tissue
  - Metabolism in nasal tissue
  - Integration with systemic model
- Validated with in vivo PK data

Hybrid CFD-PBPK for Nasally Inhaled Corticosteroids



CFD predictions for deposition locations of fluticasone propionate droplets, from Kimbell et al.[3]

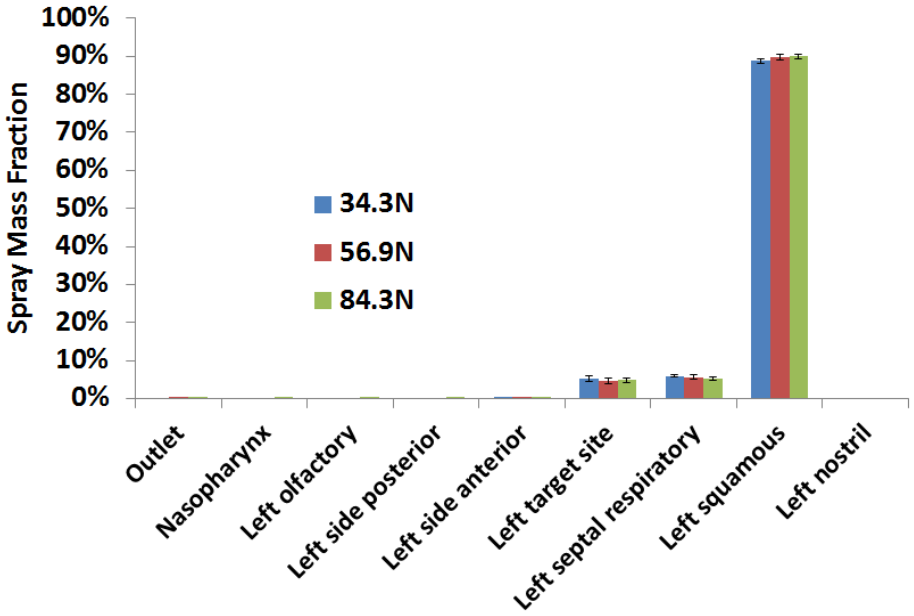


PK predictions of fluticasone propionate nasal spray, from Schroeter et al.[4]

- Applied Research Associates, Inc.
  - Grant #1U01FD005201: 2014-2018
  - Contract #75F40119C10079: 2019-present
  - Principal Investigator (PI): Jeffry Schroeter
- Fully 3D CFD model predicts deposition
- PBPK model for nasal absorption
- CFD results serve as inputs to the PBPK model
  - Models are run independently
  - Constant mucociliary clearance (MCC) velocity
- Investigation of device and usage parameters

Actuation Force Sensitivity

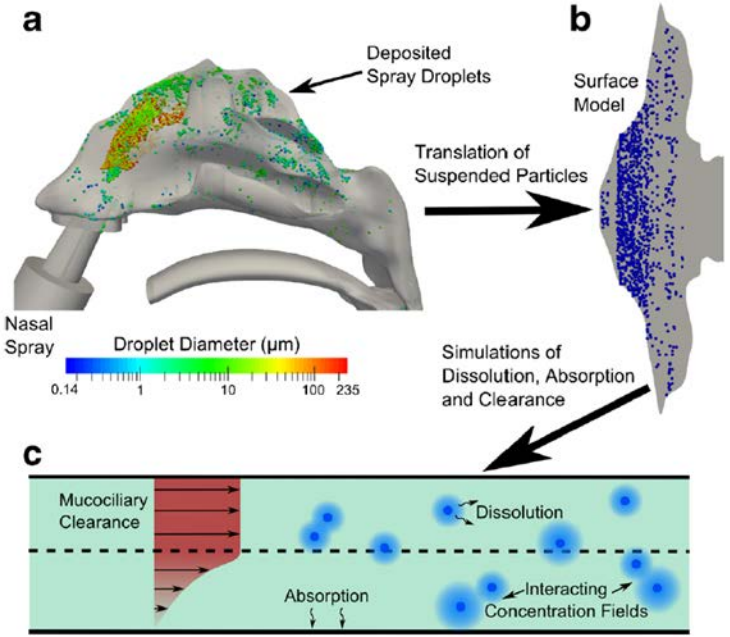
- Steady State Flow
- Three actuation forces chosen: 34.3 N, 56.9 N, and 84.3 N
- Spray velocity based on spray duration measurements
- Droplet size is measured using laser diffraction
- Cone angle is held constant at 70° (Cheng et al.[6])



CFD predictions for regional deposition fraction of fluticasone propionate droplets according to differences in actuation force, from Kimbell et al.[5]

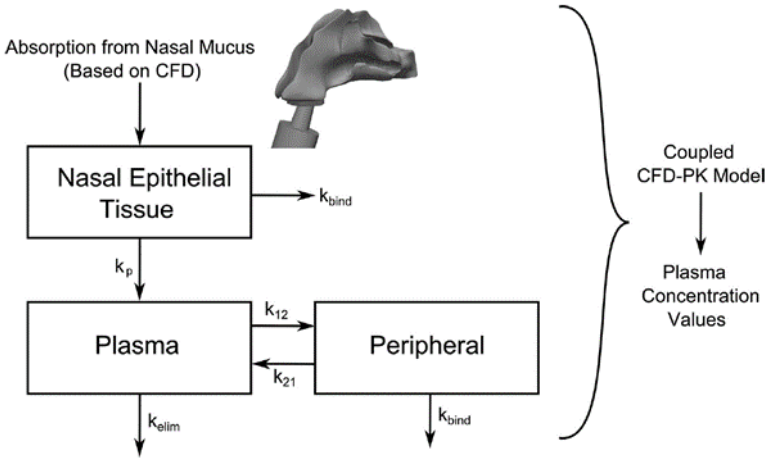
Coupled Nasal CFD-PBPK

- Virginia Commonwealth University (VCU)
  - PI: P. Worth Longest
  - Grant #1U01FD004570: 2012-2016
- Predict local delivery of nasal suspension spray droplet using CFD
- Simultaneously predict MCC and dissolution using CFD with 2D surface model

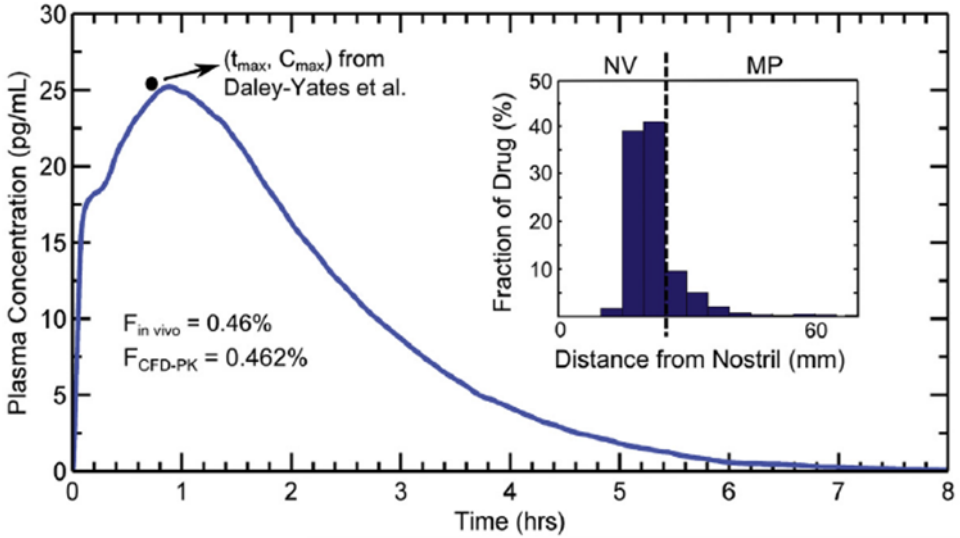


Nasal absorption process, with a) CFD prediction of deposition, b) mucociliary transit model, and c) dissolution, advection, and absorption model. (Fig.1 from Rygg et al.[7])

PK Predictions Using Coupled Model



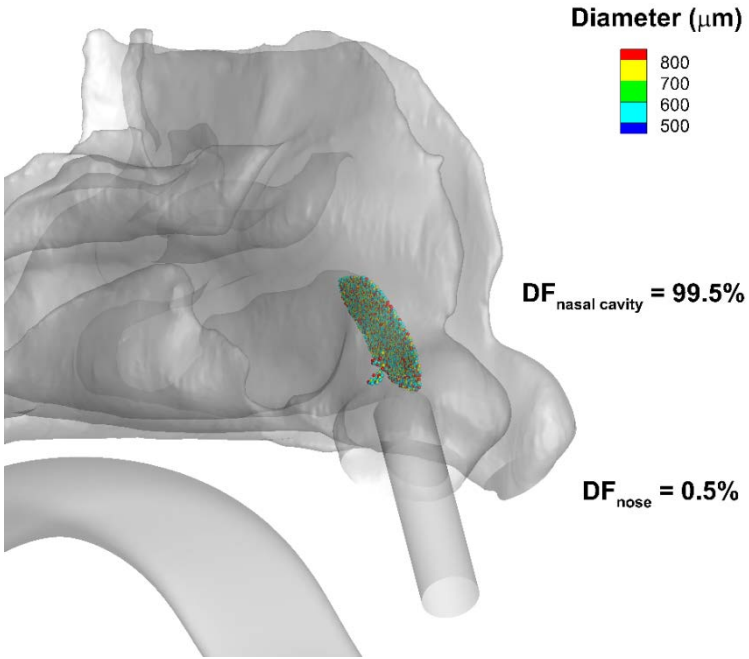
Two-compartment PK model structure. (Fig. 4 from Rygg et al.[8]



PK profile prediction as compared with in vivo data from Daley-Yates et al.,[9] as well as comparison of bioavailability (F). The inset bar-graph shows distance of drug deposited from nostril in either the nasal vestibule (NV) or the middle passage (MP). (Fig. 6 from Rygg et al.[8])

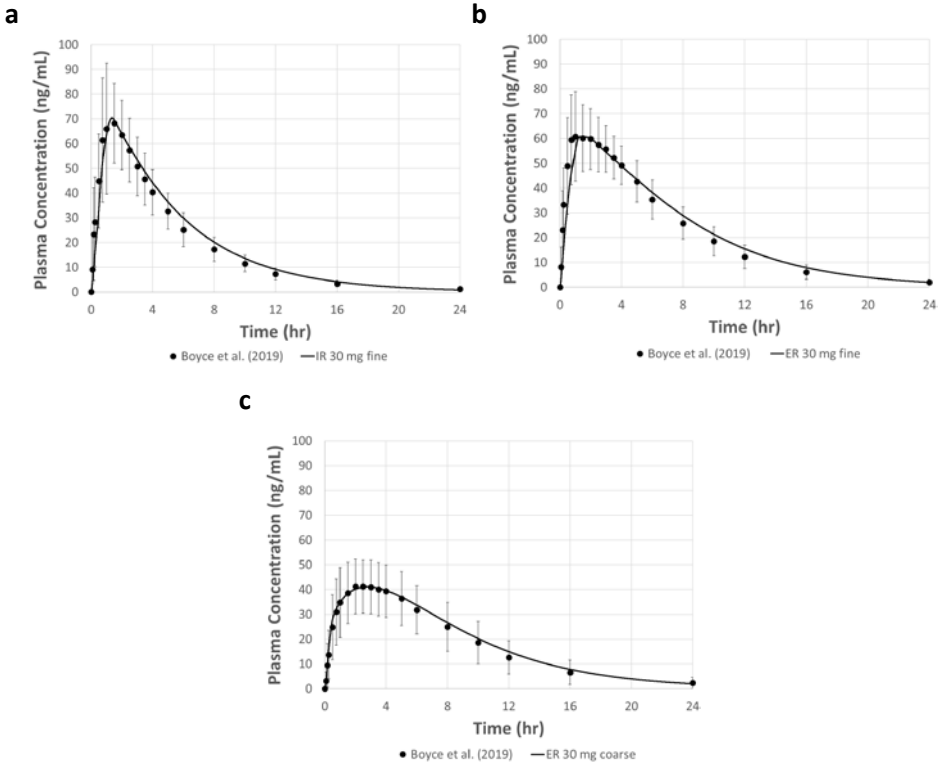
Nasal Insufflation of Oxycodone Hydrochloride (HCl) Extended Release (ER) Tablet

- Internal Research Project
- Used base model from grant with VCU to predict PK profiles of milled abuse-deterrent formulations (ADFs) in human nasal insufflation PK studies
- Validate with in-house PK data from nasal insufflation study
- Predict the PK of milled oxycodone HCl immediate release (IR) and ER tablets as a function of particle size and strength (drug/polymer ratio)
- Dissolution data using method developed by Feng et al.[10] are used as model inputs



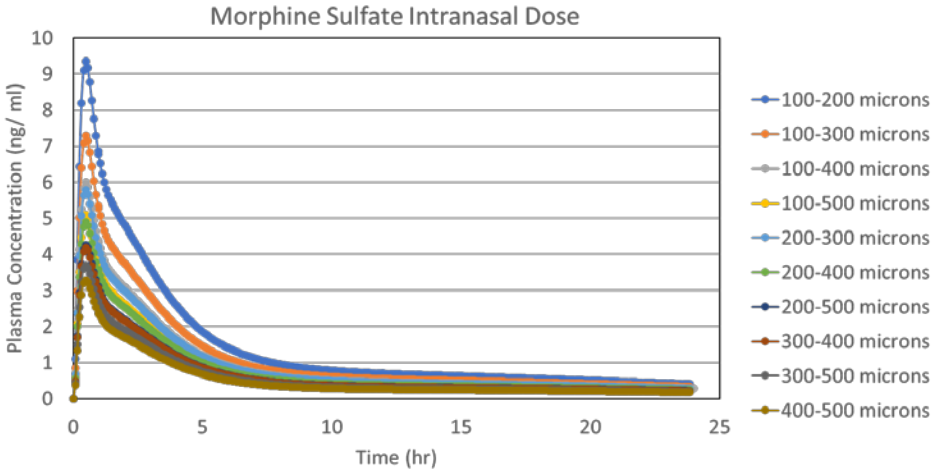
Deposition fraction (DF) predictions following nasal insufflation of coarsely milled ER formulation (Fig. 2 of Walenga et al.[11])

PK Predictions of Nasally Insufflated Oxycodone HCl ER Tablet



Plasma concentration CFD-PBPK predictions following nasal insufflation of a) finely milled IR, b) finely milled ER, and c) coarsely milled ER tablet formulations as compared with in vivo data from Boyce et al.[12] (Fig. 3 of Walenga et al.[11])

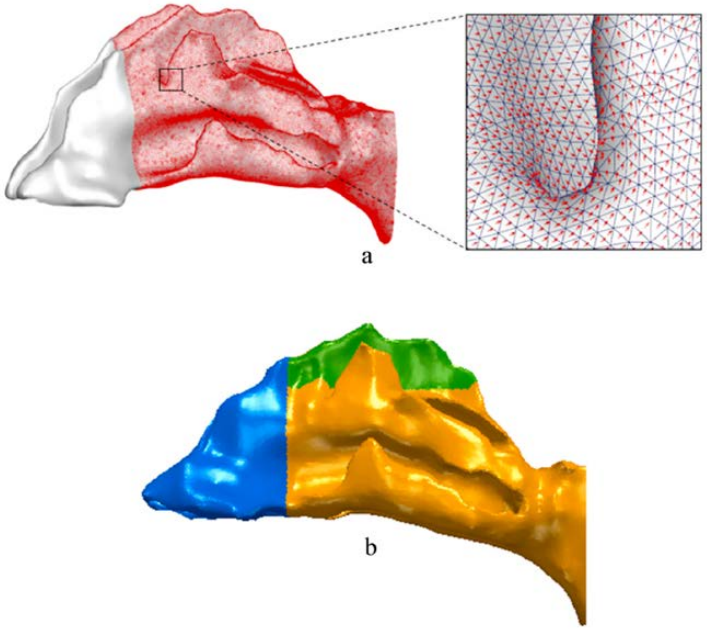
Nasal Insufflation of Morphine Sulfate and Naltrexone HCl ER Capsules



Plasma concentration predictions following nasal insufflation of crushed capsules in different particle size ranges (Fig. 3b of Chopski et al.[13])

- Internal Research Project
- Compartmental PBPK model using GastroPlus™ (V9.7, Simulations Plus, Inc., Lancaster, CA, USA).
- Validate with PK data from nasal insufflation study (Setnik et al.[14])
- Predict the PK of crushed morphine sulfate and naltrexone HCl ER capsules as a function of particle size
- Results from separate models according to particle size showed strong dependence for morphine sulfate, but not for naltrexone HCl

Fully 3D Nasal MCC Model

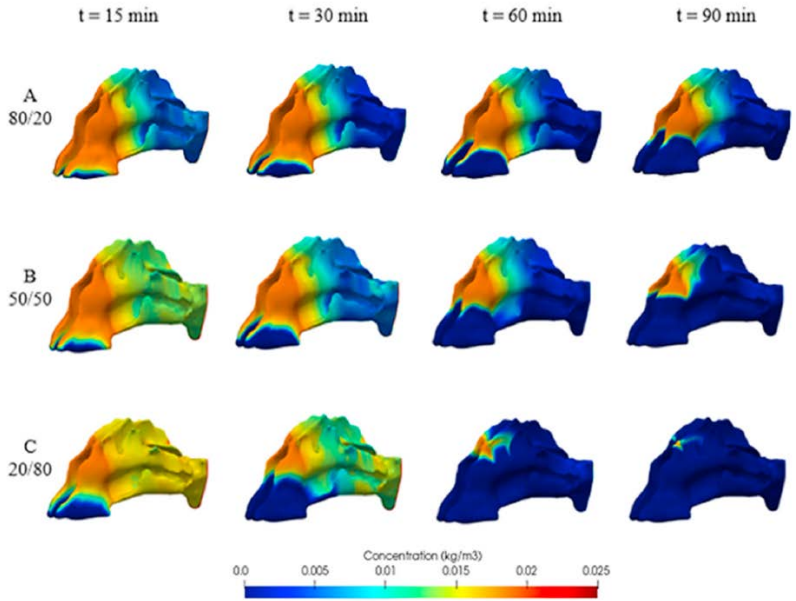


Nasal MCC model features, including a) 6 mm/min mucus velocity vectors in mucus layer and b) regional definitions including olfactory (red), nasal vestibule (blue), and nasal cavity (orange) regions. (Fig. 1 of Chari et al.[15])

- North Carolina State University
  - PI: Clement Kleinstreuer
  - Grant #1U01FD006537: 2018-present
- 3D CFD model is used to predict regional deposition of NDPs
- Particle deposition locations are directly translated to fully 3D mucus layer model
- Nasal MCC model predicts transit, dissolution, and absorption simultaneously
- Can be used for predicting BBB delivery

Fully 3D Nasal MCC Model

- Model sensitivity was investigated
  - Oil-in-water partition coefficient ($K_{o/w}$)
  - Solubility (C_s)
  - Particle diameter (d)
- High values of $K_{o/w}$ and C_s produced rapid absorption
- Smaller particles show initial burst in absorption rate, but after burst rates are similar
- Effect of deposition locations was investigated



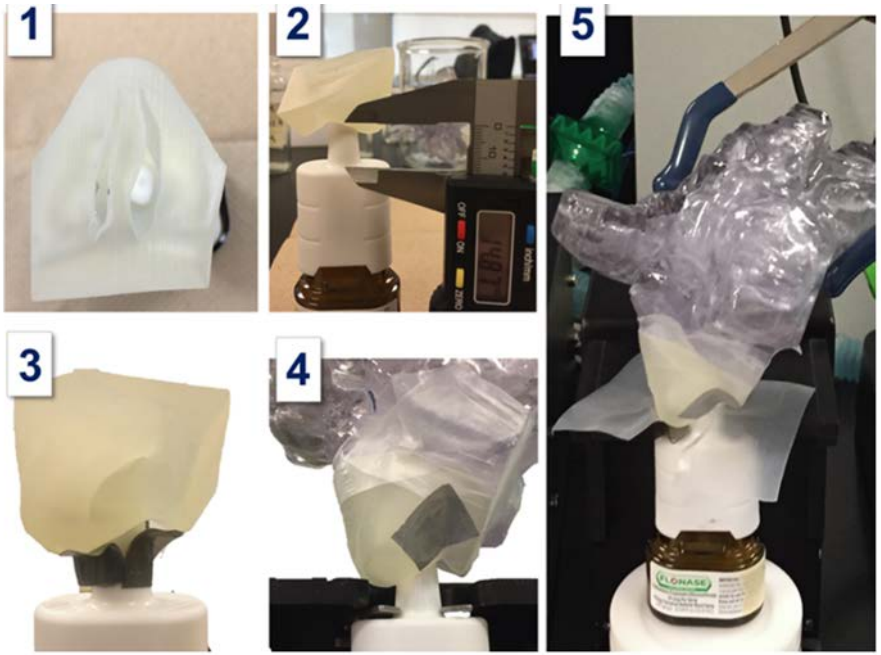
Mucus layer drug concentrations for drug with $K_{o/w}$ = 0.005, C_s = 0.02 mg/mL, and d = 5 µm for regional depositions ratios in the nasal vestibule and nasal cavity regions of a) 80/20, b) 50/50, and c) 20/80. (Fig. 15 of Chari et al.[15])

Nasal In Vitro Models

Nasal in vitro model that allows for measurement of olfactory region deposition. (Adapted from Fig. 1c of Xi et al.[16])

- Drug product is actuated into nasal model
- Deposited drug is measured from removable sections using high performance liquid chromatography (HPLC)
- May show significant intersubject variability

Regional Deposition Measurements

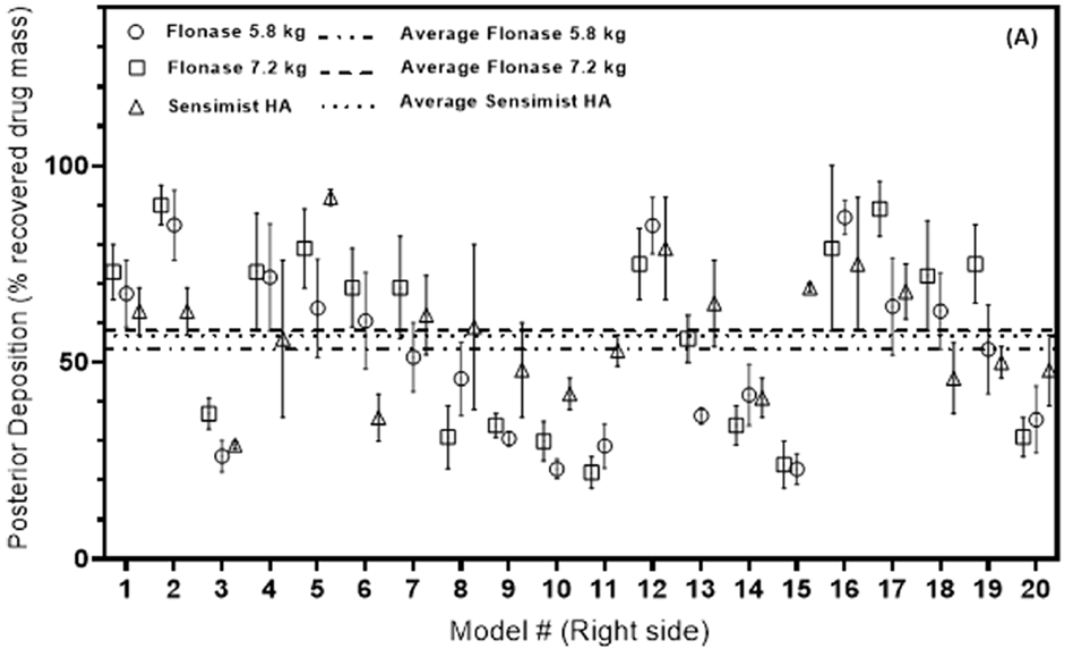


Experimental setup for measuring deposition following actuation of fluticasone propionate nasal spray. (Fig. 2 of Manniello et al.[17])

- VCU
  - PI: Laleh Golshahi
  - Contract #HHSF223201810144C (adult models): 2018-present
  - Contract #75F4012000172 (pediatric models): 2020-present
- Develop two sets of models for adult and pediatric subjects (three models for each)
  - Intersubject variability for nasally inhaled corticosteroids
- Relationships of in vitro metrics of spray properties with regional deposition

Posterior Region Deposition Measurements

- Posterior regional deposition measurements showed high variability on right sides of twenty nasal models
  - Ranges of 23-87% and 22-90% on right side for fluticasone propionate nasal spray at 5.8 kg and 7.2 kg force levels, respectively
  - Range of 29-92% on right sides for fluticasone furoate nasal spray
- Similar variability on left sides of models, although range for fluticasone furoate nasal spray was a bit tighter (42-92%)



Posterior regional deposition in right side of twenty adult nasal models (n = 5 for each model) for two force levels (5.8 kg and 7.2 kg) of fluticasone propionate nasal spray (Flonase®) and hand-actuated fluticasone furoate nasal spray (Flonase Sensimist®). (Fig. 5 of Manniello et al.[17])

Nasal Model Selection and Further Development

- Three adult nasal models have been selected to capture intersubject variability
- Models have been sectioned into several regions
- CFD model has been developed to allow for deeper investigation of relationships between in vitro metrics and regional deposition
- In vitro testing including particle size, spray pattern, and plume geometry has been conducted with reference and test products, along with regional deposition
- Early work on pediatric model development has commenced

Conclusions

1. GDUFA supports several external research grants and contracts for enhancing generic NDP development.

2. A variety of hybrid CFD-PBPK models are being developed to investigate relationships between in vitro test metrics and regional drug delivery and to better understand regional delivery of drugs that target the BBB.

3. In vitro nasal models may be used to explore relationships between in vitro test metrics and regional deposition measurements while considering intersubject variability.

Call to Action

1. Generic NDPs may benefit from model-integrated approach to product development and demonstration of bioequivalence, which may be facilitated via pre-ANDA meetings with the U.S. FDA.

2. Researchers working in this area may consider future scientific collaborations with the U.S. FDA through grants and contracts.

Acknowledgements

- FDA/CDER/OGD/ORS
  - Sharon Ahluwalia
  - Andrew Babiskin
  - Betsy Ballard
  - Elizabeth Bielski
  - Susan Boc
  - Steven Chopski
  - Denise Conti
  - Sneha Dhapare
  - Liangfeng Han
  - Bryan Newman
  - Miyoung Yoon
- FDA/CDER/OGD/ORS
  - Lanyan (Lucy) Fang
  - Myong-Jin Kim
  - Darby Kozak
  - Liang Zhao
  - Markham Luke
  - Lei Zhang
  - Robert Lionberger
- FDA/CDER/OGD/OB
  - Kimberly Witzmann
- FDA/CDER/OPQ/OLDP
  - Srinivas Behara
- FDA/CDER/OPQ/ONDP
  - Renishkumar Delvadia
- FDA/CDER/OPQ/OTR
  - Geng Tian
  - Maziar Kakhi
- FDA/CDER/OTS/OCP
  - Bhawana Saluja
- Applied Research Associates, Inc.
  - Jeffrey Schroeter
- University of North Carolina
  - Julie Kimbell
  - William (Bill) Bennett
- VCU
  - P. Worth Longest
  - Laleh Golshahi
  - Michael Hindle
- North Carolina State University
  - Clement Kleinstreuer
  - Sriram Chari


FDA
U.S. FOOD & DRUG
ADMINISTRATION

References

1. Dastan A, Abouali O, Ahmadi G. CFD simulation of total and regional fiber deposition in human nasal cavities. J Aerosol Sci. 2014;69:132-49.
2. Andersen ME, Green T, Frederick CB, Bogdanffy MS. Physiologically based pharmacokinetic (PBPK) models for nasal tissue dosimetry of organic esters: assessing the state-of-knowledge and risk assessment applications with methyl methacrylate and vinyl acetate. Regulatory Toxicology and Pharmacology. 2002;36(3):234-45.
3. Kimbell J, Schroeter J, Tian G, Walenga R, Babiskin A, Delvadia R. Estimating size-specific numbers of active pharmaceutical ingredient particles in the regional deposition of a nasal spray. J Aerosol Med Pulm Drug Deliv. 2017;30(3):18-19.
4. 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. 2017;30(3):13-14 Bonsmann U, Bachert C, Delank KW, Rohdewald P. Presence of fluticasone propionate on human nasal mucosal surface and in human nasal tissue over a period of 24 h after intranasal application. Allergy. 2001;56(6):532-5.
5. Kimbell JS, Schroeter JD, Sheth P, Tian G, Delvadia RR, Saluja B, Walenga R. Effect of actuation force on simulated regional nasal spray deposition in a healthy nasal cavity. Respiratory Drug Delivery (Scottsdale, AZ, USA, April 17-21). 2016.
6. Cheng YS, Holmes TD, Gao J, Guilmette RA, Li S, Surakitbanharn Y, Rowlings C: Characterization of nasal spray pumps and deposition pattern in a replica of the human nasal airway. J Aerosol Med 2001, 14:267-280.

References (cont'd)

7. Rygg A, Hindle M, Longest PW. Absorption and clearance of pharmaceutical aerosols in the human nose: effects of nasal spray suspension particle size and properties. Pharm Res. 2016;33(4):909-21.
8. Rygg A, Hindle M, Longest PW. Linking suspension nasal spray drug deposition patterns to pharmacokinetic profiles: a proof-of-concept study using computational fluid dynamics. J Pharm Sci. 2016;105(6):1995-2004.
9. Daley-Yates PT, Kunka RL, Yin Y, Andrews SM, Callejas S, Ng C. Bioavailability of fluticasone propionate and mometasone furoate aqueous nasal sprays. European journal of clinical pharmacology. 2004;60(4):265-8.
10. Feng X, Zidan A, Kamal NS, Xu X, Sun D, Walenga R, Boyce H, Cruz CN, Ashraf M. Assessing drug release from manipulated abuse deterrent formulations. AAPS PharmSciTech. 2020;21(2):1-11.
11. Boyce H, Sun D, Kinjo M, Raofi S, Frost M, Luke M, Kim M-J, Lionberger R, Vince B, et al. Pharmacokinetic study of physically manipulated oxycodone hydrochloride products following nasal insufflation in recreational opioid users. AAPS PharmSci 360; November 6, 2019; San Antonio, TX, USA.
12. Walenga R, Boyce H, Feng X, Zidan A, Kamal N, Xu X, Babiskin A, Kim MJ, Zhao L: Hybrid CFD-PBPK model for prediction of systemic PK following nasal insufflation of milled oxycodone hydrochloride extended-release tablets. In AAPS PharmSci 360. Virtual; 2020.
13. Chopski S, Walenga R, Boyce H, Babiskin A, Kim MJ: Physiologically-based pharmacokinetic model to describe the pharmacokinetics of crushed morphine sulfate and naltrexone hydrochloride extended-release capsules with abuse deterrent properties. In AAPS PharmSci 360. Virtual; 2020.

References (cont'd)

14. Setnik B, Goli V, Levy-Cooperman N, Mills C, Shram M, Smith I. Assessing the subjective and physiological effects of intranasally administered crushed extended-release morphine formulations with and without a sequestered naltrexone core in recreational opioid users. Pain research and management. 2013 Jul 1;18(4):e55-62.
15. Chari S, Sridhar K, Walenga R, Kleinstreuer C. Computational analysis of a 3D mucociliary clearance model predicting nasal drug uptake. Journal of Aerosol Science. 2021;155:105757.
16. Xi J, Wang Z, Nevorski D, White T, Zhou Y. Nasal and olfactory deposition with normal and bidirectional intranasal delivery techniques: in vitro tests and numerical simulations. Journal of aerosol medicine and pulmonary drug delivery. 2017;30(2):118-31.
17. Manniello MD, Hosseini S, Alfaifi A, Esmaeili AR, Kolanjiyil AV, Walenga R, Babiskin A, Sandell D, Mohammadi R, Schuman T, Hindle M. 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. 2021;593:120103.