GDUFA Research Update on Mechanistic Modeling Approaches for Generic Ophthalmic, Nasal, Implant and Injectable Drug Products

2021 CRCG PBPK Workshop: Regulatory Utility of Mechanistic Modeling to Support Alternative Bioequivalence Approaches

Day 1, Session 3: Mechanistic Modeling of Other Locally-Acting Areas

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CDER | U.S. FDA

September 30, 2021

Generic Drug Research

- Internal Research
  - Perform FDA internal research to meet the regulatory scientific needs
- External Research
  - Funding Opportunity Announcement (FOA): Grants
  - Broad Agency Announcement (BAA): Contracts

https://www.fda.gov/drugs/generic-drugs/generic-drug-research-collaboration-opportunities

Outline

- Physiologically-based pharmacokinetic (PBPK) modeling for ophthalmic drug products
- PBPK modeling approach for nasal drug products
- Model Integrated Evidence (MIE) approach for complex injectables
- Modeling approach for buccal/sublingual products
- PBPK models for complex products delivered in female reproductive tract
- Summary

Topical Ophthalmic Drug Products

- Very successful in approving generic ophthalmic solution products
- Few approvals for complex ophthalmic generics since 1984
  - Suspensions
  - Ointments
  - Emulsions

Dosage Form (2018 sales)	Number of Reference (RLD) products in USA[1]	% of RLDs that have an approved generic[2]
Solutions ($17.9B)	~111	55%
Suspension ($1.9B)	~22	23%[3]
Emulsion ($4.4B)	4	25%
Ointment ($730M)	~15[4]	30%[3]

1. Includes RLD products that are no longer marketed but that can still serve as a reference drug
2. Although approved, a generic may not be currently marketed
3. Most (>75%) were approved pre-Hatch-Waxman (1984)
4. A number of ointment NDAs have been discontinued, but may be re-designated as RLD by industry request

Slide courtesy of Darby Kozak, modified

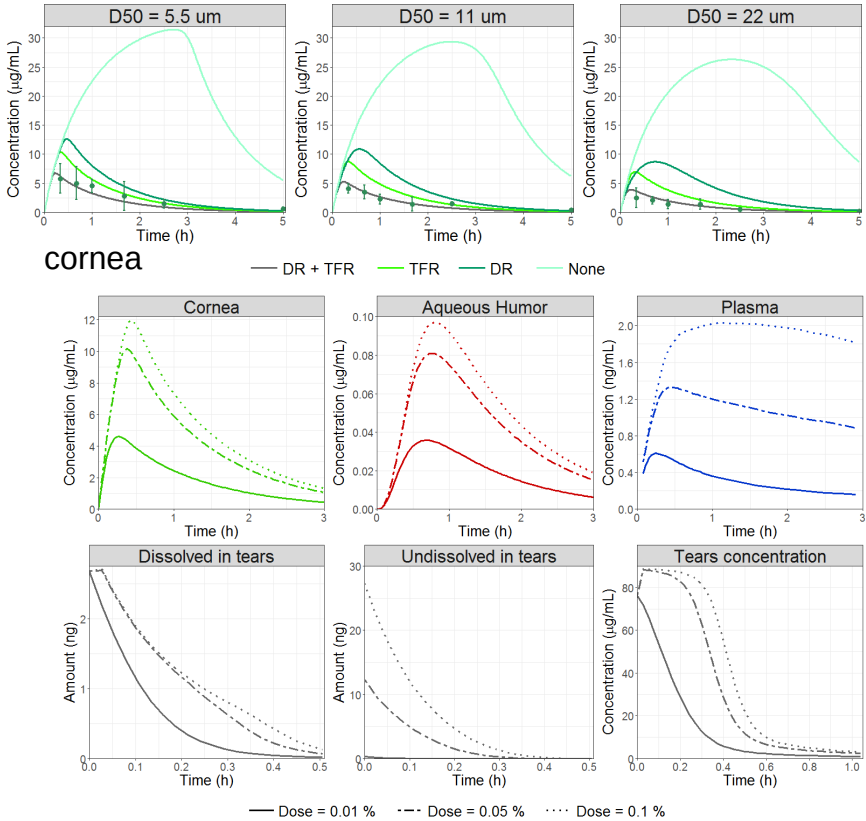
Luke M and Kozak D, *Journal of Ocular Pharmacology and Therapeutics* **37**, 157 (2021)

Ophthalmic Suspensions

***Purpose**: Use verified rabbit OCAT™ PBPK model to study formulation effect on exposure*

- Tears dynamic impact on elimination following the administration of three suspensions of Dex 0.1% with differing particle size

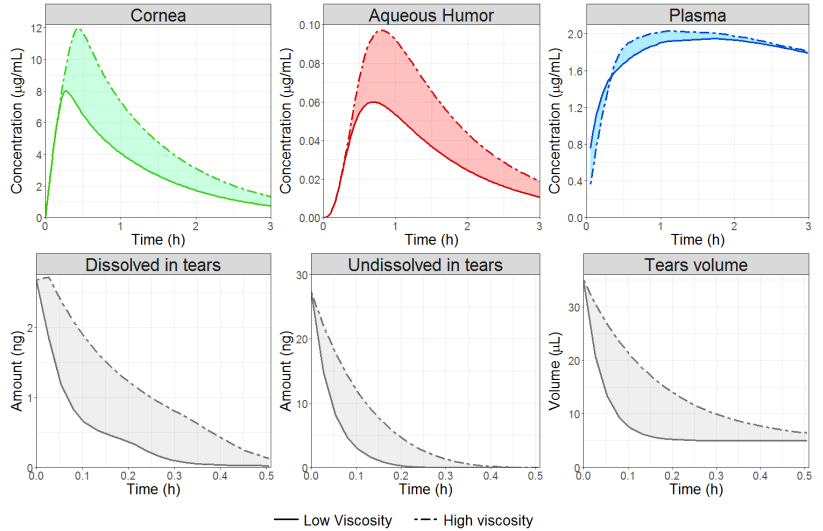
- Non-linearity of PK: simulated at three different strengths: 0.01%, 0.05% and 0.1%
  - Ocular absorption and distribution
  - Plasma exposure
  - Drug dissolved and undissolved amounts in the tear



LeMerdy, M., Tan, M. L., Babiskin, A., and Zhao, L. AAPS Journal **22**, 26 (2020)

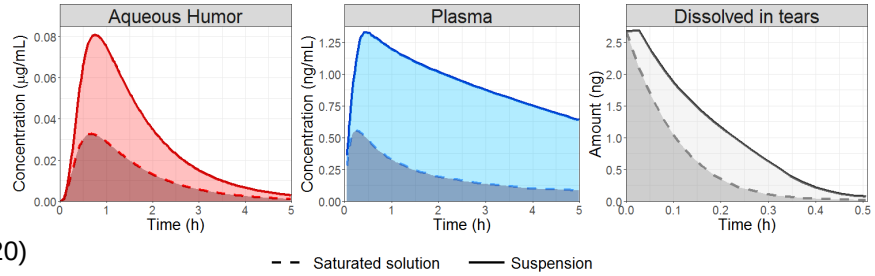
Ophthalmic Suspensions

- Role of viscosity: simulated two suspension formulations of Dex 0.1% with different viscosities
  - Concentrations in the cornea, aqueous humor, and plasma
  - Tear volume
  - Dissolved and undissolved drug amount in the tears



- Suspension and solution formulation effect on exposure

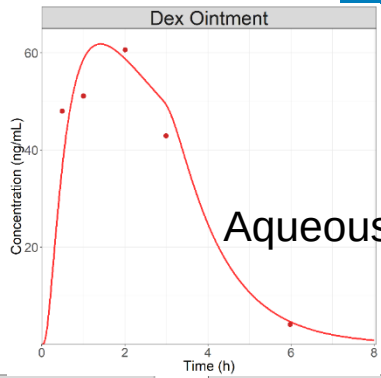
  How much does the drug in the solution contribute to the exposure relative to the total drug in solution and suspension formulations?



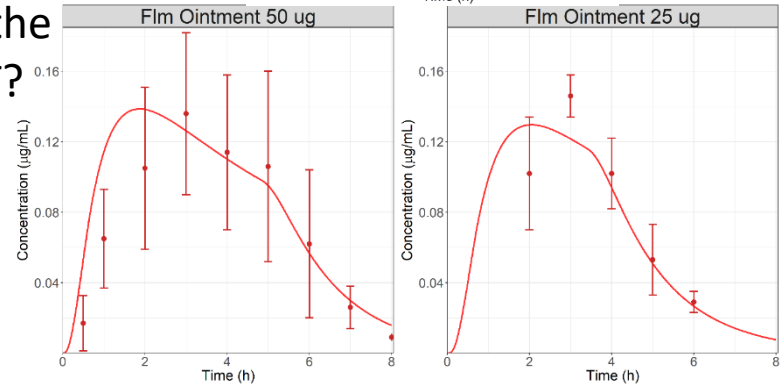
LeMerdy, M., Tan, M. L., Babiskin, A., and Zhao, L. AAPS Journal **22**, 26 (2020)

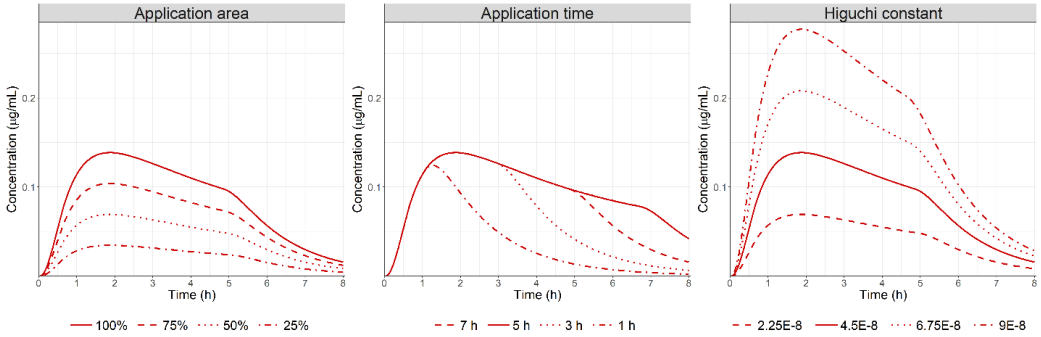
Ophthalmic Ointments

- Expanded OCAT™ model to include ocular ointment formulation
- Dexamethasone and fluorometholone ointment rabbit models
- Sensitivity of application surface area, application time, and the Higuchi release constant
- Higuchi release constant most significantly impact the ocular exposure and Cmax, biopredictive from IVRT?



Aqueous humor





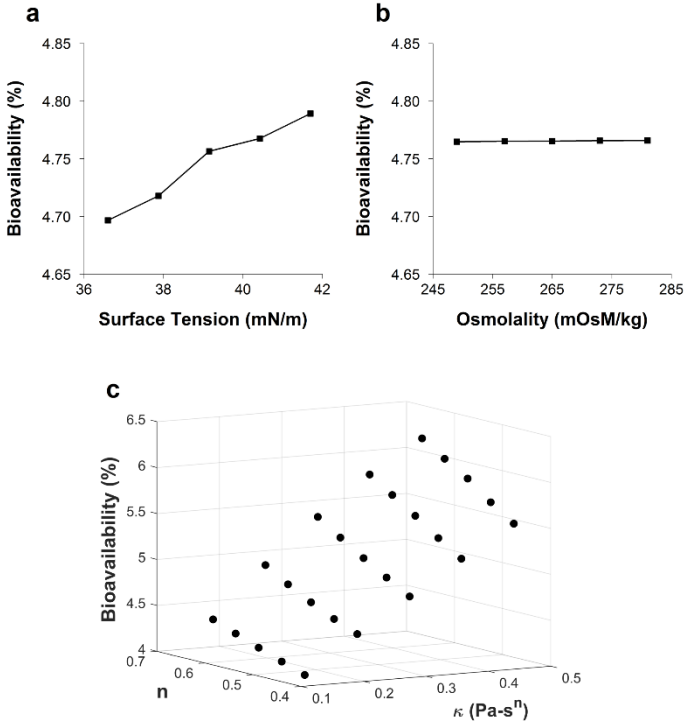
Simulations Plus, HHSF223201810255P

Le Merdy M, Spires J, Viera Lukacova V, Tan M L, Babiskin A, Xu X, Zhao L, Bolger M, *Pharm Res* **37**, 245 (2020)

Cyclosporine Emulsion Modeling

***Purpose**: impact of emulsion CQAs on product performance*

- Two internally-built models:
  - Physics/fluids-based approach to modeling tear film breakup time (TBUT)
  - Compartmental-based approach to predict bioavailability
- Studied impact of surface tension, osmolality, and power law viscosity on conjunctival bioavailability (figure at right) and TBUT
- Viscosity had the greatest influence on both outcomes

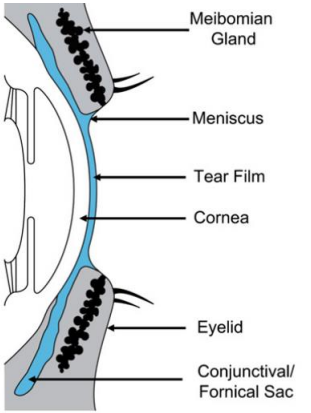


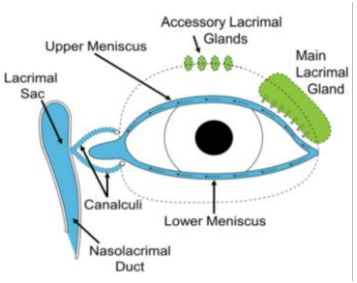
CQA: critical quality attribute

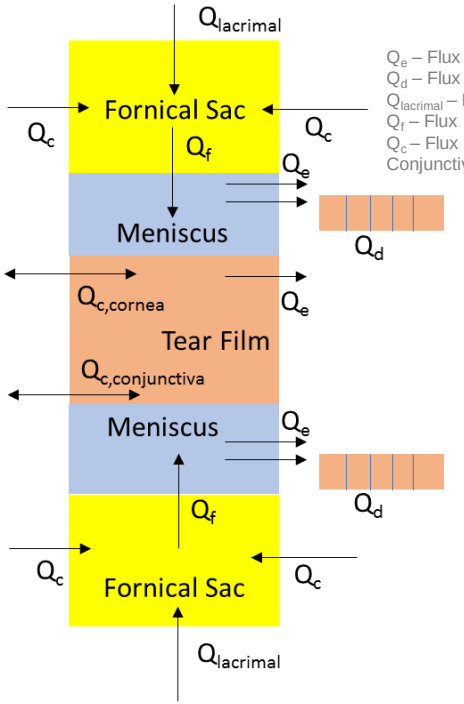
Walenga et al, *J Pharm Sci* 108, 620 (2019)

Ocular Tear Films Models

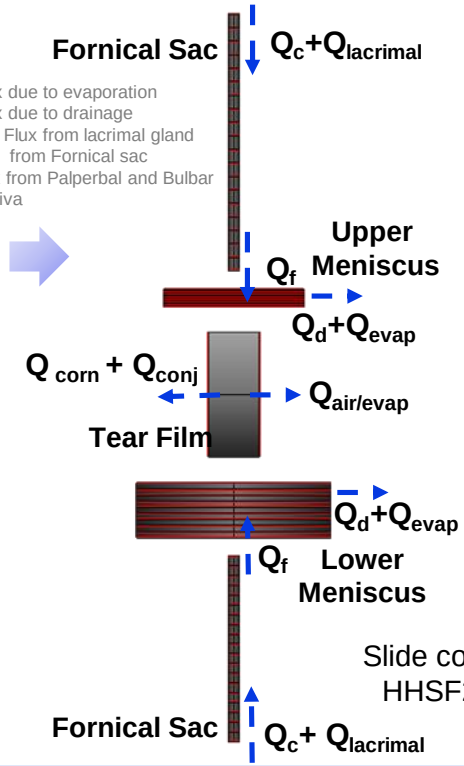
Tear Film Anatomy → ***CoBi-Compartment*** → ***CoBi-Q3D***







Q_e – Flux due to evaporation
Q_d – Flux due to drainage
$Q_{lacrimal}$ – Flux from lacrimal gland
Q_f – Flux from Fornical sac
Q_c – Flux from Palperbal and Bulbar Conjunctiva



Slide courtesy of CFD RC HHSF223201810151C

Tear film models (with accurate anatomical description and blink dynamics) are developed for simulating drug delivery and transport using CoBi-Compartment and CoBi-Q3D capabilities.

Ocular Cyclosporine Emulsion Model Validation

Rabbit Tear Film Measurements to verify the model

- **Internal collaboration with OTR**

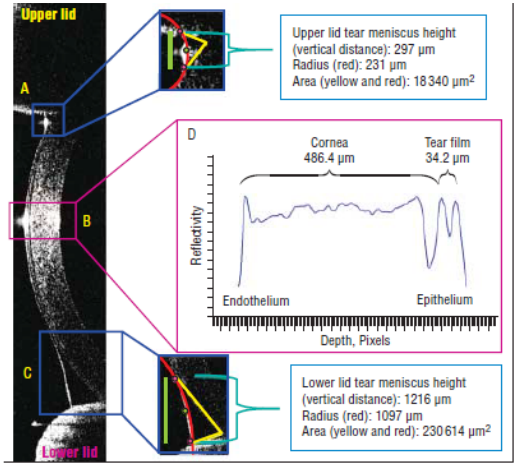
Five formulations with the desired globule sizes and viscosities were manufactured.

- **External collaboration with Absorption Systems (IDIQ 75F40119D10024)**

Optical coherence tomography to measure tear film and tear film menisci thickness in rabbits.

  - Instillation of cyclosporine ophthalmic emulsion
  - Already have human data from Wang et al. (2008)

Model validation of previously developed rabbit model



Tear Film Thickness and Tear Meniscus Measurement Wang et al, Arch Ophthalmol, 126, 619 (2008)

OTR: Office of Testing and Research, OPQ

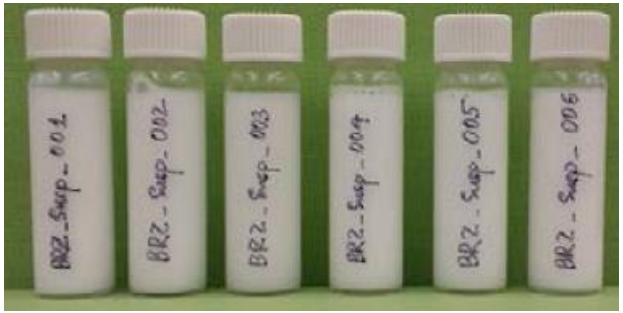
Ocular PBPK-PD Model Development

***Purpose**: to relate the ophthalmic suspension formulation changes to PD effect*

- **Internal collaboration with OTR:**

Six formulations prepared with the desired particle sizes and viscosities.

PSD, rheology, polymorphism, interfacial tension and interfacial rheology, pH, osmolality, assay, and drop weight were characterized



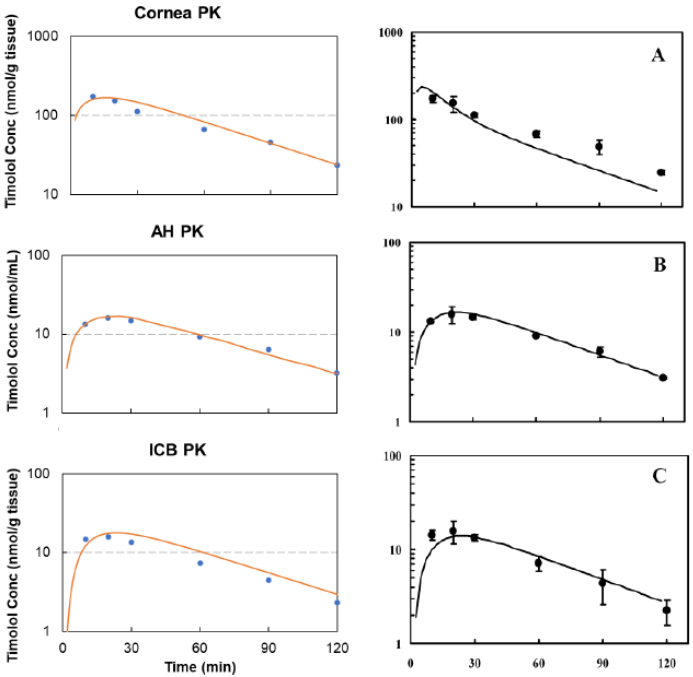
- **External collaboration with Absorption Systems (IDIQ 75F40119D10024)**

Products to be tested

Task Order	Pharmacological Class	API and concentration	Trade Name	Dosage form	NDA	Sponsor	Approval
2a	Placebo						
	Topical carbonic anhydrase inhibitors	Brinzolamide 1%	AZOPT®	Suspension	N020816	Novartis	April 1, 1998
		Brinzolamide 1%	--	Suspension	FDA's in-house formulation		
		Dorzolamide hydrochloride (EQ 2% Base)	TRUSOPT®	Solution	N020408	Merck	Dec 9, 1994
2b	Topical carbonic anhydrase inhibitor and/or Alpha-2 agonist or beta blockers (beta-adrenergic)	Brimonidine tartrate 0.2%	ALPHAGAN® (Discontinued, Generic available)	Solution	N020613	Allergan	Sep 6, 1996
		Brimonidine tartrate 0.2% + Brinzolamide 1%	SIMBRINZA™	Suspension	N204251	Novartis	Apr 19, 2013
		Betaxolol 0.25%	BETOPTIC®	Suspension	N019845	Novartis	Dec 29, 1989

Timolol Rabbit PD models

PK model



Durairaj PD model

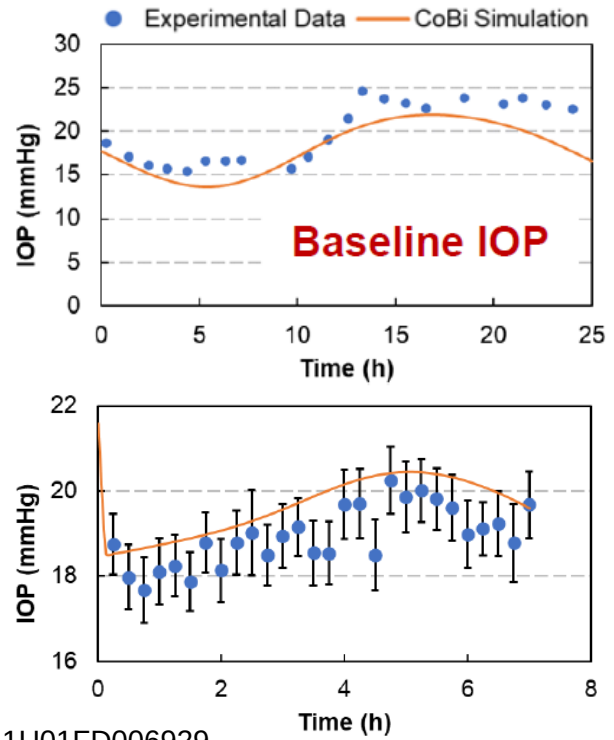


Figure courtesy of CFD RC, 1U01FD006929

Translation from Preclinical to Human

- Determine likely changes in ocular physiology between rabbit and human
- Extrapolate rabbit models to human models
- Validate the extrapolated human models

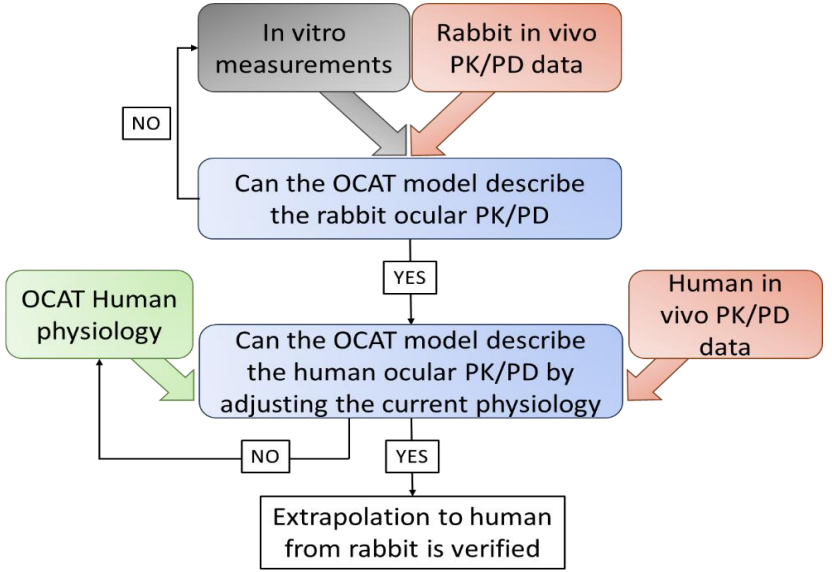


Figure courtesy of Simulations Plus, 1U01FD006927

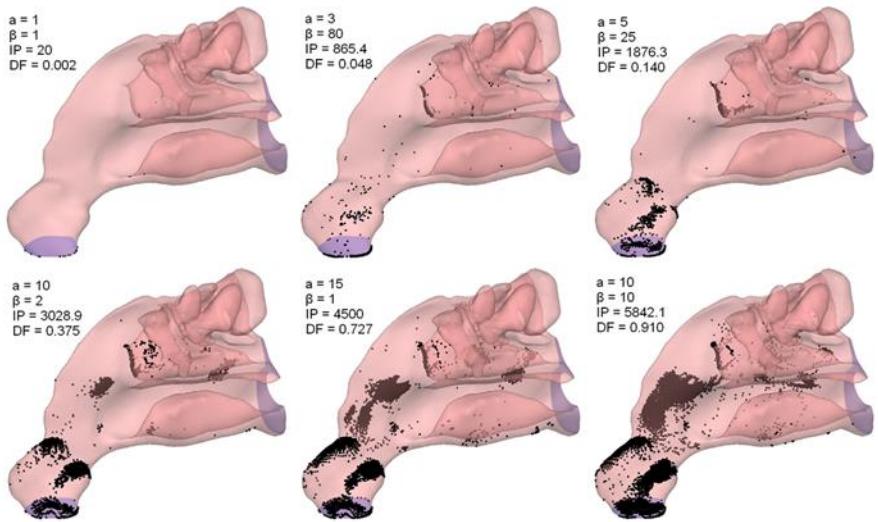
Nasal Drug Products (NDPs)

- Eight external grants and contracts (six ongoing)
- Variety of academic and consulting experts
- Includes in vivo, in vitro, and in silico research
- In silico studies have two primary goals
  - Influence of device and formulation differences on regional deposition and absorption
  - Prediction of olfactory region absorption for nose-to-brain delivery

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

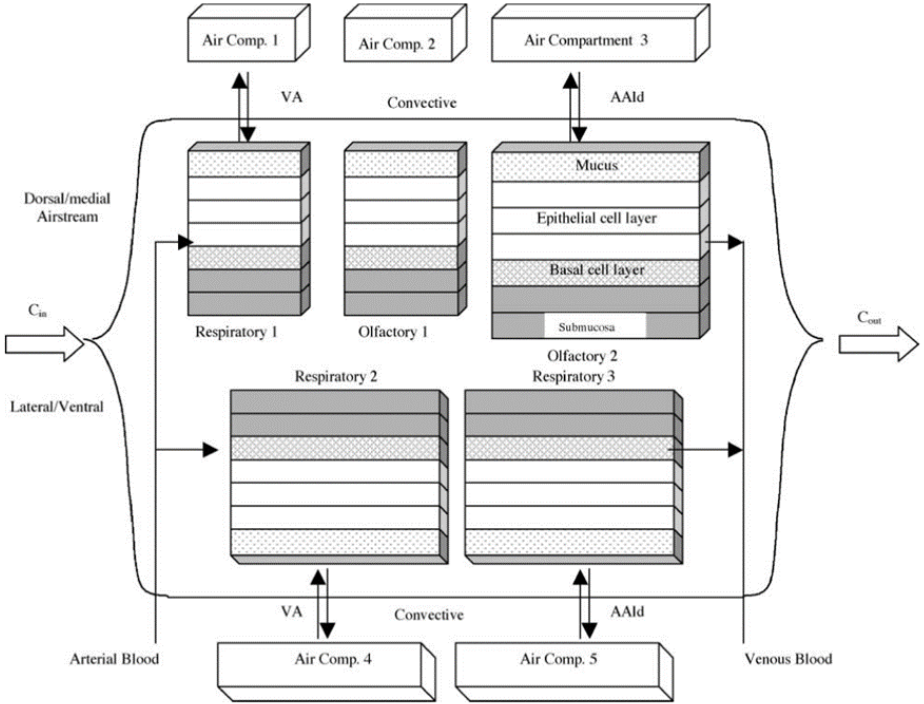
CFD: Computational Fluid Dynamics



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.

Dastan A, Abouali O, Ahmadi G. J Aerosol Sci. 69, 132 (2014)

PBPK Modeling of NDPs



Nasal PBPK model structure

Andersen M E et al, Regulatory Toxicology and Pharmacology. 36, 234 (2002)

- 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

Model Approach for Buccal/Sublingual Products

- Assess the effect of formulation excipients on API permeability in presence of artificial saliva

    - Utilize different cellular model for buccal and sublingual drug products

- Develop models to correlate atomic and molecular descriptors of the API with experimental permeability

- Develop a “dynamic in vitro dissolution and absorption model” (DIVDAM)

- Establish in vivo in vitro relationship (IVIVR)

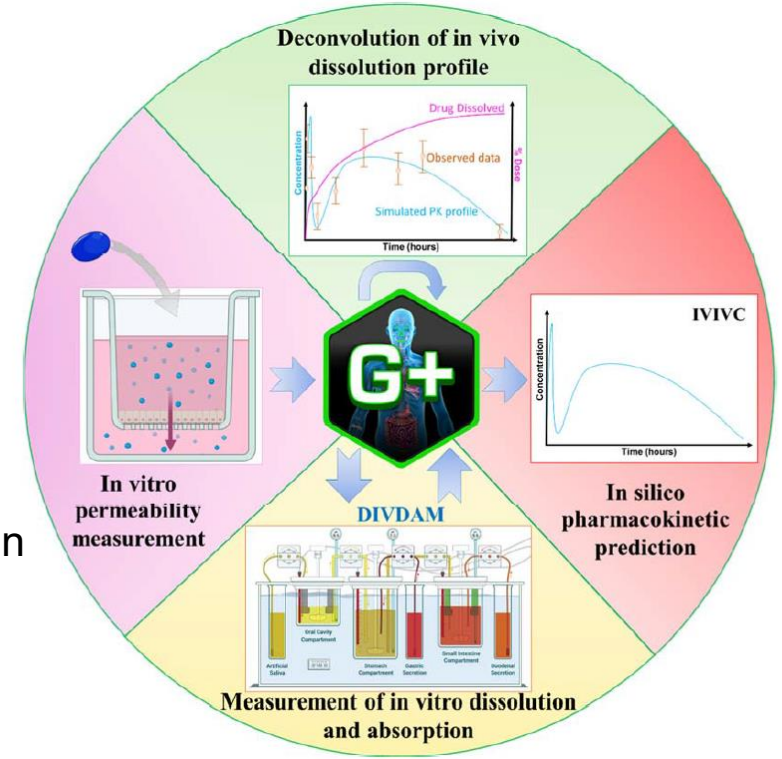


Figure courtesy of St. Louis College of Pharmacy/Simulations Plus: 75F40120C00150

MIE Approach for Complex Injectables

- Develop systems-based multiscale models to capture biological and physicochemical events that affect the transport and residence of nanoparticle (NP) (e.g., liposome) and its cargo API (e.g., doxorubicin)
- Measure the NP- and API-specific model parameters in vitro studies
- Identify and specify CQA and non-CQA parameters by MIE model

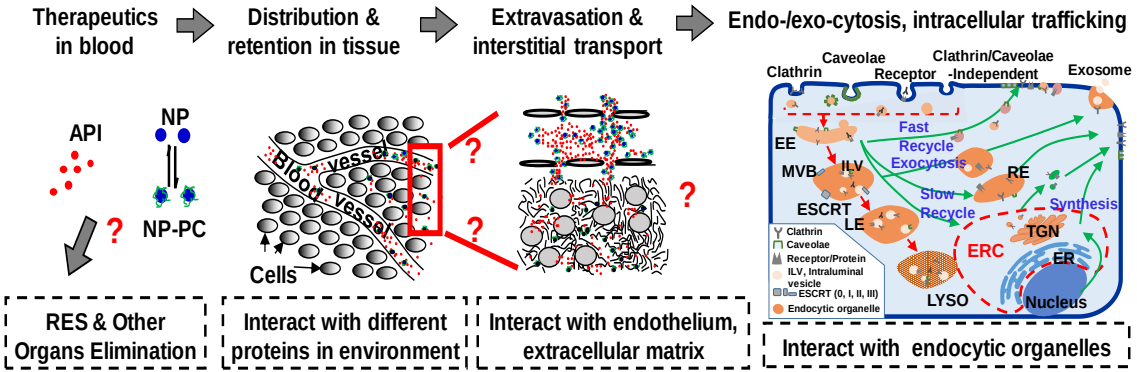


Figure courtesy of Institute of Quantitative Systems Pharmacology: 75F40119C10139

- Validate the model predictions using animal model. Verify potential CQA and establish its specification

MIE Approach for Complex Injectables

- Improve understanding about the disposition of nanoparticles in human body
- Predict bioavailability of NP and its cargo API in target site (e.g., tumor)
- Identify CQAs and establish safe space to ensure equivalent target site (e.g., tumor) and bioavailability of two drug products

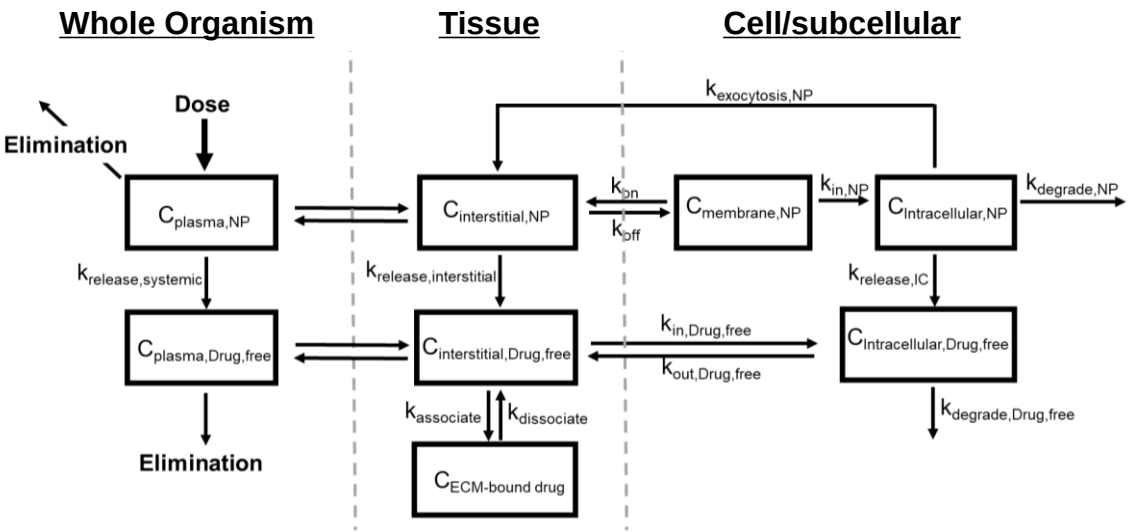


Figure courtesy of Institute of Quantitative Systems Pharmacology: 75F40119C10139

PBPK Models for Complex Products Delivered in Female Reproductive Tract

Purpose: Develop an open-source, user-friendly, generalized PBPK modeling and simulation platform

- Collect available information from literature and previous modeling efforts
- Conduct several in vitro, in vivo, and ex vivo studies to fill gaps in knowledge
- Develop and validate PBPK model

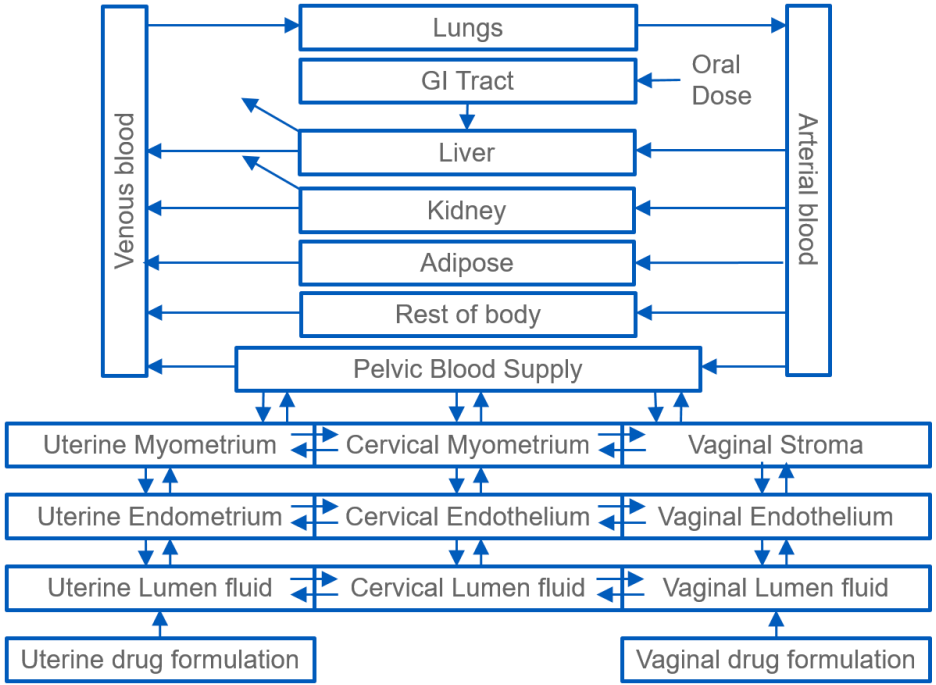


Figure courtesy of University at Buffalo: HHSF223201810188C

Summary

- Demonstrating BE for locally-acting products may be challenging
- PBPK models can integrate physiology, drug/drug product properties, existing in vitro and in vivo data
- Mechanistic modeling may bridge the knowledge gaps in generic drug development and assessment
- PBPK modeling approaches may be utilized in regulatory submissions for generic drugs

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