Bioequivalence Testing: Can Systemic Pharmacokinetic Profiles from Corticosteroid Nasal Sprays be used to Elucidate Local Drug Deposition within the Nose?

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Introduction

- Demonstration of bioequivalence is required for a generic drug product to enter the market

- Bioequivalence: The absence of a significant difference in the rate and extent to which the active ingredient … in a pharmaceutical equivalent … becomes available at the site of drug action when administered at the same molar dose … [1]
  - Same rate and extent
  - Specific site
  - When delivered at the same dose

Same local dose concentration profile

[1] Li, Jin, and Lee (2013) The AAPS Journal 15:875-883

Introduction

- Corticosteroid nasal spray products represent a large market ($10 billion / year)
- Bioequivalence for a nasal spray suspension product in the US is currently based on a weight of evidence approach (adapted from [1])

Equivalent In Vitro Performance

- Single actuation dose content
- Droplet size distribution
- Drug in small particles/droplets
- Spray pattern
- Plume geometry
- Priming and re-priming

Equivalent Systemic Exposure

- Pharmacokinetic (PK) study

Equivalent Local Delivery

- Clinical endpoint study

Formulation Sameness

- Formulation: Q1/Q2 equivalence

Device Similarity

- Valve, pump, and actuator designs as close as possible in all critical dimensions

Introduction

- Equivalent local delivery
  - Most difficult to establish
  - Currently based on a “clinical endpoint study”
  - Clinical endpoints related to inflammation are challenging to define
- Suggested that this could be assessed based on drug plasma profiles
  - Determined from a pharmacokinetic (PK) study
  - PK studies are conducted for systemic exposure
- However, a direct link between nasal drug deposition and drug plasma profiles has not been established

Objective

- Objective: Implement a new nasal transport model to investigate the relationship between nasal spray deposition and drug plasma profiles

- Critical questions:
  - Are drug plasma profiles sensitive to deposition patterns of spray droplets in the nasal airways?
  - Is the use of drug plasma profiles a practical way to determine equivalent local delivery?
  - Should we consider a different technique to determine equivalent local delivery?

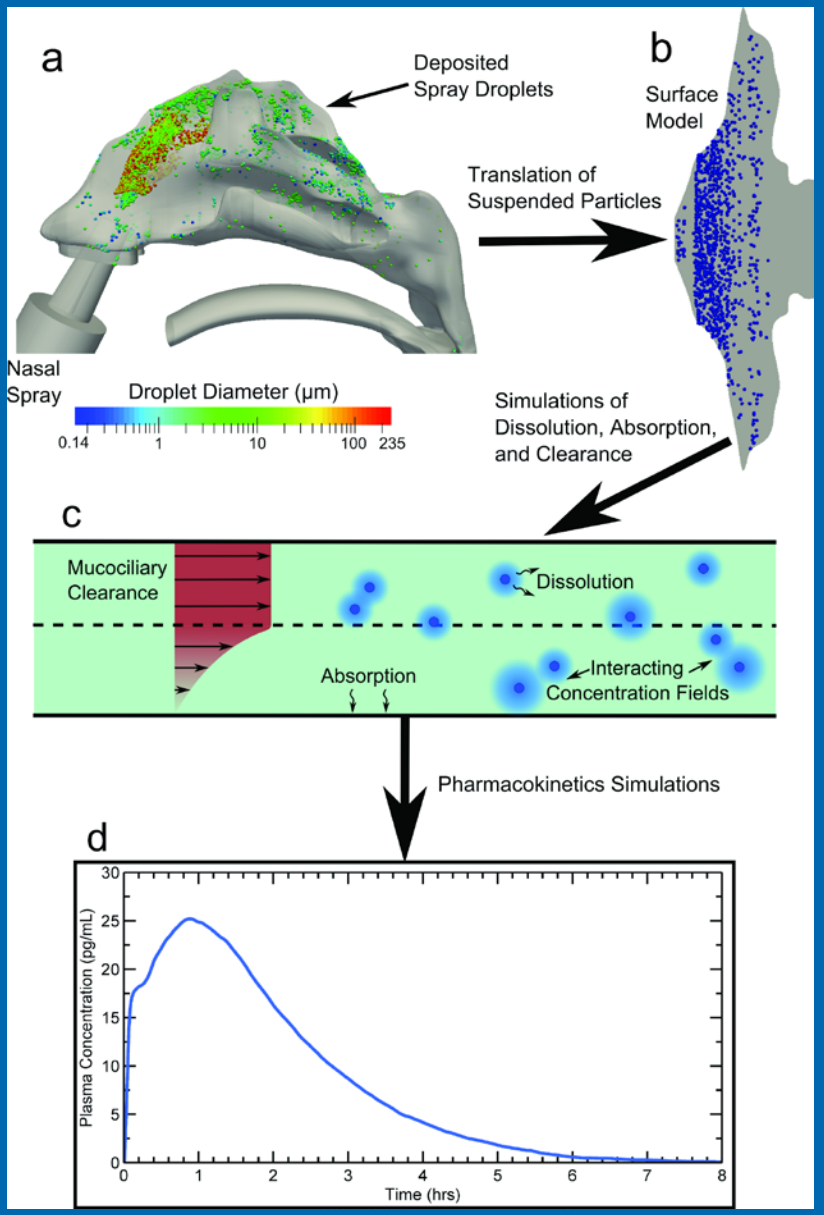
Methods

CFD-PK Nasal Transport Model

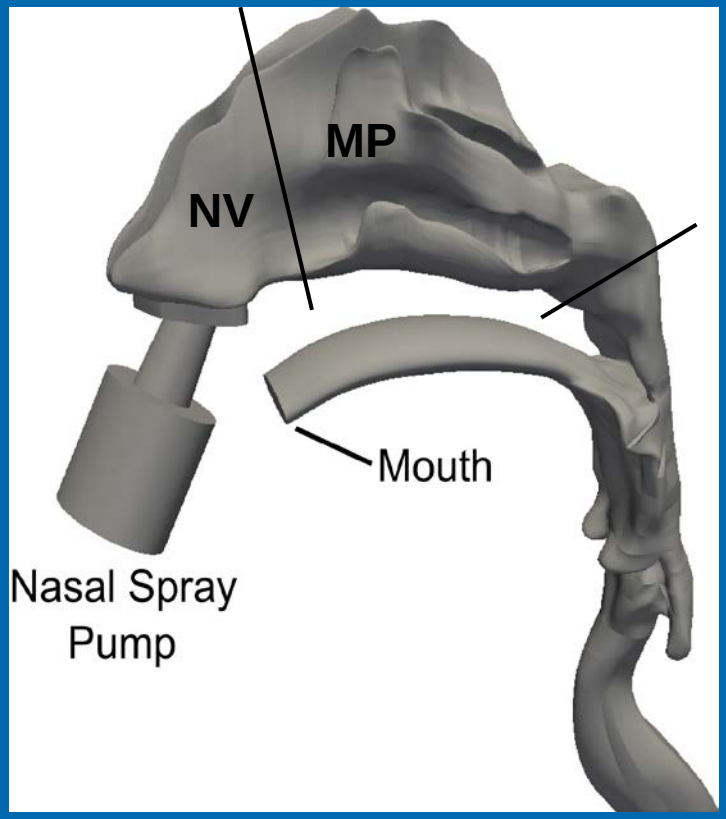
(a) CFD model used to predict local nasal spray deposition

(b and c) CFD simulations are used to predict dissolution, absorption and clearance

(d) Following absorption, a PK model is used to predict drug plasma profiles



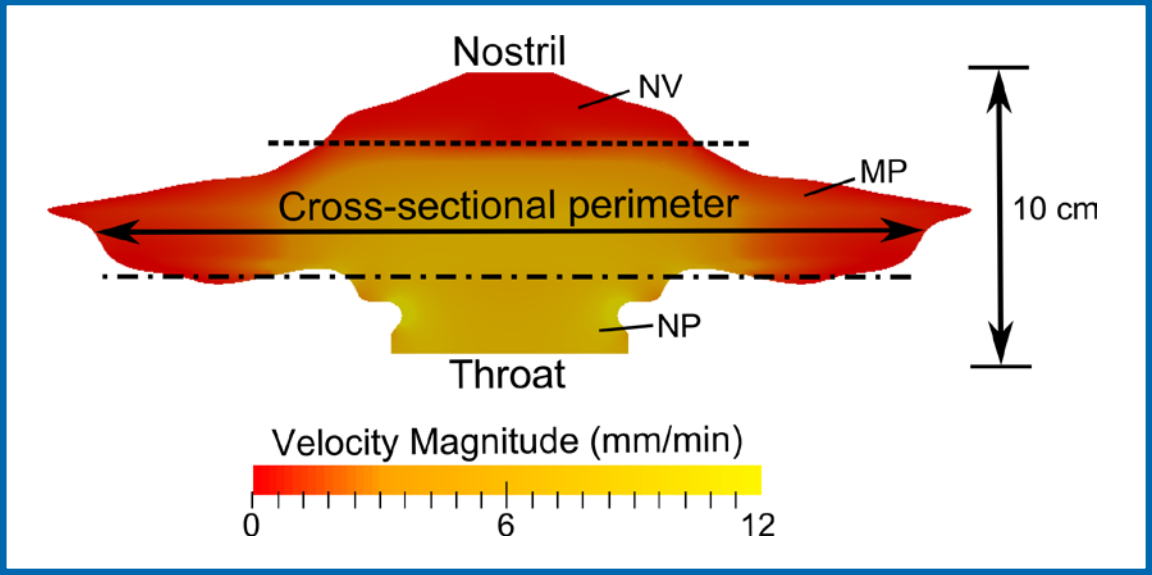
Components - Deposition



Nasonex nasal spray product: Mometasone furoate (MF)

- *In vitro* assessment of nasal spray droplet size distribution
- CFD simulation of droplet transport from spray nozzle to site of initial deposition
- Nose is divided into the nasal vestibule (NV) and middle passage (MP) regions

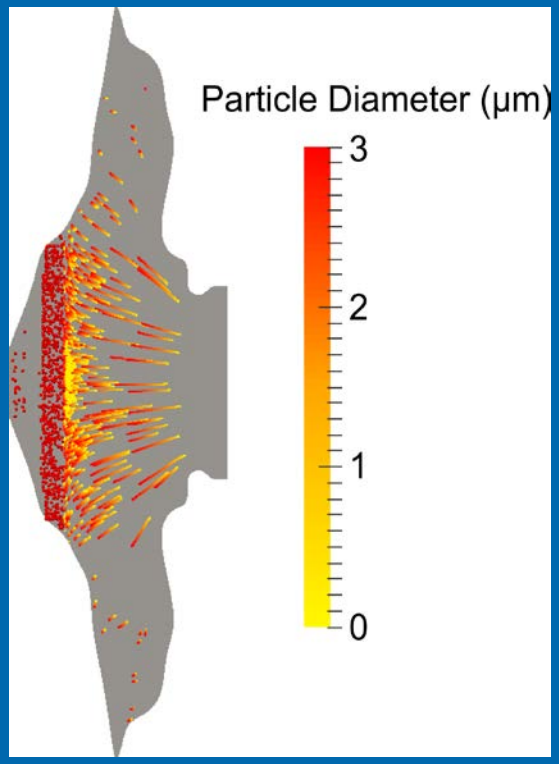
Components – Mucus Motion



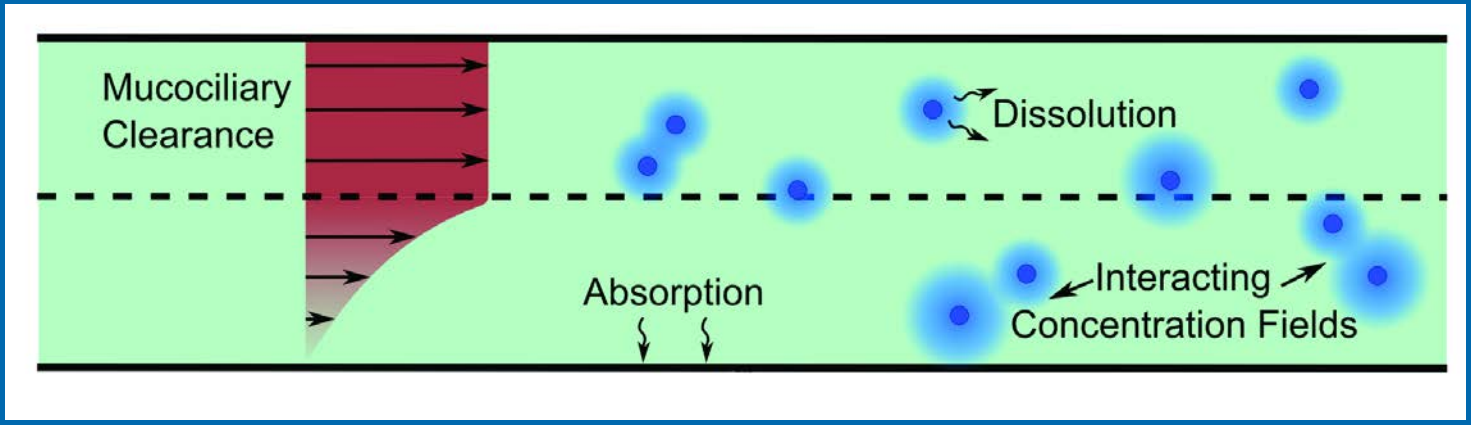
- Surface model was used to represent 7 µm thick layer of airway surface liquid (ASL)

- ASL injected at constant rate in the MP to generate an average clearance velocity of 5 mm/min
- No mucus injected in the NV
- Variable mucus velocity field

Components – Absorption

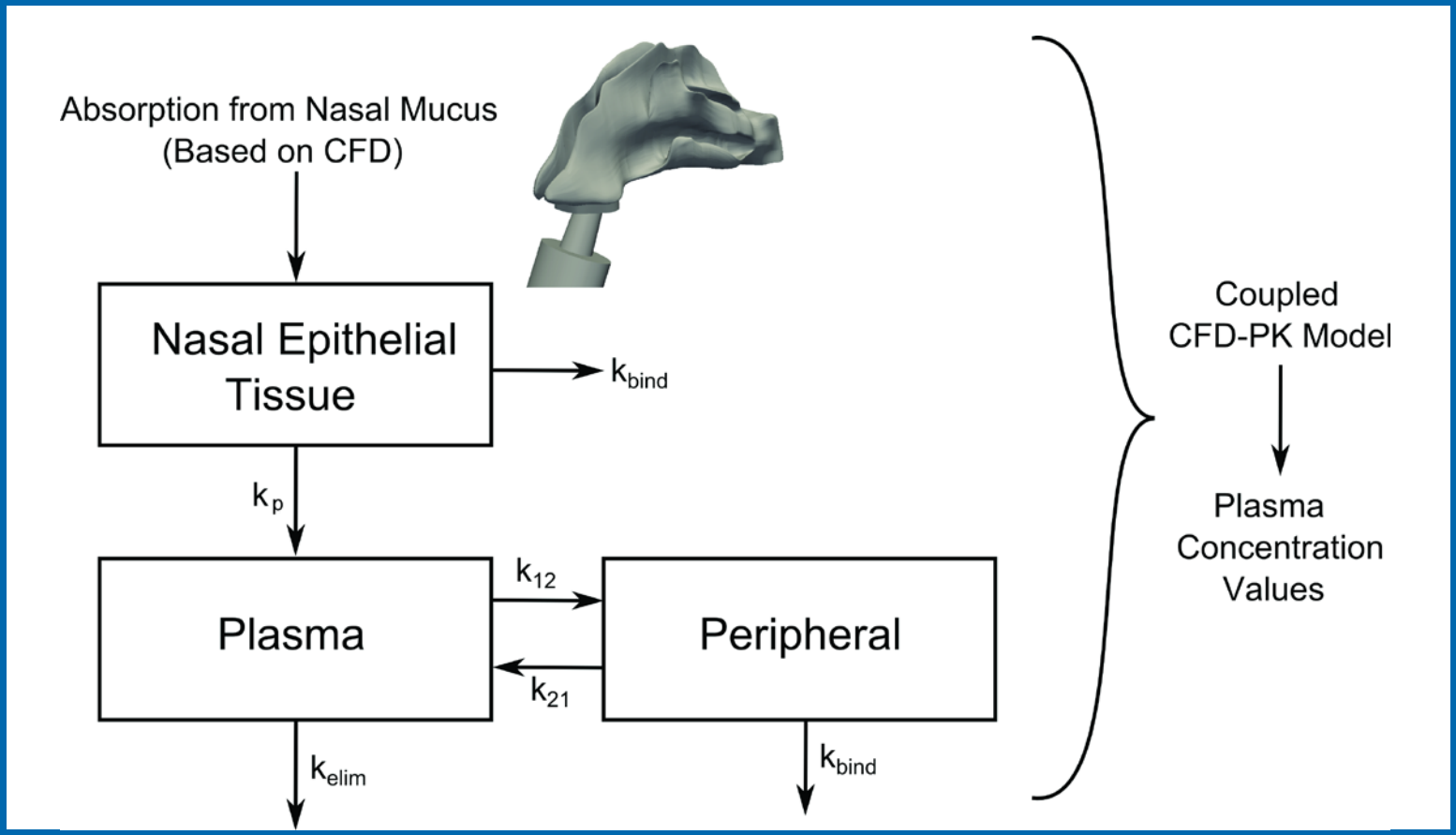


- Suspended drug particles released at droplet deposition locations
- Dissolution, diffusion, convection, and absorption simulated with CFD
- No absorption in NV and no resistance to absorption in MP

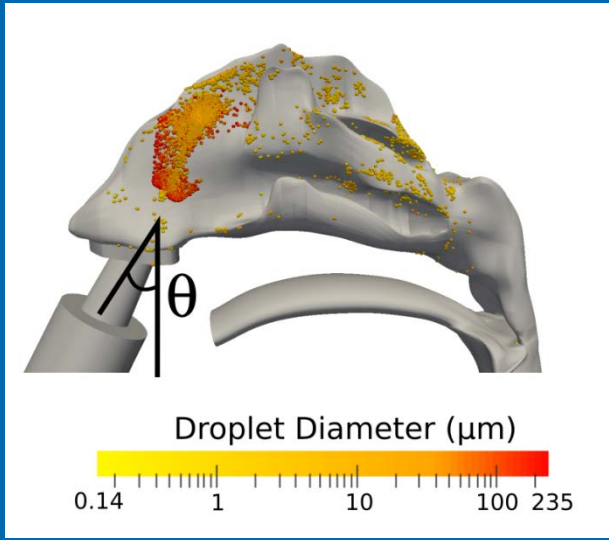


Components – PK Model

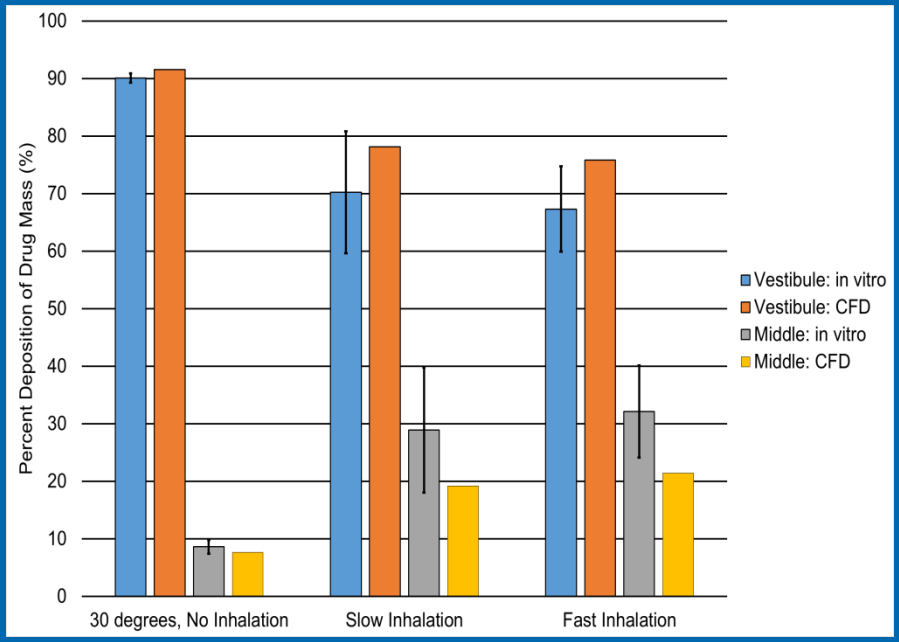
- Starting point is absorption into nasal epithelial tissue
- Rate constants determined from *in vivo* data



Validation – Spray Deposition



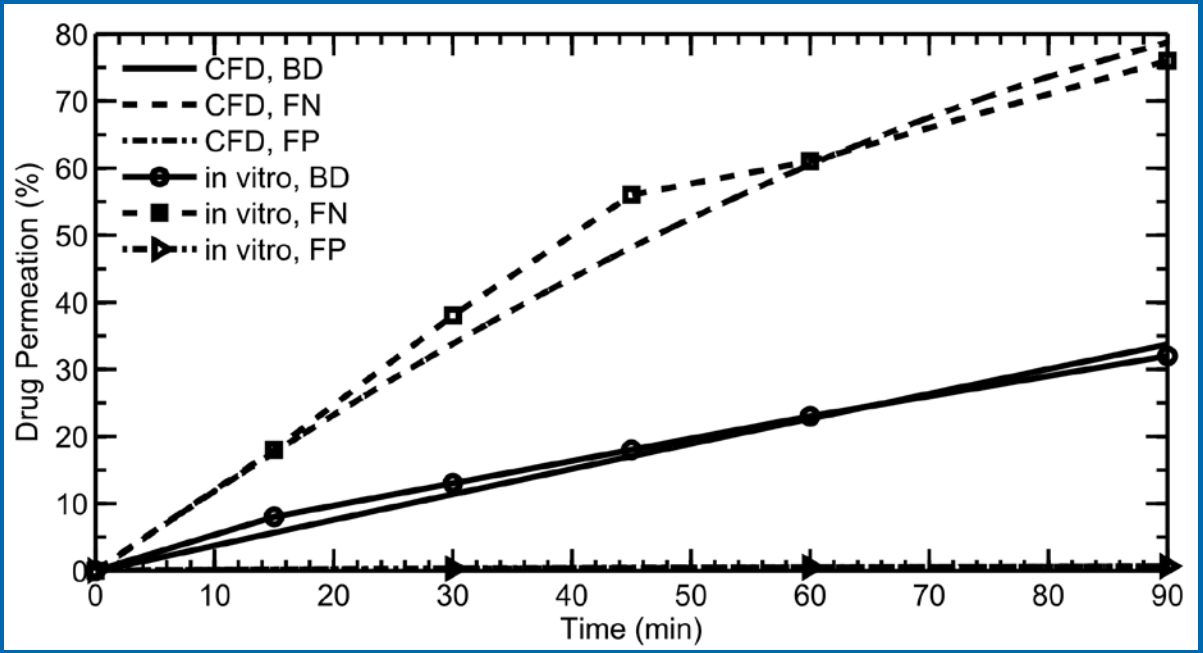
- Considered NV and MP deposition
  - *In vitro* vs. CFD
- Spray angles: 30, 40 & 50º
  - Good agreement
- Also considered 30º with:
  - No inhalation
  - Slow nasal inhalation
  - Fast nasal inhalation



[2] Azimi, Longest and Hindle (2015) RDD Europe 1:121-130

Validation – Particle Dissolution

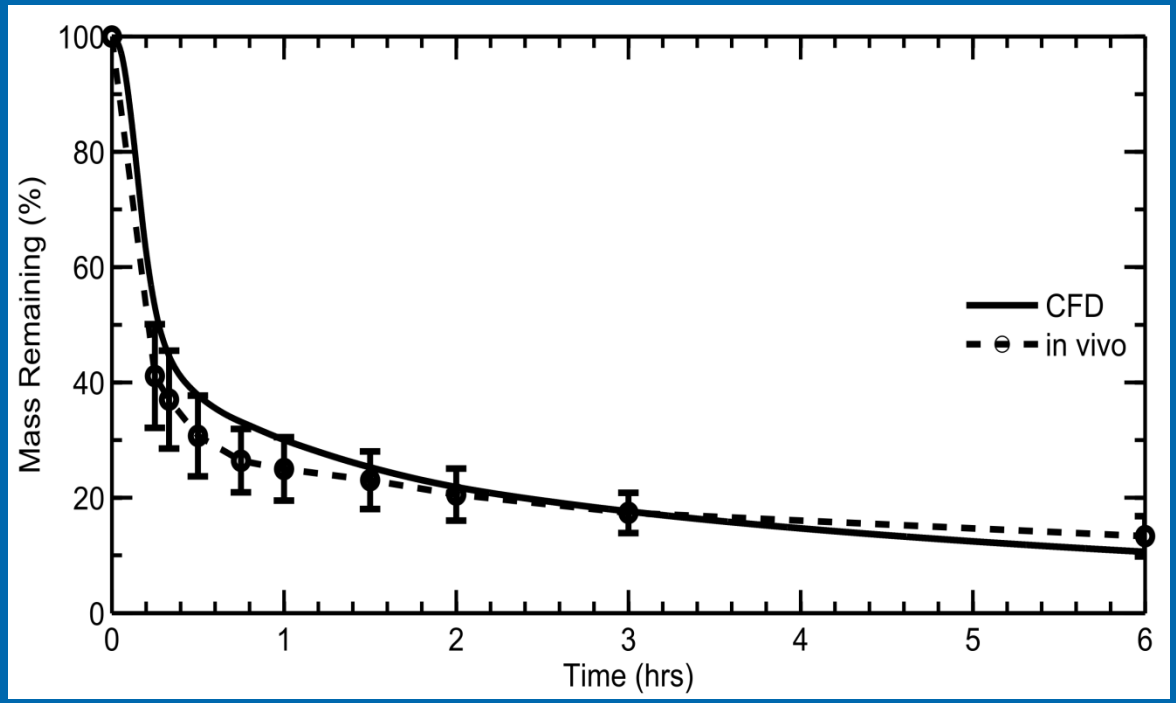
- *In vitro* system [3]:
  - Transwell with 0.04 mL aqueous fluid
  - Separated from basolateral receptor compartment by a semi-permeable membrane
  - CFD and *in vitro* results for 3 different corticosteroids each delivered as drug particles

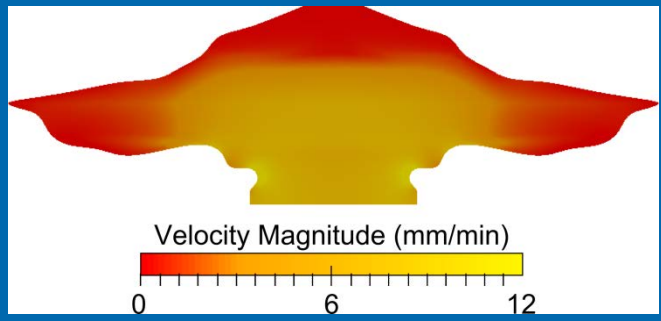


[3] Arora et al. (2010) Pharm Res 27:786-795

Validation – *In Vivo* Clearance

- *In vivo* study of Shah et al. [4]:
  - Radiolabelled solution delivered as a nasal spray that was not absorbed by epithelium
  - Gamma scintigraphy used to determine nasal clearance
  - *In vivo* conditions reproduced with CFD model

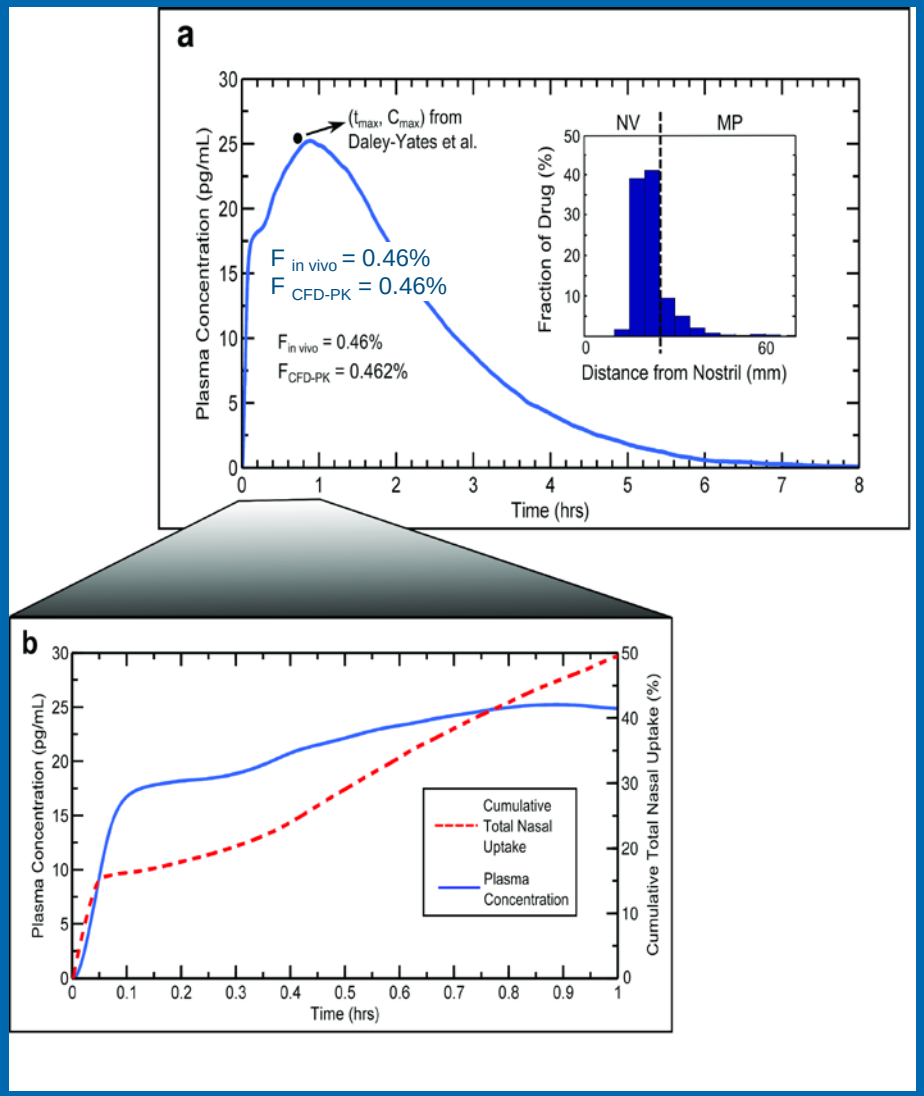




[4] Shah et al. (2015) Allergy and Asthma Proceedings 36:48-57

PK Model Constants

- *In vivo* study (Daley-Yates et al). [5]
  - 800 µg dose of MF
- Reasonable values of PK constants lead to accurate predictions of *in vivo* C_{max}, t_{max}, and bioavailability (F)
  - C_{max} relative diff: 1.2%
  - T_{max} relative diff: 17%
  - F relative diff: 0%



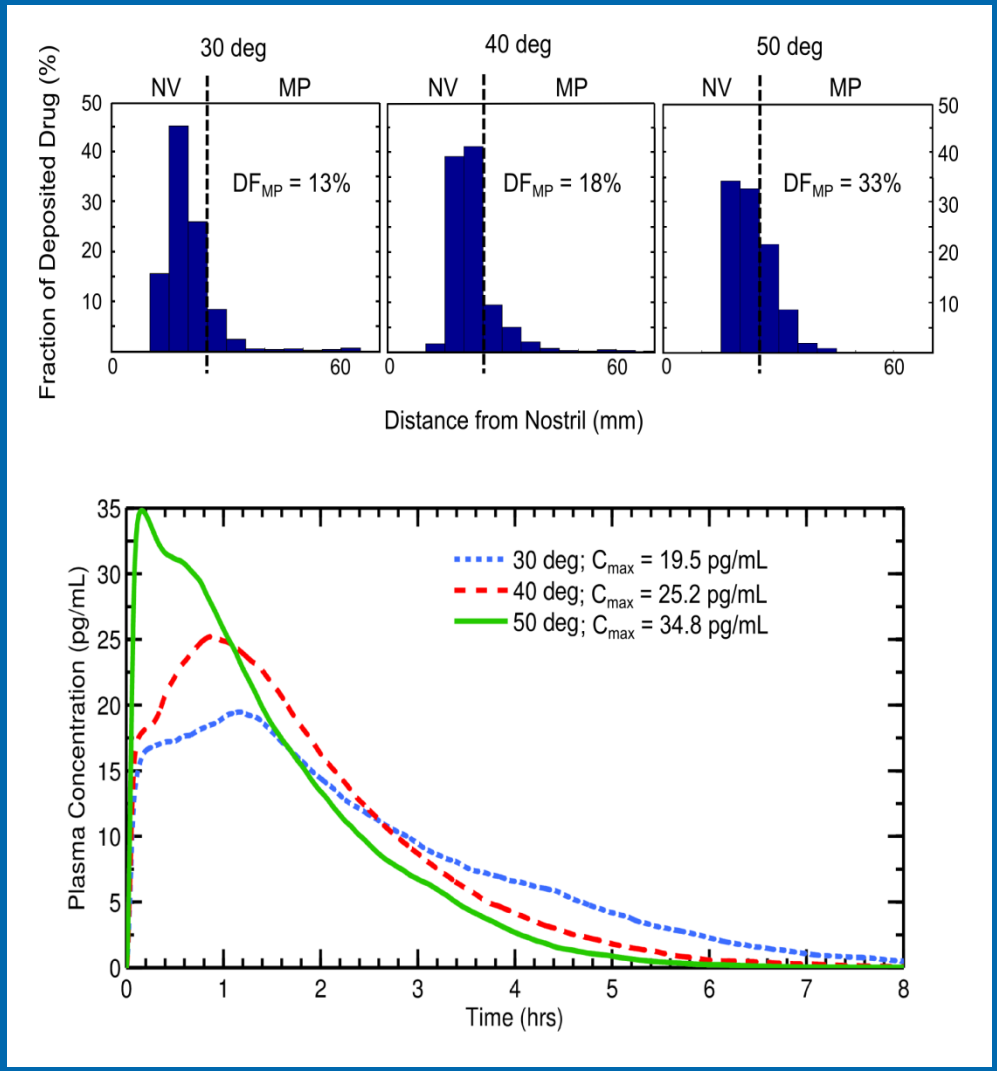
[5] Daley-Yates et al. (2004) Eur J of Clin Pharm 60:265-268

Applications and Results

Drug plasma profiles are sensitive to local nasal deposition patterns

Effect of Spray Angle

- Nasal spray insertion angles of 30, 40, & 50º
- MP deposition fraction (DF) = 13 ⟶ 33%
  - Relative diff: 87%
- C_{max} = 19 ⟶ 35 pg/mL
  - Relative diff: 56%

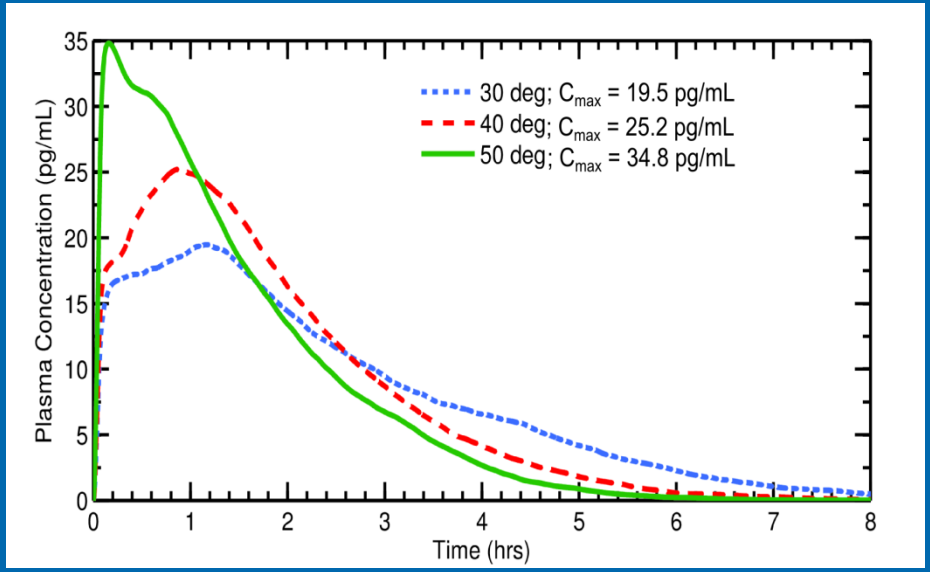


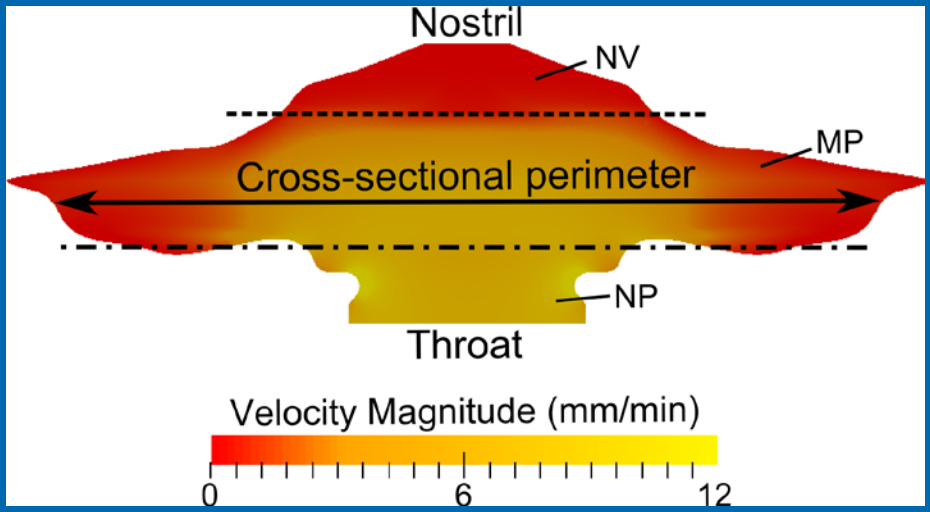
C_{max} is sensitive to changes in deposition

C_{max} is a better indicator of local nasal deposition compared with bioavailability estimates

Bioavailability Estimates

- Nasal spray insertion angles of 30, 40, & 50^{o}
- For all three cases:
  - F = 0.46%
  - Relative diff: ~0%
- Arises from fluid connection between NV and MP
- Requires NV dose to remain undisturbed

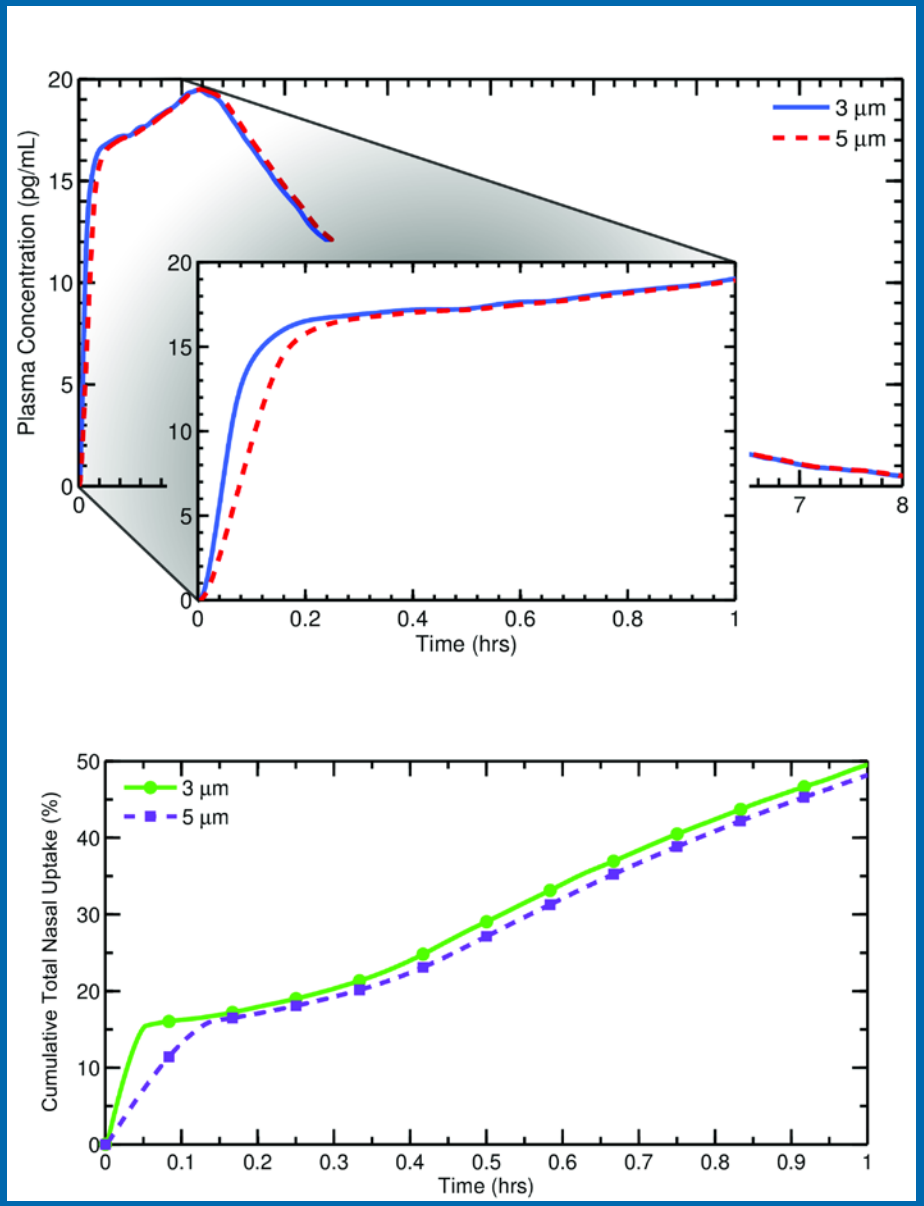




Suspended drug particle size may not have a large impact on local delivery

Effect of Particle Size

- Same nasal spray with 3 or 5 µm suspended drug particles
  - Minimal changes in drug plasma profile
  - Only a small change in total epithelial absorption that disappears after 6 minutes

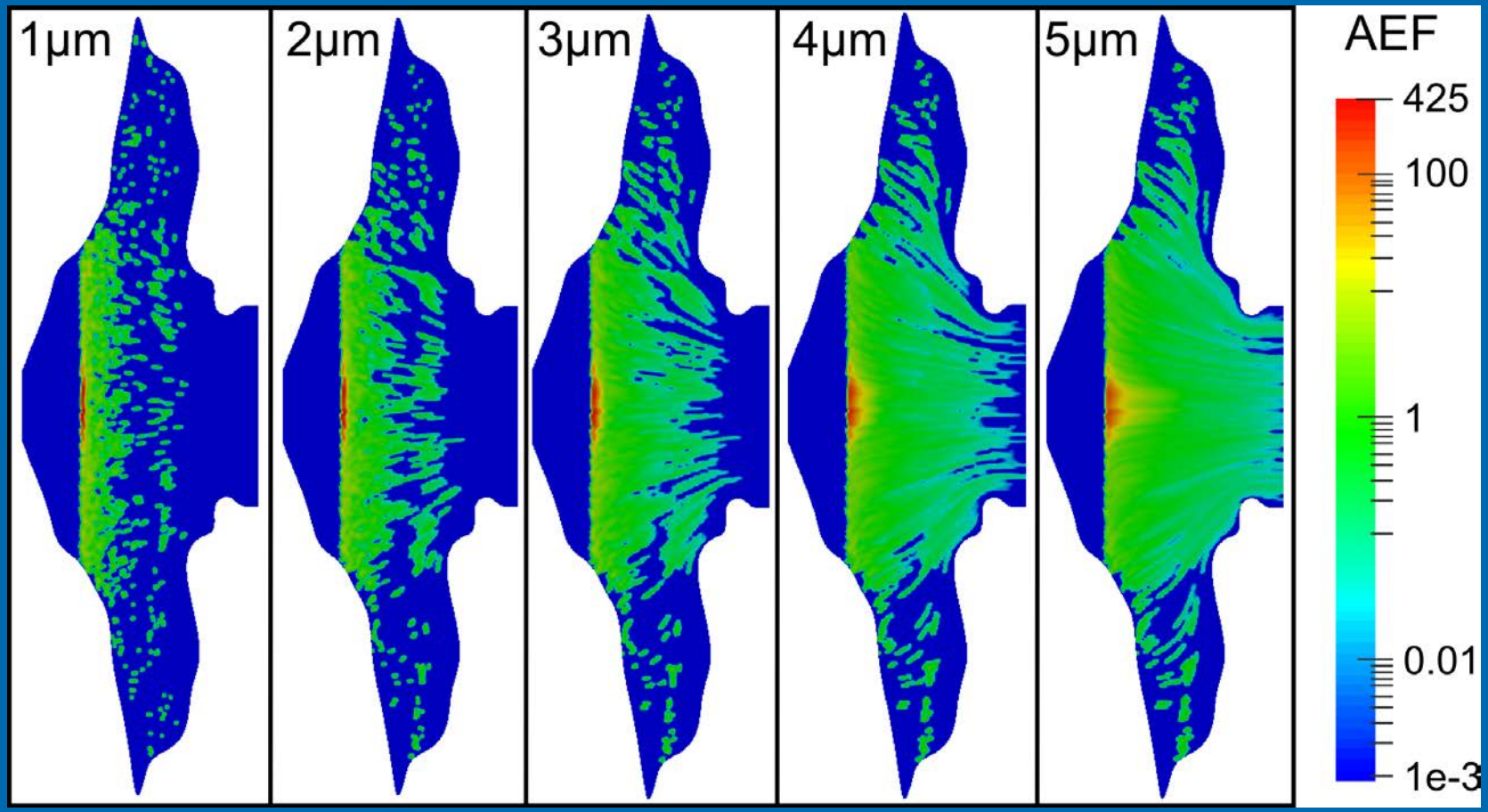


Suspended particle size may not have a large impact on local delivery

or does it?

Microscale Nasal Absorption

- Suspended drug particles sizes of 1 to 5 μm
  - Absorption enhancement factor (AEF)
  - Microscale dose/area relative to total dose/total area



So nasal drug deposition patterns strongly affect PK profiles…

Can we use PK profiles to establish equivalent local delivery?

PK and Bioequivalence

- Yes, it is possible, but it may not be practical
- We have observed large differences in nasal deposition and drug plasma profiles for:
  - Disturbing the NV dose over an 8 hour period
  - Effect of insertion angle (same geometry)
  - Effect of nasal inhalation (see Azimi et al. poster)
  - Effect of nasal geometry (see Azimi et al. poster)
- A patient-specific crossover study is a minimum requirement to reduce these effects, which are difficult to control in clinical studies

A direction forward…

A Direction Forward

- The challenge remains “equivalent local delivery”
  - Same local dose concentration profile
- An *in vivo* / *in vitro* / *in silico* approach offers a solution
  - Conduct a small (~3-5 subjects) *in vivo* study:
    (i) Radiolabeled local nasal deposition study to determine clearance
    (ii) Systemic PK
  - Use a standardized protocol and record:
    (i) Spray nozzle and head angles
    (ii) Spray nozzle position in nostril
    (iii) Inhalation profile and post delivery behavior
    (iv) Nasal geometry with MRI or CT

A Direction Forward

- *In vitro* & *in silico* models validated using i*n vivo* data
- *In vitro* model establishes same local deposition in individual nasal models under controlled conditions
- *In silico* model establishes the same epithelial tissue dose during dissolution, absorption, and clearance
  - Nasal-DAC model

→ Provides a controllable scientific way to establish same local delivery

→ Similar bioequivalence issues and solutions arise with inhalation aerosol products

Conclusions

- PK profiles are sensitive to regional nasal deposition
  - C_{max} was a reasonable quantitative marker
- Drug particle size (1-5 μm) did not affect MP absorption
  - Microdosimetry profiles are strongly affected
- Difficult to achieve equivalent local dose *in vivo*
  - Local dose is sensitive to a number of uncontrolled factors
- An *in vivo* / *in vitro* / *in silico* method provides a solution
  - Can be applied to evaluate local and systemic doses

Acknowledgements

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