U.S. FOOD & DRUG ADMINISTRATION

Modeling of CNS Delivery for Nose-to-Brain Targeted Drug Products

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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

Targeting Central Nervous System (CNS) Delivery with Nasal Drug Products (NDPs)

- Treat CNS disorders without the need to overcome the blood-brain-barrier
- Reduce dose needed and possibly increase rate of delivery
- Many treatments are in development
  - Alzheimer's Disease[1]
  - Parkinson's Disease[2]
  - Migraines[3]

Nasal Drug Products (NDPs) with Olfactory Targeting Claims

- Trudhesa® (dihydroergotamine mesylate nasal spray)
  - Approved September 2, 2021
  - Indicated for treatment of migraines
  - Olfactory targeting not specified on product label
- Precision Olfactory Delivery® system[4]
  - Large or small molecules, liquid or powder, to upper nasal cavity or upper turbinates
- Onzetra Xsail® (sumatriptan succinate nasal powder)
  - Approved January 27, 2016
  - Indicated for treatment of migraines
  - Olfactory targeting not specified on product label
- Optinose® system[5]
  - Aims to deliver deep into nasal cavity
  - Hypothesis that there may be local uptake via olfactory and trigeminal nerves

Nose-to-Brain Drug Delivery

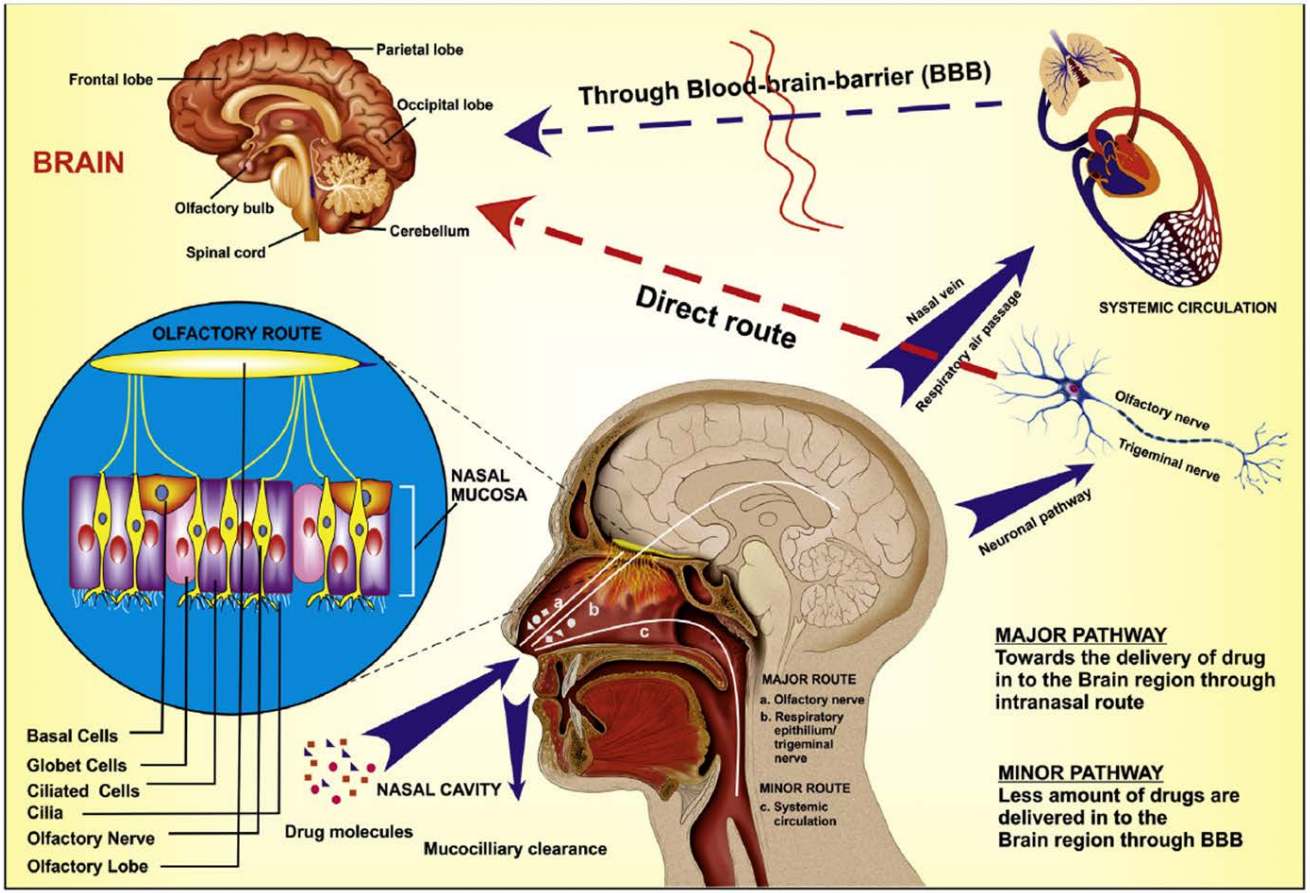


Figure 2 from Agrawal et al.[1]

Bioequivalence (BE) at the Site of Action for Locally-Acting NDPs

- For locally-acting NDPs, nasal tissue is the site of action
- Regional deposition is upstream of local tissue drug exposure and systemic pharmacokinetics (PK) is downstream

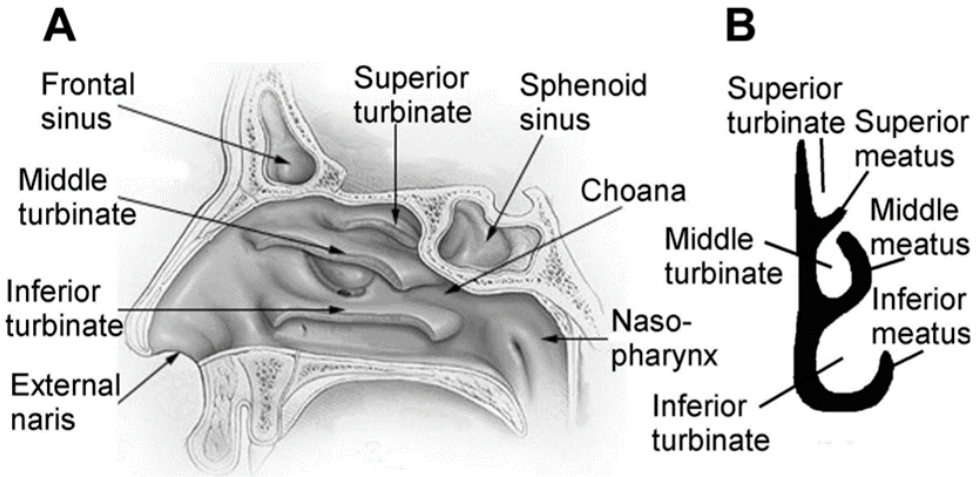


Figure 1 from Liu et al.[7]

Weight of Evidence Approach for Locally-Acting Nasal Sprays

BE recommendations include in vitro studies, in vivo studies, and formulation and device sameness[8]

In vitro studies	In vivo studies
❖ Single Actuation Content ❖ Droplet Size Distribution (DSD) by Laser Diffraction ❖ Drug in Small Particles/DSD by Cascade Impaction ❖ Spray Pattern ❖ Plume Geometry ❖ Priming and Repriming	❖ Comparative PK with fasting, two-way crossover design in healthy subjects (suspensions only) ❖ Comparative Clinical Endpoint or Pharmacodynamic (suspensions only)

Product-Specific Guidances (PSGs) for Products with Nose-to-Brain Drug Delivery

- NDPs that target systemic uptake such as esketamine nasal spray may have PSG recommendations for in vitro or in vivo PK option.[9]
- Sumatriptan succinate nasal powder recommends combination of in vitro studies and in vivo PK study as well as formulation and device sameness.[10]
- What recommendations may be appropriate for NDPs with confirmed nose-to-brain drug delivery?

Quantification of Drug Delivery to Brain

- Receptor binding in brain may be quantified using positron emission tomography (PET) scan data
  - Ethical concerns with conducting BE study
- Alternative BE approach?
  - Combination of in vitro and/or silico studies
  - Can modeling be used to design such an approach?

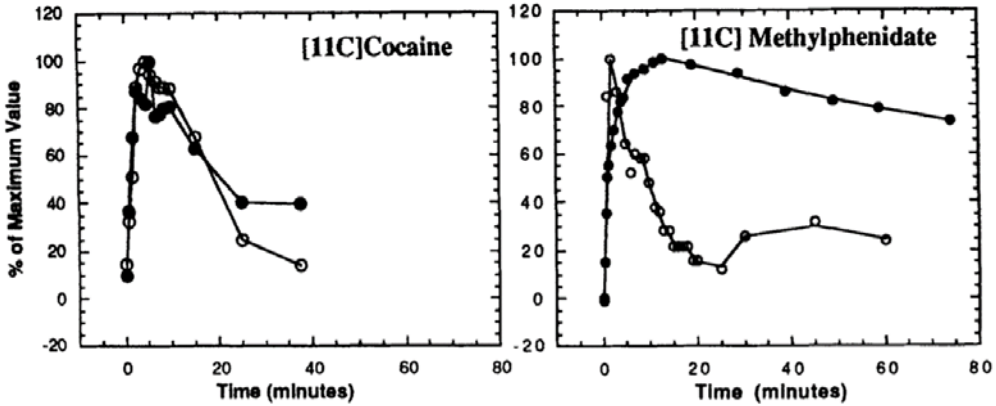
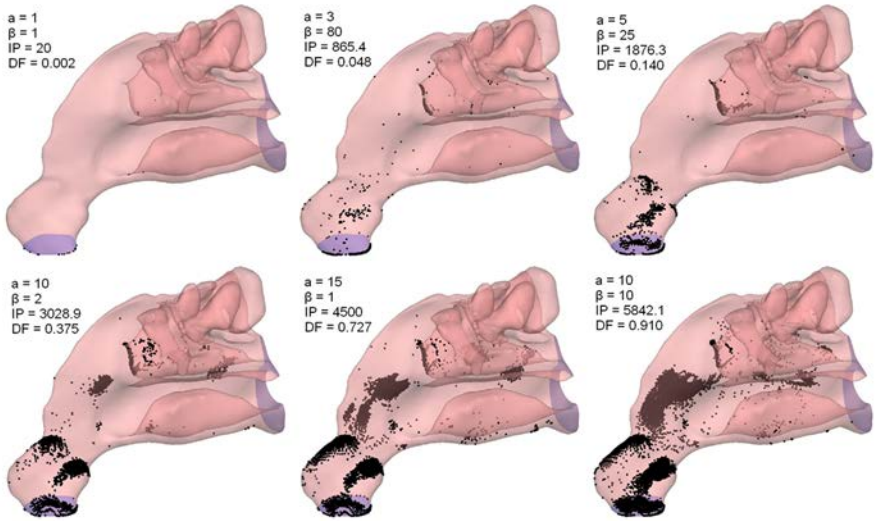


Figure 1 from Fowler et al.[11]: Percent of maximum receptor binding value from PET scan data

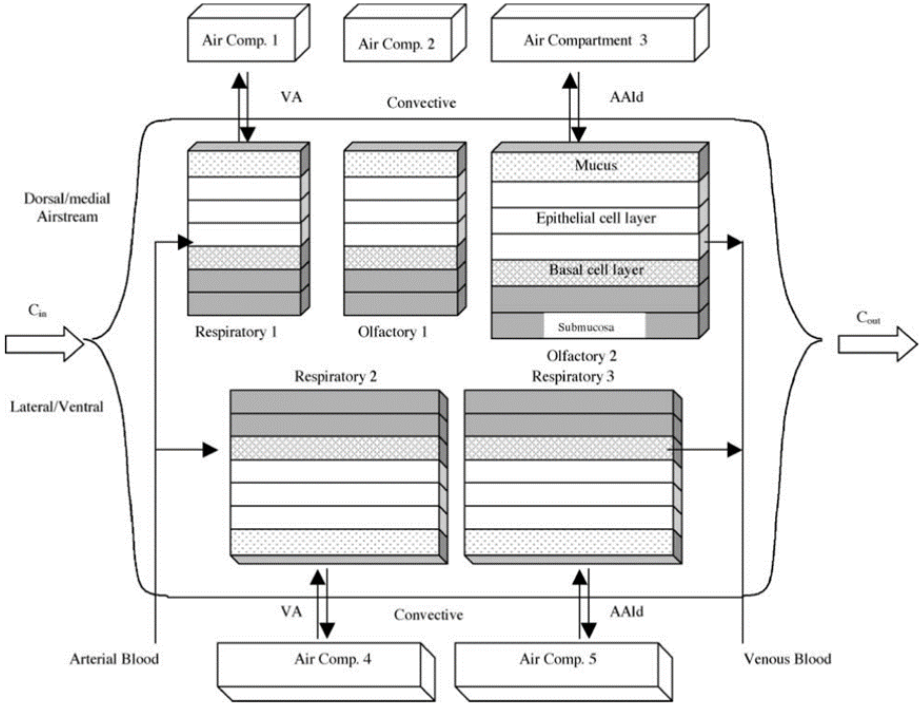
Computational Fluid Dynamics (CFD) Modeling of NDPs

- Predict influence of device and formulation parameters
  - Particle size distribution, spray angle, spray velocity
  - Regional deposition
    - Intersubject variability
  - 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.[12])

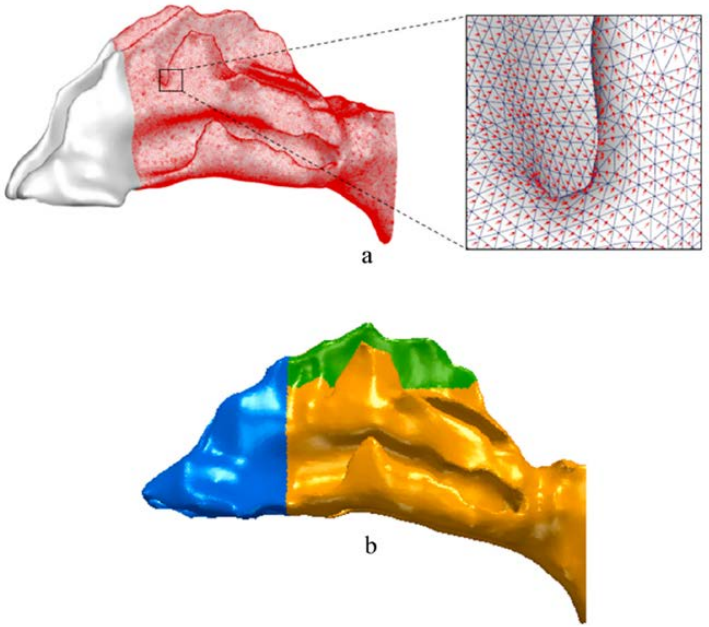
PBPK Modeling of NDPs



Nasal PBPK model structure as shown in Fig. 2 of Andersen et al.[13]

- 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

Fully 3D Nasal Mucociliary Clearance (MCC) Model

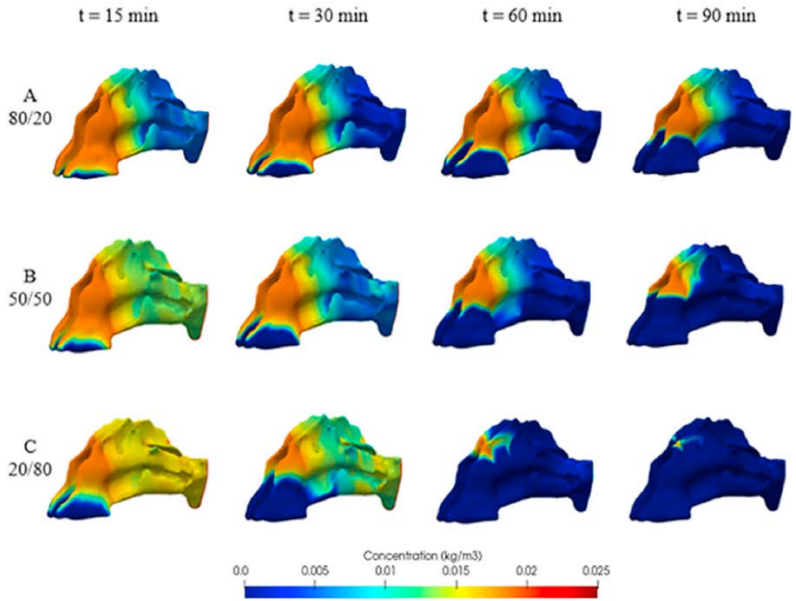


Nasal MCC model features, including a) 6 mm/min mucus velocity vectors in mucus layer and b) regional definitions including olfactory (red), nasal vestibule (blue), and nasal cavity (orange) regions. (Fig. 1 of Chari et al.[14])

- North Carolina State University
  - PI: Clement Kleinstreuer
  - Grant #1U01FD006537: 2018-2021
- 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 olfactory region deposition and absorption

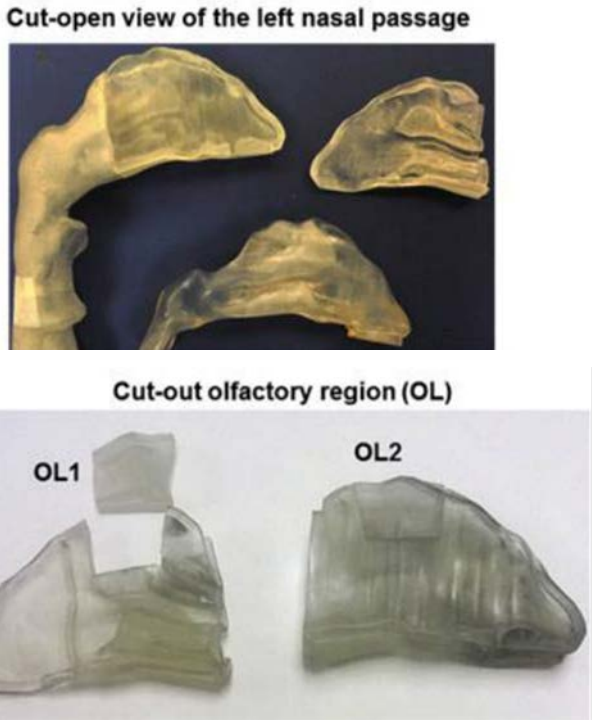
Fully 3D Nasal MCC Model – Results

- 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.[14])

Nasal In Vitro Models



Nasal in vitro model that allows for measurement of olfactory region deposition. (Adapted from Fig. 1c of Xi et al.[15])

- Drug product is actuated into nasal model
- Deposited drug is measured from removable sections using high performance liquid chromatography (HPLC)
- Deposition may show significant intersubject variability according to anatomical differences
- Olfactory deposition may be measured with separate section

Currently Available PBPK Models

- Commercially available nasal PBPK model includes compartments for nasal cavity and nasopharynx, but not for the olfactory region.[16]
- There are no known open-source nasal PBPK models that include olfactory region-specific absorption.
- Development of a nasal PBPK model with olfactory-region specific absorption will ideally include several pathways.
- PBPK model development is needed to facilitate use as part of alternative BE approach for nose-to-brain NDPs.

Conclusions

1. Nose-to-brain drug delivery is an emerging area for product development.

2. Absorption for nose-to-brain drug delivery may occur via several distinct pathways.

3. Determining BE for potential generic nose-to-brain NDPs may be complicated if it is demonstrated that the effectiveness of the reference product relies on nose-to-brain drug delivery.

Conclusions (cont'd)

4. Modeling may be used with relevant in vitro studies to develop an alternative BE approach if nose-to-brain drug delivery must be considered for BE.

5. Current PBPK models lack nose-to-brain pathways and further development is needed to facilitate their use for this application.

Call to Action

Notice of Funding Opportunity (NOFO) has been posted for nose-to-brain PBPK grant. The request for applications (RFA) will be posted later in fiscal year 2022.

https://www.grants.gov/web/grants/view-opportunity.html?oppId=336327

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