Use of PBPK Model to Evaluate Impact of Ophthalmic Drug Product's Critical Quality Attributes on BA/BE Assessment

ASCPT 2019 Annual Meeting Pre-Conference:
PBPK Modeling for the Development and Approval of Locally Acting Drug Products

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Session 3: Ophthalmic Drug Products

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Disclaimer: My remarks today do not necessarily reflect the official views of the FDA

Topically-Applied Ophthalmic Dosage Forms

- Various levels of complexity
- Regardless, successful drug delivery is countered by natural processes such as blinking, tear production, and drainage -> significantly reduced bioavailability (BA) for intraocular tissues
- Dosage forms:
  - Solution: single-phase; active pharmaceutical ingredient (API) completely dissolved
  - Suspension: solid API particles dispersed in liquid vehicle; liquid phase is a saturated solution of API
  - Emulsion: generally dispersions of oily droplets in an aqueous phase (o/w); API can appear in multiple phases; improved solubility and sustained drug release
  - Ointment: dispersion of API in ointment base (API can be dissolved or undissolved); generally leads to greater retention precorneally with less frequent administration

Patel, Ashaben, et al. "Ocular drug delivery systems: an overview." *World journal of pharmacology* 2.2 (2013): 47.

General Ophthalmic Bioequivalence (BE) Paradigm

Ophthalmic solutions

In vitro demonstration *302.22(b)(1)*
In vivo (clinical or PK)

CQA – critical quality attribute

Ophthalmic suspensions, emulsion and ointments

In vitro demonstration of CQA sameness
In vivo (clinical or PK)

Same principle as solution BE, but additional testing to account for added formulation complexity

E.g., aqueous humor PK or comparative clinical endpoint with intraocular pressure (IOP)

Adapted from Dr. Darby Kozak, DTP/ORS/OGD/CDER

Q1/Q2/CQA In Vitro Bioequivalence Approach

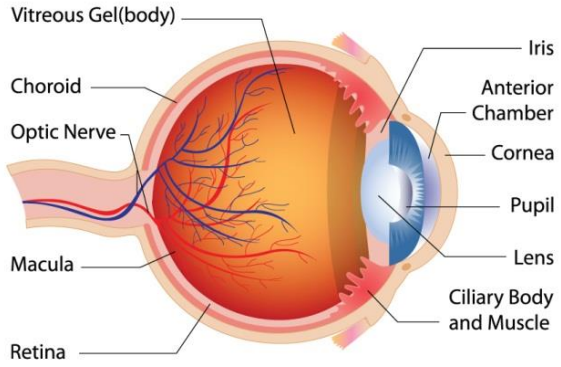
- Totality of evidence approach to confirm that the physicochemical properties of two products are comparative, such that they must have comparable in vivo bioavailability, and bioequivalence may be considered self-evident.*

Identification of CQAs is product-specific and dependent on dosage form, formulation, and manufacturing process

* "A product that meets Q1/Q2 sameness, comparability of physicochemical properties, and an acceptable comparative in vitro release rate should become available at the site of action at a rate and to an extent that is not significantly different from that of the RLD, thus meeting the requirement for demonstrating bioequivalence." FDA-2014-P-2301, FDA-2016-P-2781, FDA-2016-P-2782

Source: Dr. Darby Kozak, DTP/ORS/OGD/CDER, 2018 SBIA Complex Generic Drug Product Development Workshop

Modeling Ocular BA and Pharmacodynamics (PD)



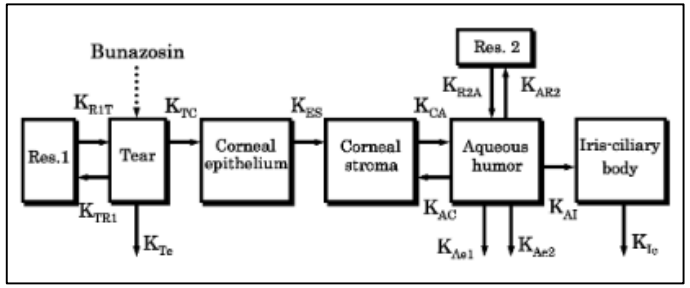
QSAR models of corneal permeability

Several literature and commercial (e.g., Simulations Plus ADMET predictor) models

$$\begin{aligned}\log perm = &-0.005(\pm0.003)MW + 0.005(\pm0.002)MW \\ &-0.166(\pm0.061)HBD - 0.081(\pm0.075)HBA \\ &+0.164(\pm0.092)\log P + 0.209(\pm0.075)\log D_{7.4} \\ &-5.994(\pm4.483)\delta_H(max) - 3.740(\pm0.364) \quad n = 47, \\ &R = 0.879,\ SE = 0.349,\ F = 18.870 \qquad (3)\end{aligned}$$

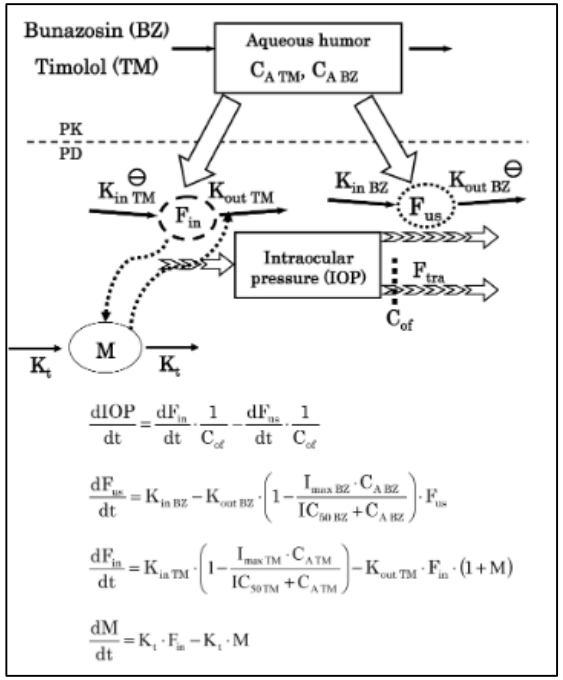
Ghorbanzad'e, Mehdi, et al. "Quantitative and qualitative prediction of corneal permeability for drug-like compounds." *Talanta* 85.5 (2011): 2686-2694.

Mathematical PK models: diffusion-based or compartmental models



Sakanaka, Koji, et al. "Ocular pharmacokinetic/pharmacodynamic modeling for multiple anti-glaucoma drugs." *Biological and Pharmaceutical Bulletin* 31.8 (2008): 1590-1595.

Mathematical PD models: IOP



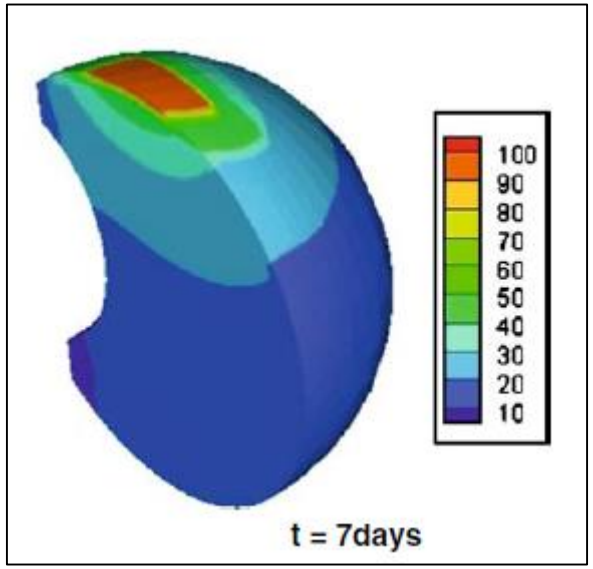
$$\frac{dIOP}{dt} = \frac{dF_{in}}{dt}\cdot\frac{1}{C_{of}} - \frac{dF_{us}}{dt}\cdot\frac{1}{C_{of}}$$

$$\frac{dF_{us}}{dt} = K_{in\,BZ} - K_{out\,BZ}\cdot\left(1 - \frac{I_{max\,BZ}\cdot C_{A\,BZ}}{IC_{50\,BZ} + C_{A\,BZ}}\right)\cdot F_{us}$$

$$\frac{dF_{in}}{dt} = K_{in\,TM}\cdot\left(1 - \frac{I_{max\,TM}\cdot C_{A\,TM}}{IC_{50\,TM} + C_{A\,TM}}\right) - K_{out\,TM}\cdot F_{in}\cdot(1+M)$$

$$\frac{dM}{dt} = K_t\cdot F_{in} - K_t\cdot M$$

Mathematical PK models: Geometric CFD/FEM-based models



Balachandran, Ram K., and Victor H. Barocas. "Computer modeling of drug delivery to the posterior eye: effect of active transport and loss to choroidal blood flow." *Pharmaceutical research* 25.11 (2008): 2685-2696.

Ghemtio, Leo, et al. "Predictive modeling of ocular pharmacokinetics and adverse effects." *Current pharmaceutical design* 22.46 (2016): 6928-6934.

Regulatory Utility of Ocular PBPK Models

Model integrated evidence for generic drug development and approval

- Support product development -> gain confidence in formulation selection to conducting local PK, PD, or comparative clinical endpoint (CCE) BE study
- Potentially support in vitro only BE approaches in lieu of in vivo studies
- Guide selection of clinically-relevant in vitro tests for BE
- Define a safe space for CQAs of ophthalmic products
- Justify differences in CQAs from the reference-listed drug (RLD)

Conduct virtual bioequivalence studies

Product-specific guidance development

Zhao et al., Clin Pharmacol Ther. 2018 Nov 10 doi: 10.1002/cpt.1282

Challenges for Ocular PBPK Models

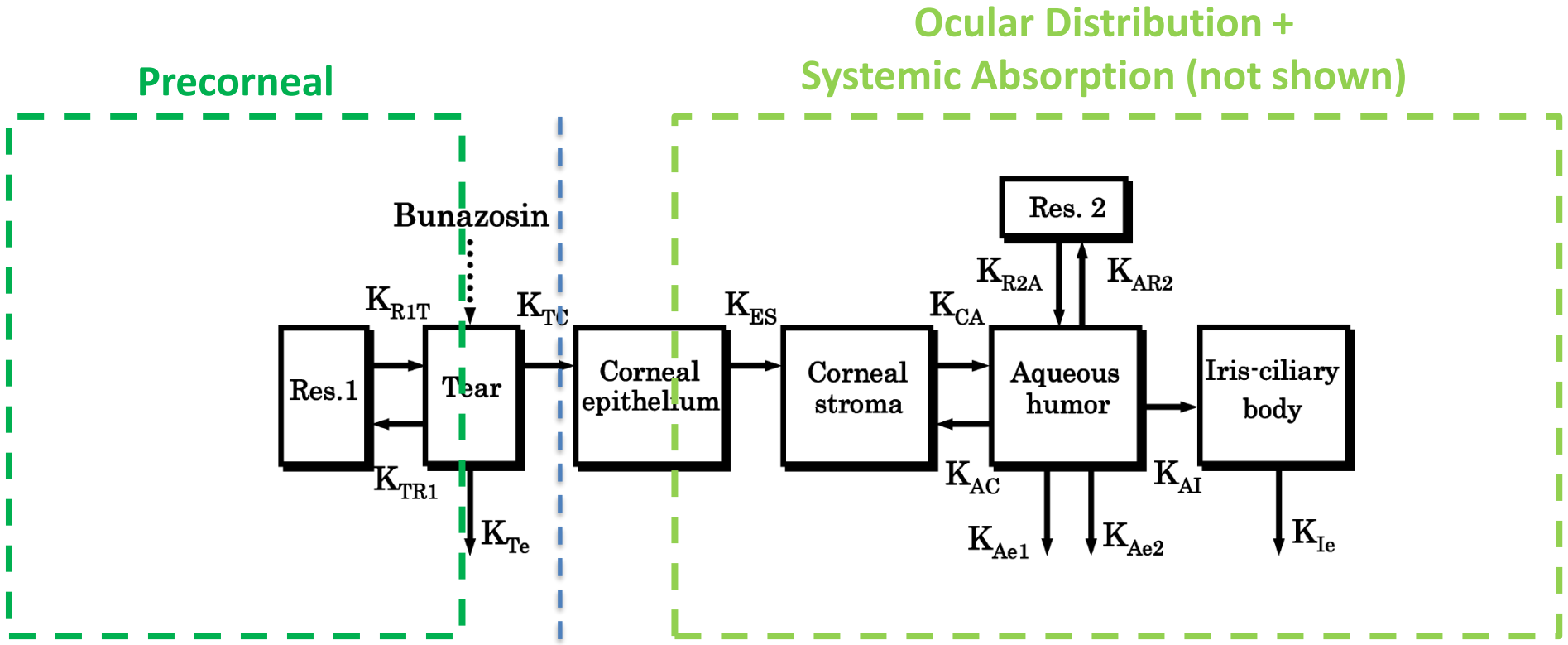
Data availability?

- Ideal case: multiple formulations with PK/PD/clinical endpoints -> build in vitro in vivo correlations (IVIVC)
- Unified model approach: test multiple products with a range of formulation characteristics and API properties; i.e., verification of modeling platform to predict differences between products
- Majority of data in rabbits ….

Species?

- Rabbit modeling can inform formulation selection for eventual in vivo study
- Can rabbit ocular PBPK models be extrapolated to human? Central challenge
- Human modeling can support BE and product specifications

Ocular PBPK – Focus for BE Assessment



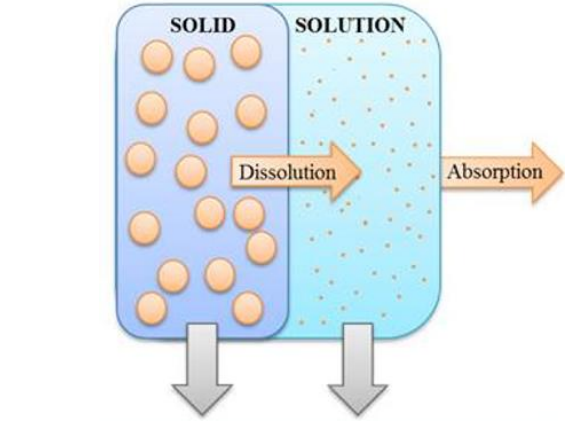
- Includes modeling (i.e., mechanistic description) of the **formulation**
- Includes what happens to the product after topical application and interaction with tear film and eye blinking
- Complexity dependent on drug product
- For BE assessment, here is where the difference between two products are inputted into the model

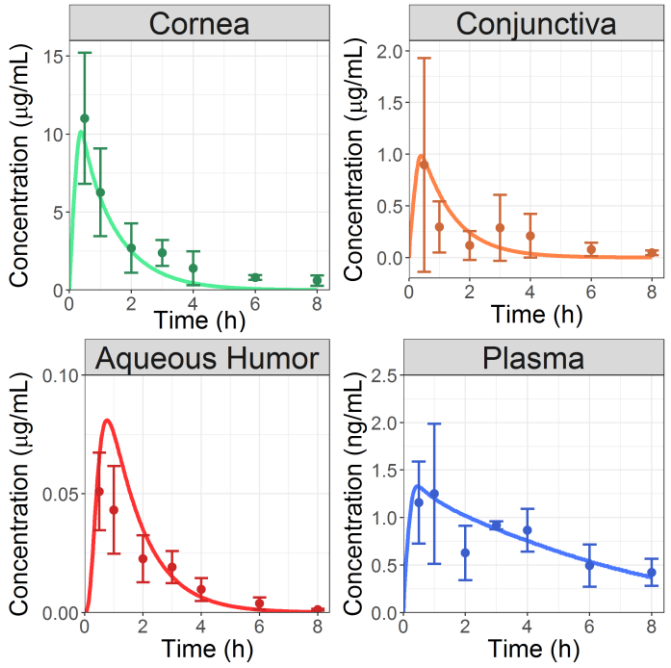
- Critical for accurate prediction of local concentrations -> protein (including enzymes) binding and effect modeling
- Critical for verification – confidence in local and systemic concentration predictions

Modeling Ophthalmic Suspensions

Internal case study - Dexamethasone

- After instillation, several routes of API transport:
  - Dissolved API diffusing from tear film through cornea or conjunctiva
  - Solid particles and dissolved API cleared from eye surface through nasolacrimal drainage -> systemic circulation
- OCAT Model Development – internally conducted rabbit study with PK sampling from multiple ocular tissues and plasma
- Model Verification with multiple datasets showing:
  - Particle size impact on ocular absorption
  - Viscosity impact on ocular absorption
  - Non-linear dose-exposure relationship

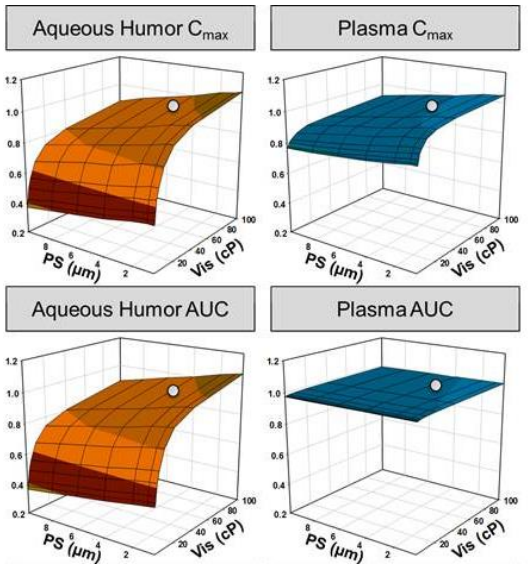




Chockalingam, Ashok, et al. "Protocol for evaluation of topical ophthalmic drug products in different compartments of fresh eye tissues in a rabbit model." Journal of pharmacological and toxicological methods 96 (2019): 9-14.
LeMerdy, Maxime, et al. "Application of Mechanistic Ocular Absorption Modeling and Simulation to Understand the Impact of Formulation Properties on Ophthalmic Bioavailability in Rabbits: A Case Study using Dexamethasone Suspension." *In submission*

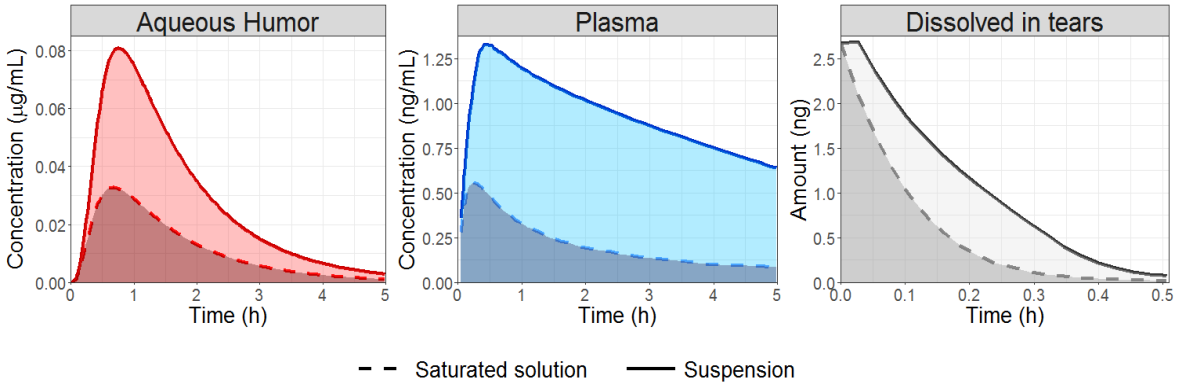
Modeling Ophthalmic Suspensions

Internal case study – Dexamethasone (cont'd)



Parameter sensitivity analysis in rabbit on PS and viscosity

- Viscosity is a critical attribute affecting BE
- Plasma/systemic PK is not reflective of local concentrations



Saturated solution vs. suspension simulations

- Solid particles in formulation leads to higher aqueous humor concentrations, BUT …
- Also higher systemic exposure
- A tool for product development that can weigh benefits and risks

LeMerdy, Maxime, et al. "Application of Mechanistic Ocular Absorption Modeling and Simulation to Understand the Impact of Formulation Properties on Ophthalmic Bioavailability in Rabbits: A Case Study using Dexamethasone Suspension." *In submission*

LeMerdy, Maxime, et al. "Physiologically-based Pharmacokinetic Model to Support Ophthalmic Suspensions Development." ASCPT AM 2019 poster.

Modeling Ophthalmic Suspensions

Next Steps - Brinzolamide

- 2 rabbit studies:
  1. Biodistribution/PK study with RLD (AZOPT – NDA 20816) only
  2. Impact of CQAs on IOP with multiple formulations

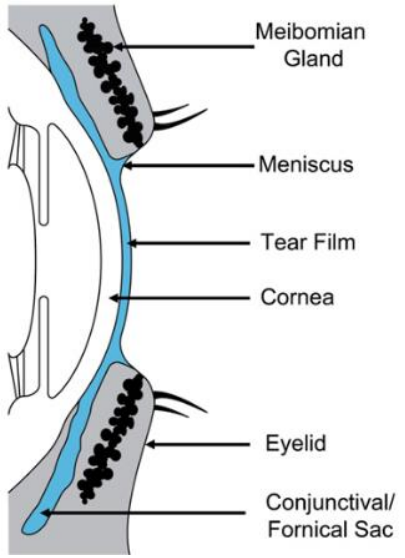
- FDA Office of Testing and Research (OTR): Q1/Q2 formulations to AZOPT that differ in specific CQAs expected to impact BE (preliminarily confirmed through PBPK modeling)

- Future considerations for verifying human ocular PBPK models through IOP sampling

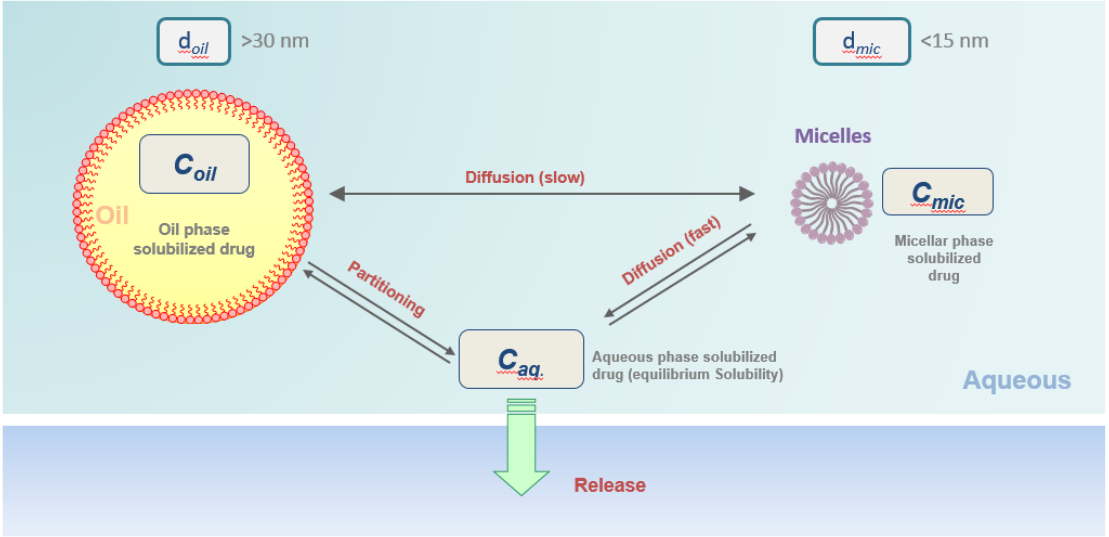
Modeling Ophthalmic Emulsions

Key characteristics of emulsions

- API in emulsion can be found in multiple phases
- FDA internal and external research into such measurements and in vitro API release
- Integration of tear film dynamics and API/vehicle dynamics at ocular surface into PBPK platforms
- Emulsion modeling part of Contract HHSF223201810151C with CFDRC

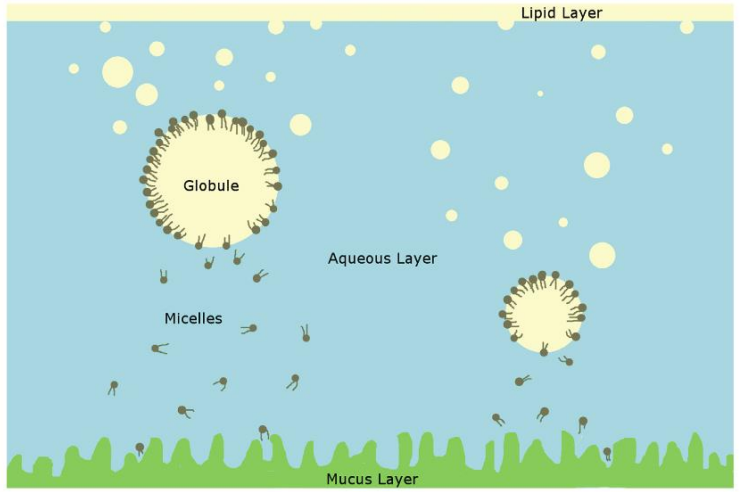


Gaffney, E. A., et al. "A mass and solute balance model for tear volume and osmolarity in the normal and the dry eye." *Progress in retinal and eye research* 29.1 (2010): 59-78.



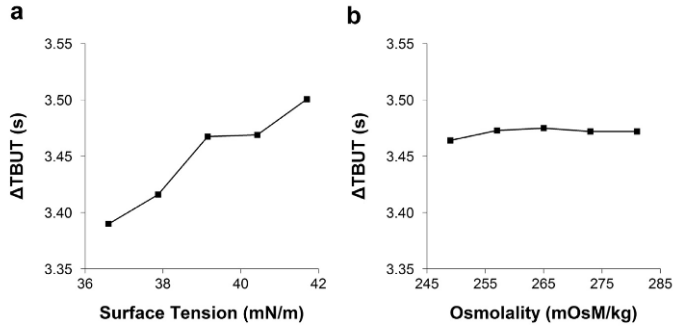
Courtesy of Dr. Xiaoming Xu, DPQR/OTR/OPQ/CDER

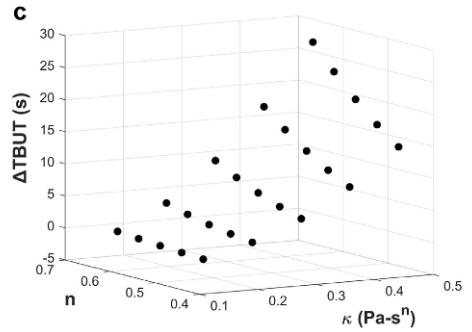
Modeling Ophthalmic Emulsions



Internal case study – Tear Film Modeling

- Example of modeling formulation-physiology interaction
- Tear film breakup time (TBUT):
  - A test used to assess for evaporative dry eye disease
  - Once applied, emulsion mixes with tear film and then oily globules break down and attach to the lipid layer of the tear film
- TBUT model – fluid mechanics approach incorporating certain CQAs: **non-Newtonian viscosity**, osmolality, and **surface tension**





Potential Next Steps

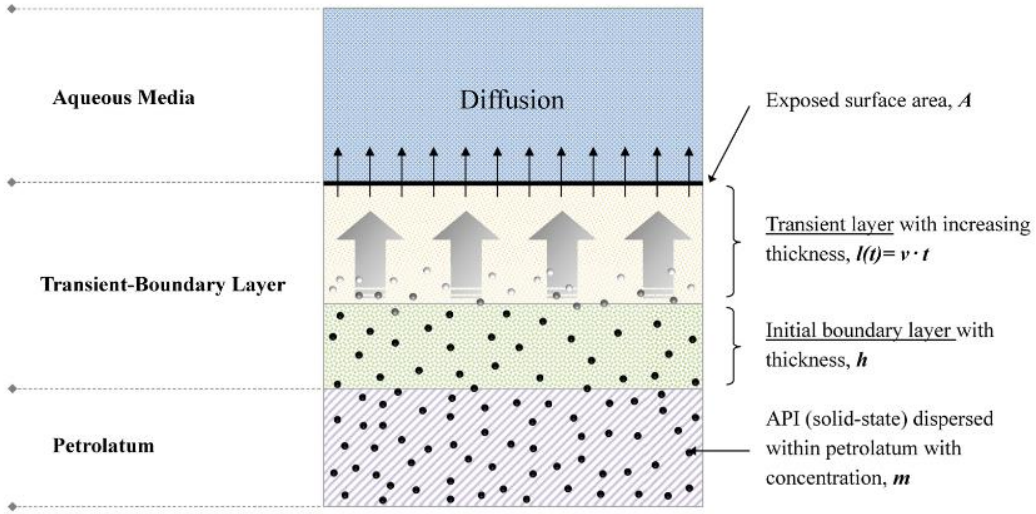
- Further tear film modeling and validation
- Rabbit studies with multiple Q1/Q2 formulations where tear film thickness and menisci measurements will be taken from the ocular surface

Walenga, Ross L., et al. "Impact of Vehicle Physicochemical Properties on Modeling-Based Predictions of Cyclosporine Ophthalmic Emulsion Bioavailability and Tear Film Breakup Time." Journal of pharmaceutical sciences 108.1 (2019): 620-629.

Modeling Ophthalmic Ointments

Ongoing Activities

- Subject of Contracts HHSF223201810151C (CFDRC) and HHSF223201810255P (Simulations Plus)
- Critical modeling aspects:
  - Incorporation of drug release models into PBPK Platforms
  - Rheological considerations – longevity on ocular surface, ointment redistribution upon blinking



Xu, Xiaoming, et al. "Kinetics of drug release from ointments: role of transient-boundary layer." *International journal of pharmaceutics* 494.1 (2015): 31-39.

Summary

- **Ocular PBPK modeling** is more than just predicting ocular biodistribution
- Successful regulatory application of PBPK models necessitates a full understanding of the drug product and how to input the drug product (i.e., CQAs)
- While verification in human is challenging/limited, verifying mechanistic formulation descriptions with preclinical data should translate to human models
- In rabbit vs. human, formulation-physiology interactions may differ (e.g., impact of blinking rate)
- GDUFA regulatory science program will continue to fund advancements in ocular PBPK modeling and ophthalmic formulation characterization

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