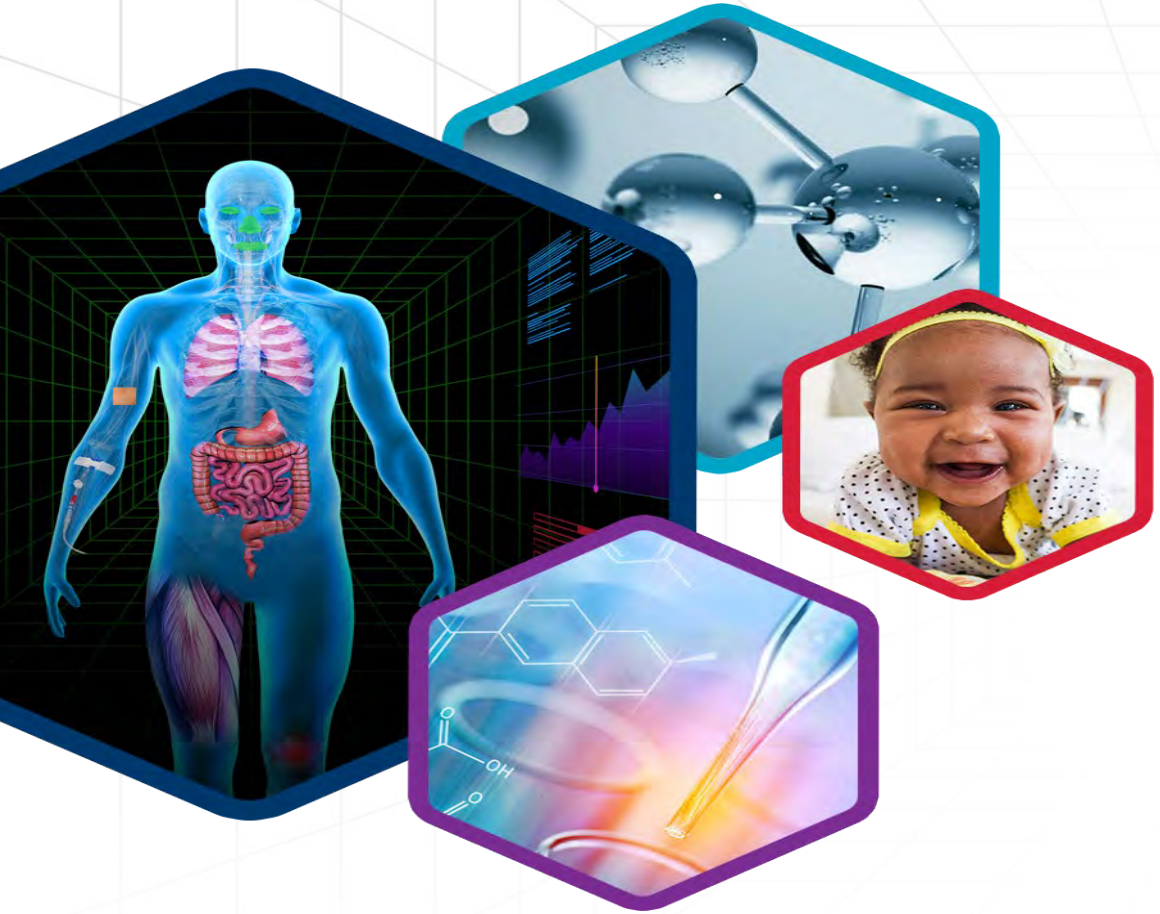


SimulationsPlus

Cognigen | DILIsym Services | Lixoft

Complex Delivery Routes and Generics: The Next Frontier for PBBM/PBPK Modeling

Dr. Jessica Spires

Controlled Release Society Annual Meeting

July 2022

Generic Drug Development for Locally Acting Products

- Generic drug development for locally acting drug products is a fast-growing field of interest
- For locally acting drug products, traditional bioequivalence (BE) approaches used with orally administered drugs may not be relevant or applicable
- BE for locally acting products may be assessed through *in vitro* and/or *in vivo* testing; however, *in vivo* testing may be difficult or expensive, especially when assessing local concentration or effect data

PBPK Modeling to Support Generic Formulation Development

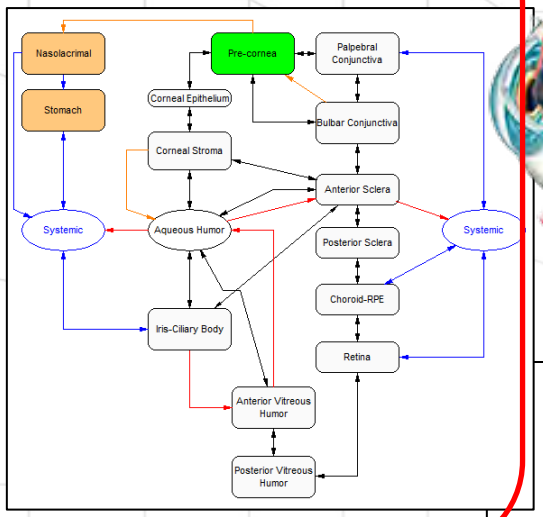
- The composition of formulations can affect the absorption of APIs through formulation attributes such as particle size, solubility and diffusivity of the API in the formulation, and formulation viscosity
- Mechanisms of absorption will vary according to the local physiology of the route of administration and the nature of the formulation
- *In silico* physiologically based biopharmaceutics (PBBM) / pharmacokinetics (PBPK) modeling can simulate the mechanisms by which formulation attributes influence absorption, informing development of generic formulations and reducing the need for animal and human testing

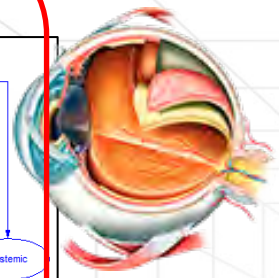
PBPK Modeling in GastroPlus

- GastroPlus is a mechanistically based simulation software package that simulates absorption, biopharmaceutics, pharmacokinetics, and pharmacodynamics of drugs or chemicals in humans and animals
- The software can model absorption from intravenous, oral, oral cavity, ocular, inhalation, dermal, subcutaneous, and intramuscular routes of administration

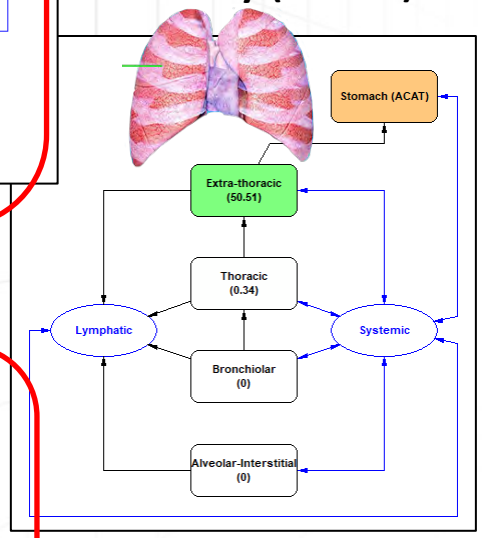
Pathways Beyond Oral Absorption…

Ocular (OCAT™)

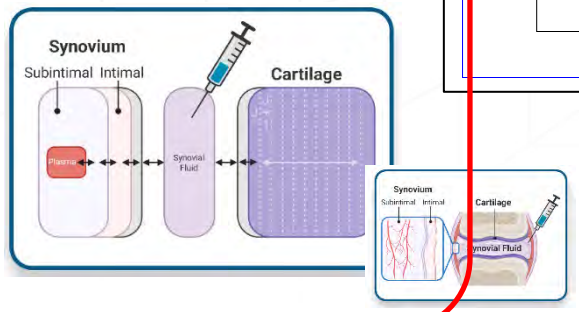


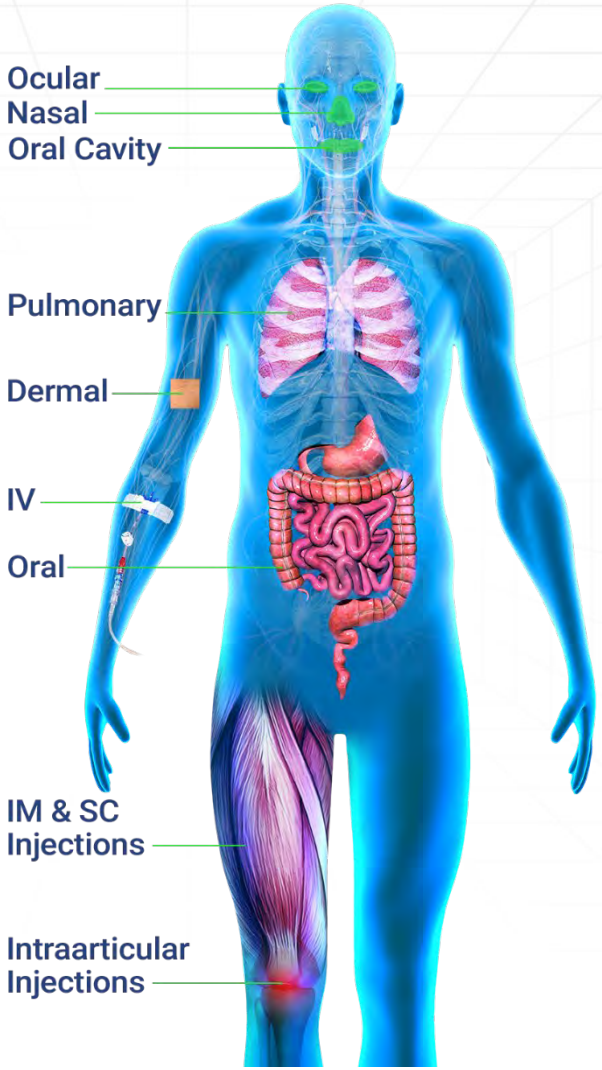


Pulmonary (PCAT™)

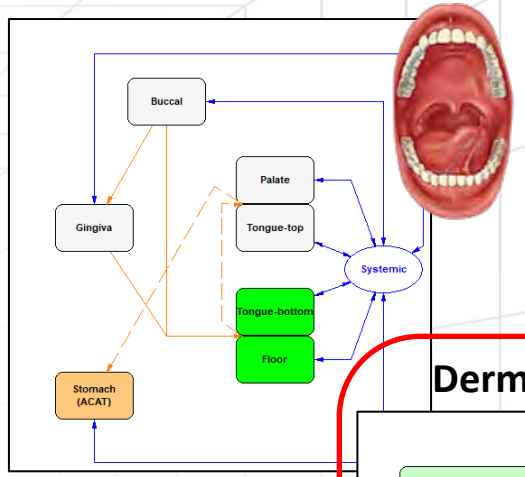


Intra-articular (ICAT™)

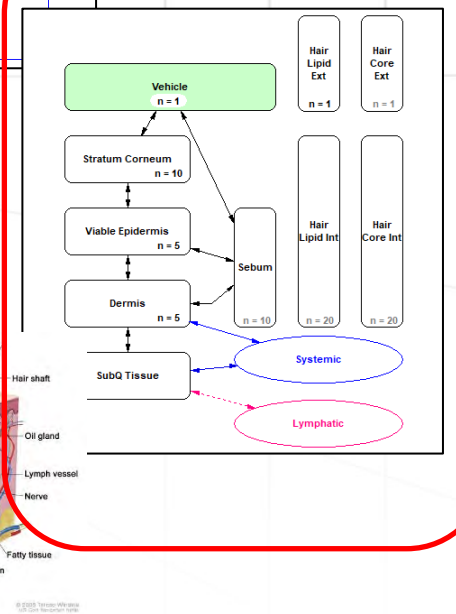


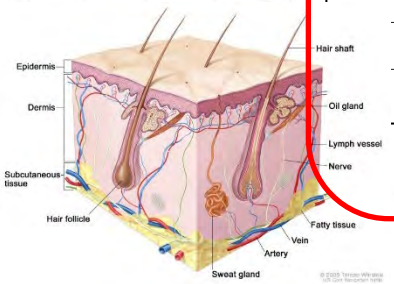


Oral Cavity (OCCAT™)



Dermal (TCAT™)



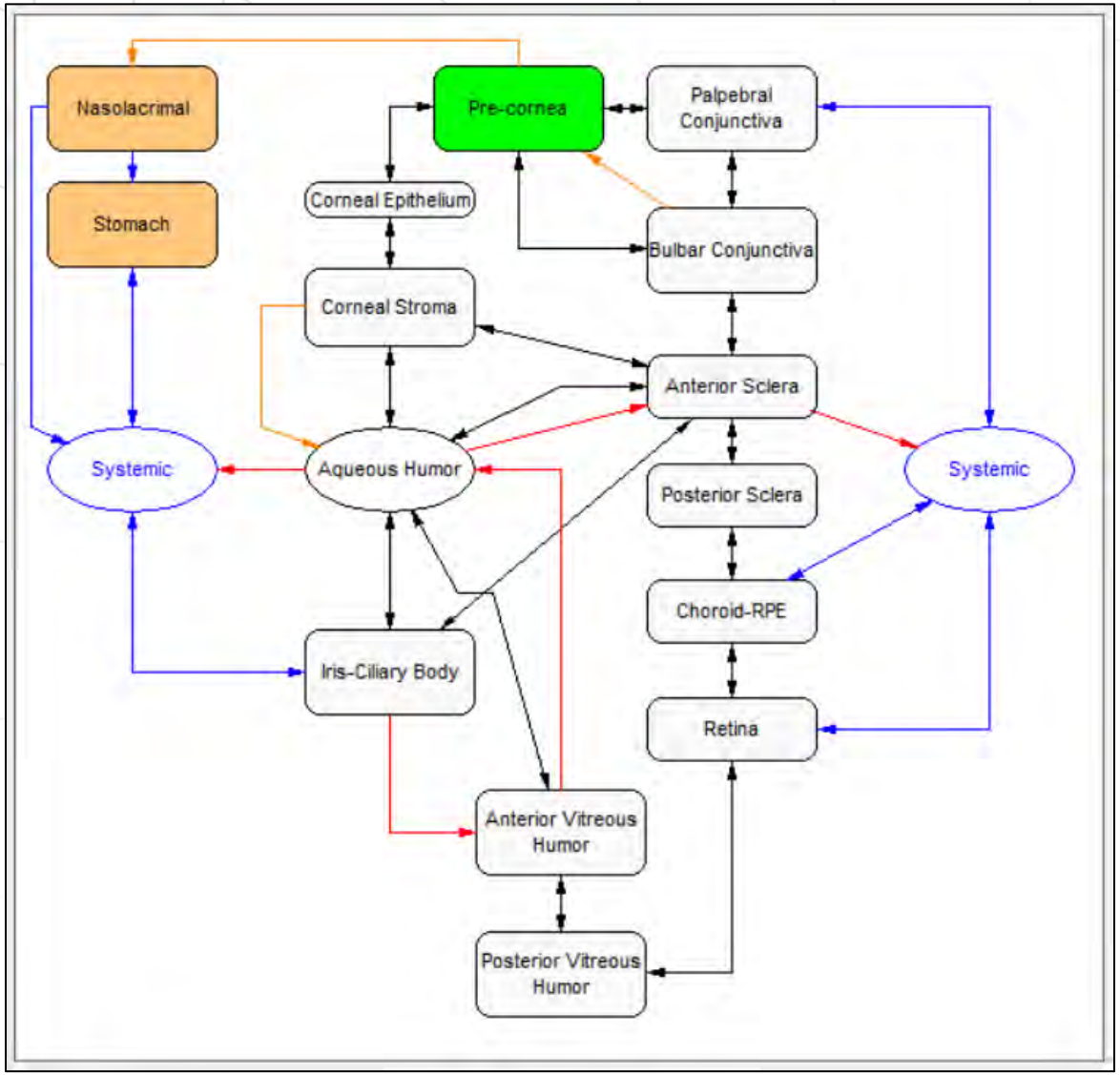


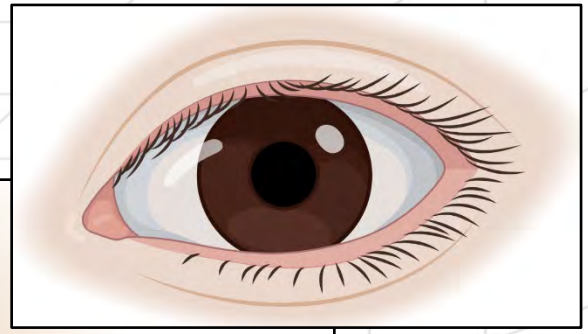
SimulationsPlus

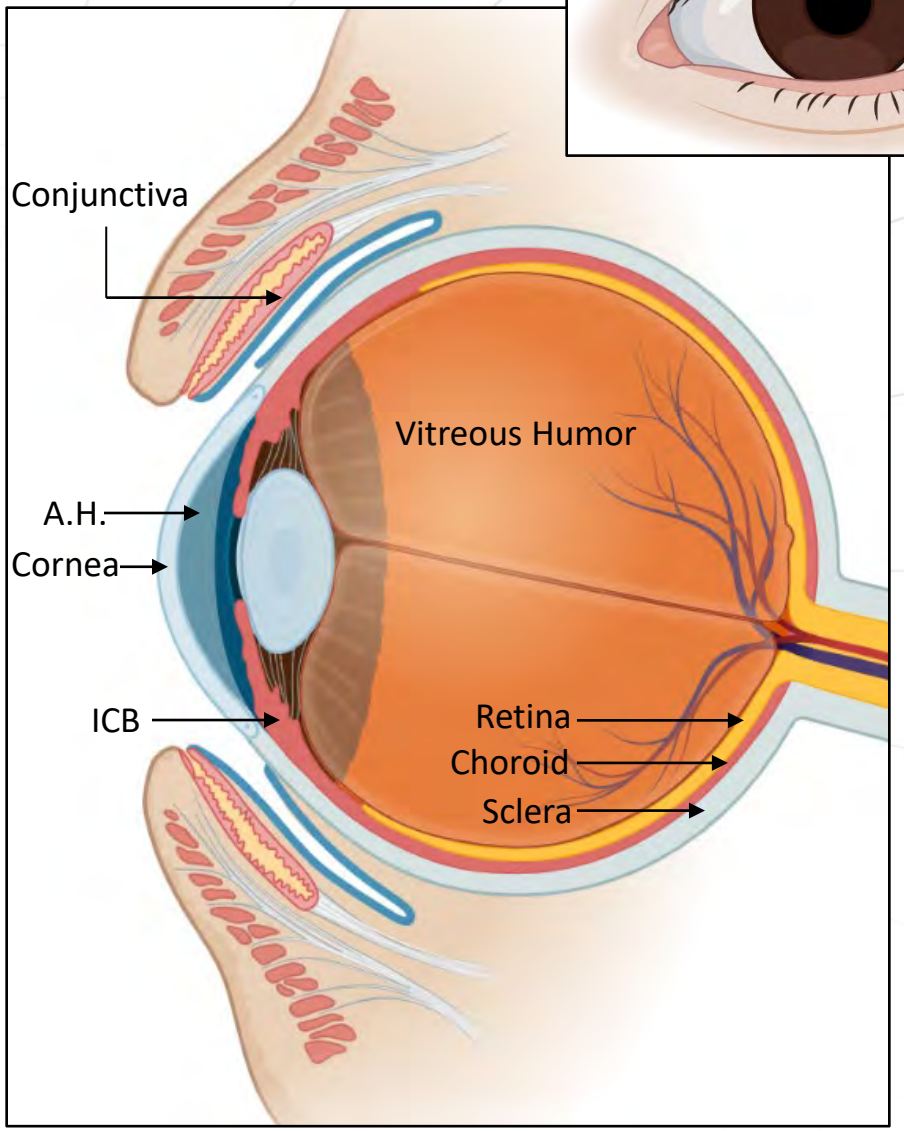
Cognigen | DILIsym Services | Lixoft

Ocular Delivery

The Eye and the OCAT™







Modes of Administration in the Eye

1) Topical

- < 5% reaches anterior segment
- Tiny fraction reaches Retina

2) Systemic

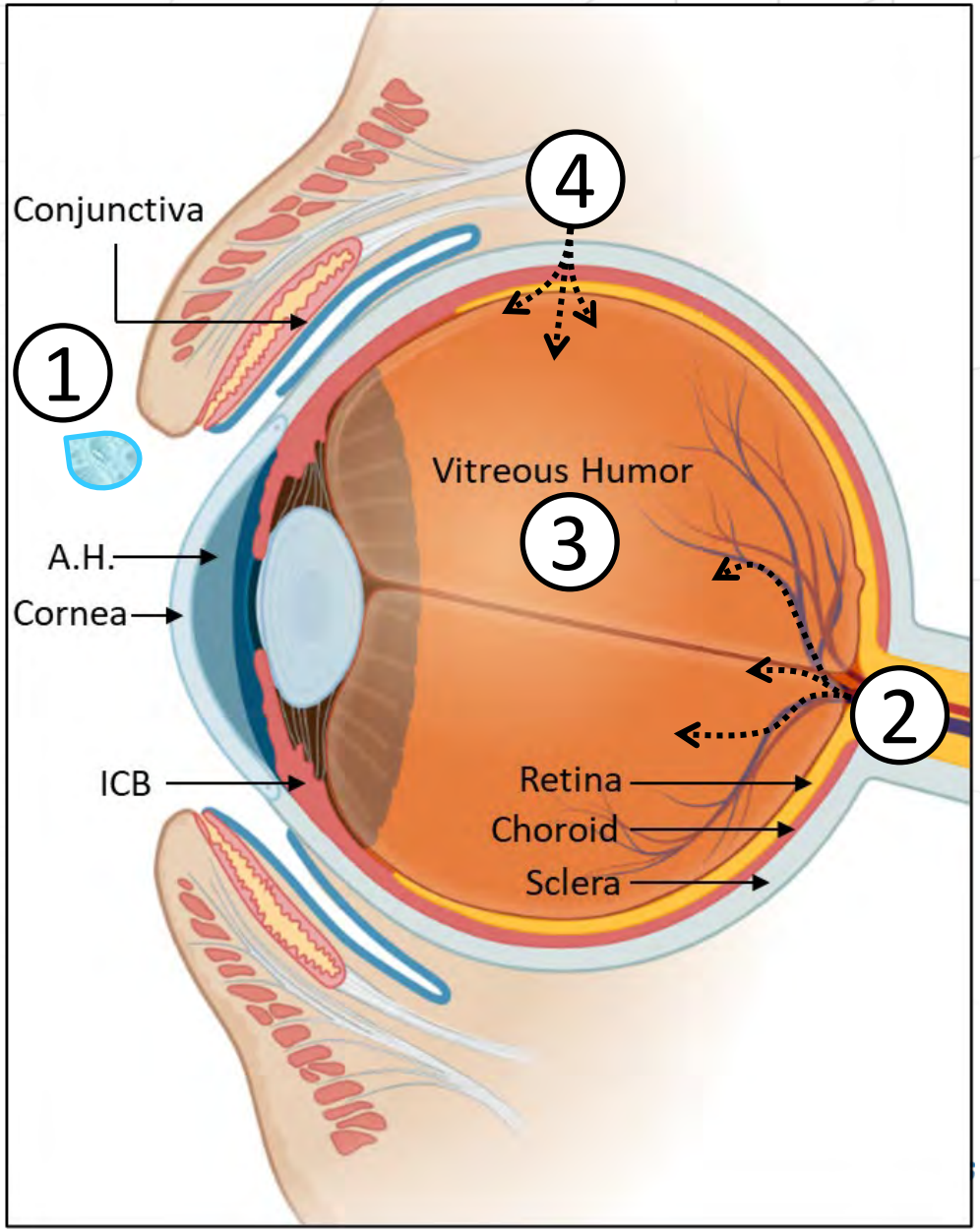
- Penetration is limited by blood aqueous and blood retinal barriers

3) Intravitreal

- Effective mode of administration for achieving therapeutic concentrations in retina

4) Transcleral

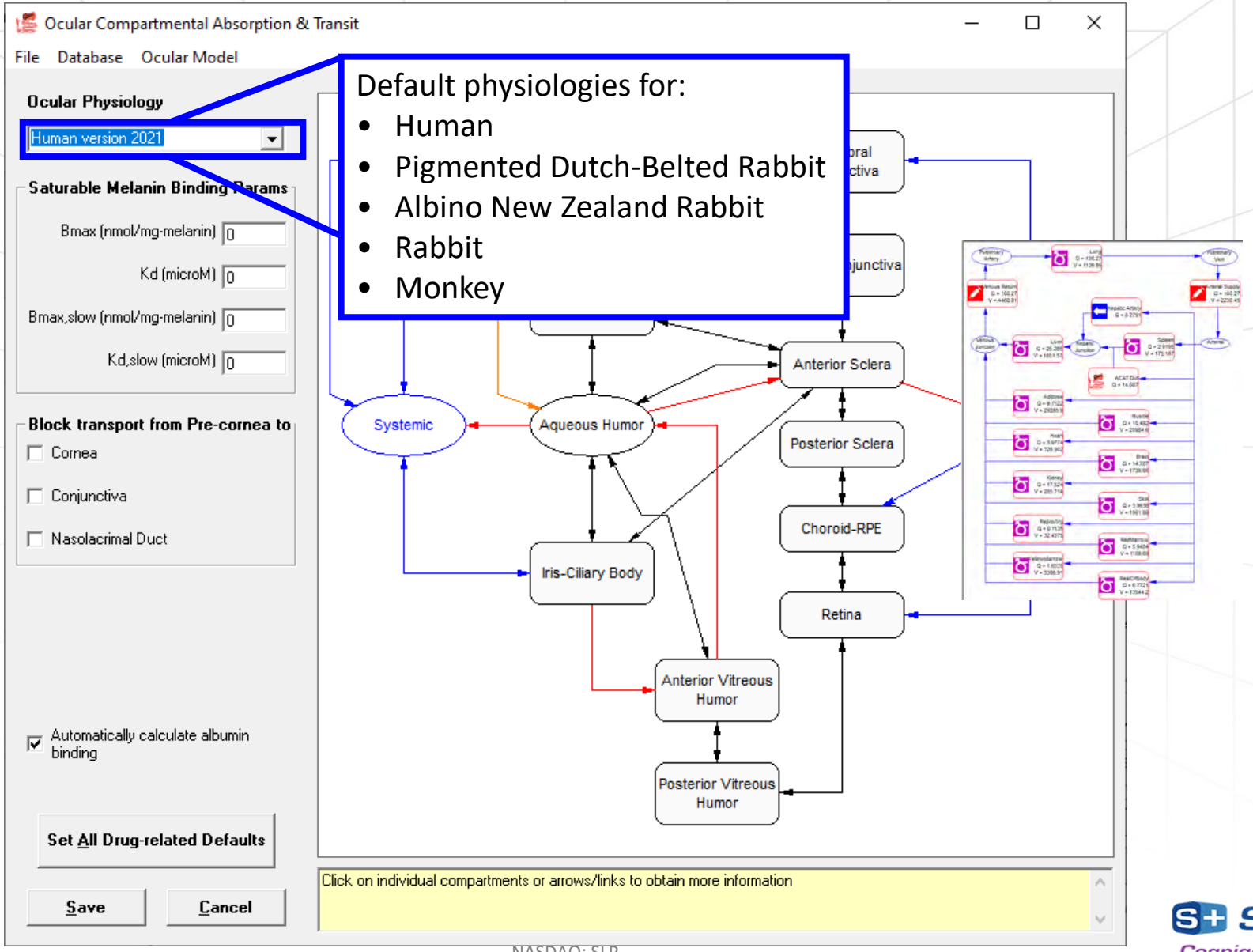
- Noninvasive
- Effectiveness is under investigation



Ocular Dosage Forms

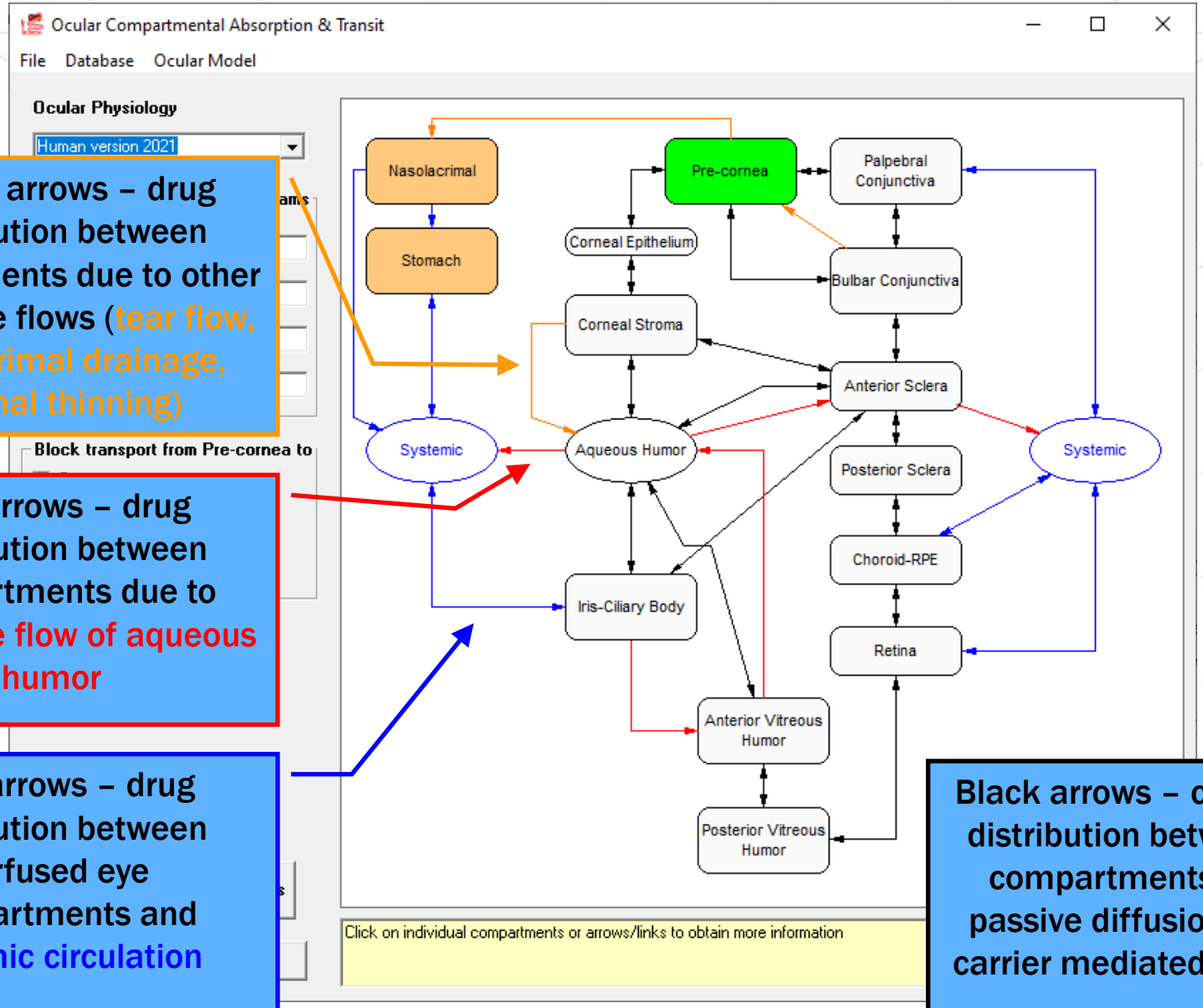
Dosage form	Description
OC: Topical Soln	Homogeneous solution of API in a liquid solvent applied to the precorneal film
OC: Topical Susp	Suspension of solid API particles in a liquid solvent applied to the precorneal film
OC: Topical Ointment	Formulation releasing API into the precorneal film according to Higuchi kinetics
OC: Vitreal Soln	Homogeneous solution of API in a liquid solvent injected into the vitreous humor
OC: Vitreal Susp	Suspension of solid API particles in a liquid solvent injected into the vitreous humor
OC: Vitreal Impt	Implant releasing dissolved API into the vitreous humor
OC: SubConj Impt	Implant releasing dissolved API into the bulbar conjunctiva

Ocular Compartmental Absorption and Transit (OCAT™)



New in 9.8.2! Breed-specific rabbit physiologies and updated human physiology

Ocular Compartmental Absorption and Transit Model



Orange arrows – drug distribution between compartments due to other convective flows (tear flow, nasolacrimal drainage, stromal thinning)

Red arrows – drug distribution between compartments due to convective flow of aqueous humor

Blue arrows – drug distribution between perfused eye compartments and systemic circulation

Black arrows – compound distribution between eye compartments due to passive diffusion and/or carrier mediated transport

Compound Specific Parameters - Defaults

Corneal Permeability:

1. QSAR model in ADMET Predictor based on published data for 130 drug-like molecules
2. Theoretical model[1] (used when ADMET Predictor value not available): permeabilities of corneal layers (epithelium, stroma and endothelium) are a function of molecular size[2] and lipophilicity

Conjunctiva, RPE, Iris-cilliary Body Permeability:

Built in correlations based on small datasets of beta-blockers (function of lipophilicity)

Sclera and Choroid Permeability:

Approximated by stromal permeability from theoretical model[1] of corneal permeability – it is a function of molecular size[2] and lipophilicity

Aqueous and Vitreous Humor Permeability:

Approximated by aqueous diffusion coefficient

Systemic Absorption Rates:

Applicable only for perfused tissues (conjunctiva, choroid-RPE, retina, and iris-ciliary body)
Currently, the default values are set to estimated permeability in each compartment

These values are then multiplied by empirical rate constants.

[1]Edwards & Prausnitz – *AIChE J* 1998, 44:214-25 and *AIChE J* 2001, 18:1497-1508
[2]Effective molecular radius is estimated using empirical equation which accounts for overall size and likely non-sperical shape of the molecule (equation was calibrated against ~1100 drug-like molecules)

Cooperation grant with the FDA (2020-2023)

3-year funded collaborative project with the FDA Office of Generic Drugs to expand the OCAT model to predict human ocular PK and pharmacodynamics for ophthalmic formulations

Published Work

Comparative Study > Pharm Res. 2020 Nov 19;37(12):245. doi: 10.1007/s11095-020-02965-y.

Ocular Physiologically Based Pharmacokinetic Modeling for Ointment Formulations

Maxime Le Merdy [1], Jessica Spires [2], Viera Lukacova [2], Ming-Liang Tan [3], Andrew Babiskin [3], Xiaoming Xu [4], Liang Zhao [3], Michael B Bolger [2]

Affiliations + expand

PMID: 33215336 PMCID: PMC7677276 DOI: 10.1007/s11095-020-02965-y

Free PMC article

Abstract

Purpose: The purpose of this study is to show how the Ocular Compartmental Absorption & Transit (OCAT™) model in GastroPlus® can be used to characterize ocular drug pharmacokinetic performance in rabbits for ointment formulations.

> AAPS J. 2019 May 20;21(4):65. doi: 10.1208/s12248-019-0334-x.

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

Maxime Le Merdy [1], Jianghong Fan [2], Michael B Bolger [3], Viera Lukacova [3], Jessica Spires [3], Eleftheria Tsakalozou [1], Vikram Patel [4], Lin Xu [4], Sharron Stewart [4], Ashok Chockalingam [4], Suresh Narayanasamy [4], Rodney Rouse [4], Murali Matta [4], Andrew Babiskin [1], Darby Kozak [5], Stephanie Choi [6], Lei Zhang [6], Robert Lionberger [6], Liang Zhao [1]

Affiliations + expand

PMID: 31111305 DOI: 10.1208/s12248-019-0334-x

Comparative Study > AAPS J. 2020 Jan 6;22(2):26. doi: 10.1208/s12248-019-0408-9.

Physiologically Based Pharmacokinetic Model to Support Ophthalmic Suspension Product Development

Maxime Le Merdy [1], Ming-Liang Tan [1], Andrew Babiskin [2], Liang Zhao [1]

Affiliations + expand

PMID: 31907674 DOI: 10.1208/s12248-019-0408-9

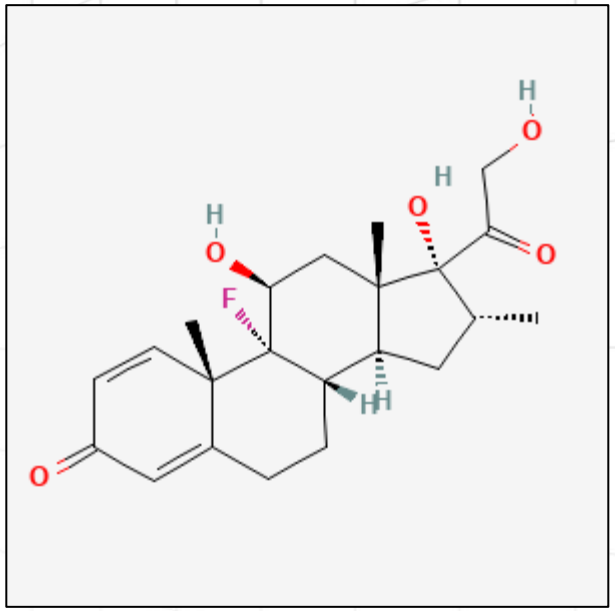
Abstract

FDA's Orange Book lists 17 currently marketed active pharmaceutical ingredients (API) formulated within ophthalmic suspensions in which a majority has 90% or more of the API undissolved. We used an ocular physiologically based pharmacokinetic (O-PBPK) model to compare a suspension with a solution for ophthalmic products with dexamethasone (Dex) as the model drug. Simulations with a

Dexamethasone

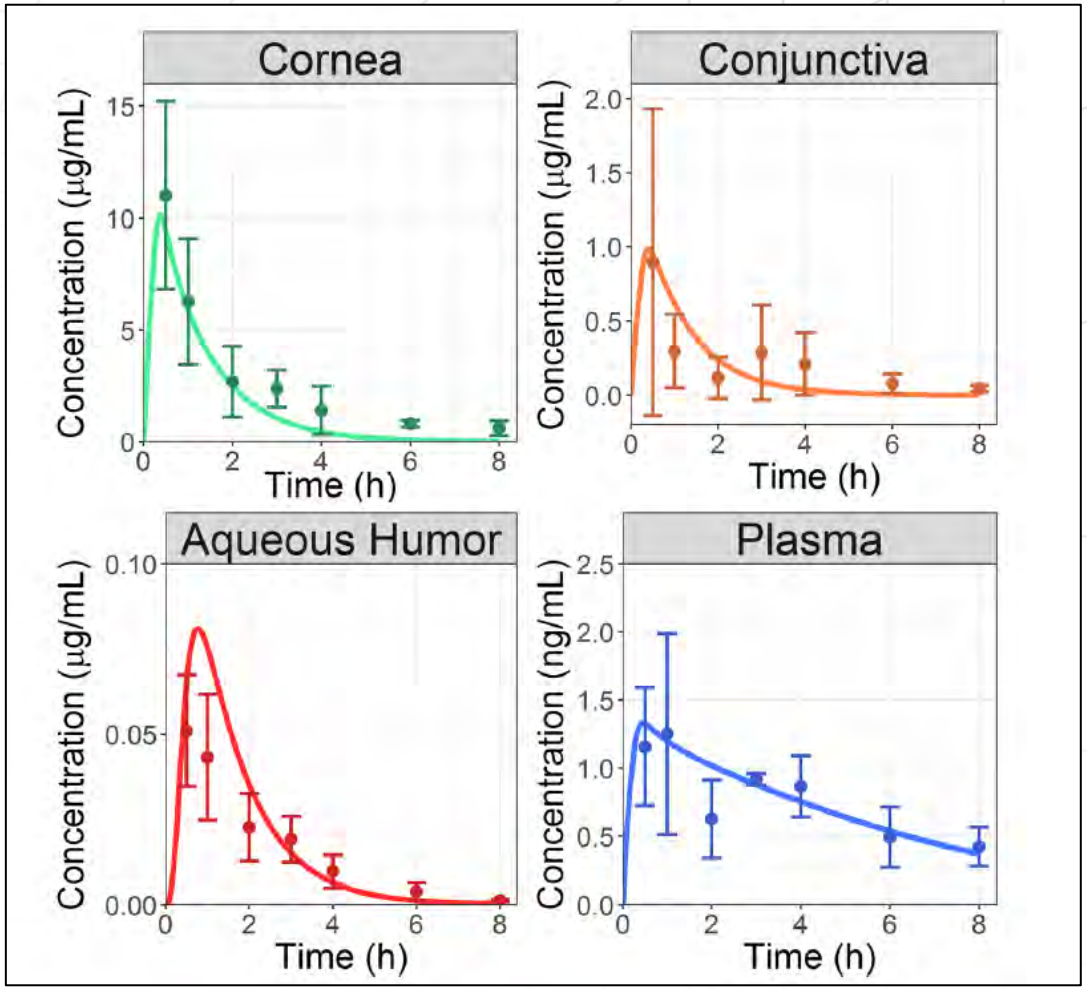
- Dexamethasone is a lipophilic glucocorticoid used to treat local eye pain following ocular surgery

- The OCAT model was used to characterize ophthalmic suspensions and explore the relationship between formulation characteristics and physiological clearance in the rabbit eye



Building and Validating the OCAT Model

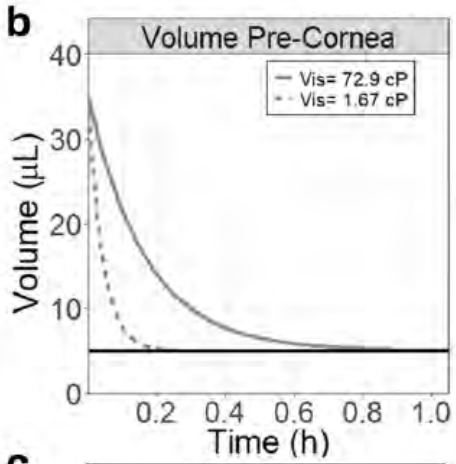
- The FDA measured concentration-time profiles of dexamethasone in cornea, conjunctiva, aqueous humor, and plasma following 30 uL of TOBRADEX ST ® 0.05% in the rabbit eye
- Formulation parameters of TOBRADEX ST® were used
- The data was used to fit permeabilities of conjunctiva, aqueous humor, and ICB permeability; other values were taken from literature or predicted from the compound structure



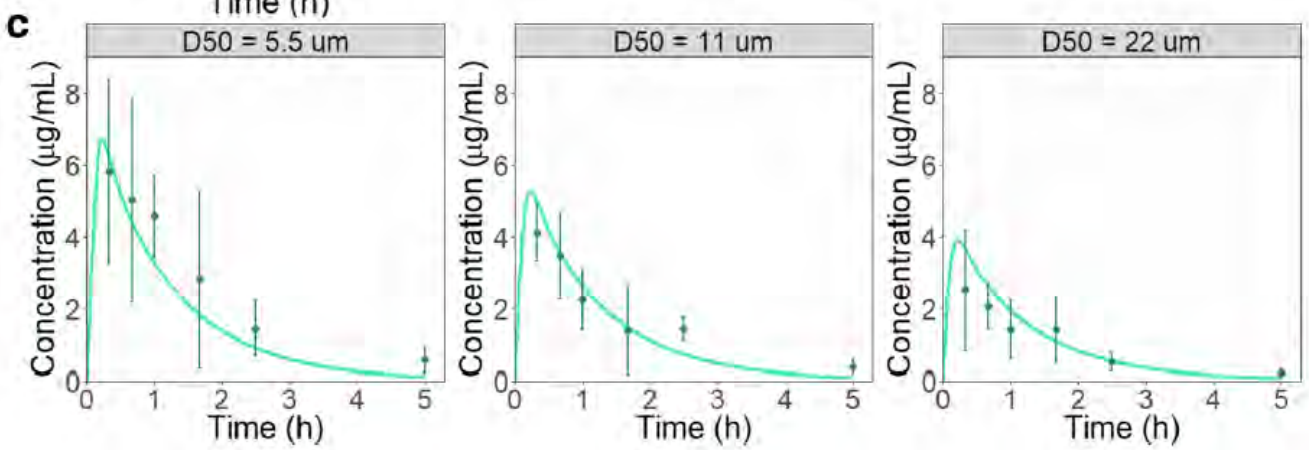
Le Merdy et al, *AAPS J*, 2019

Modeling Effects of Viscosity and Particle Size

- The model was further verified by modeling additional dexamethasone formulations applied to the rabbit eye with different strengths, viscosity, and particle size
- Changes in viscosity were modeled by adjusting the drainage rate from the pre-corneal film
- The model was able to predict the effect of viscosity on aqueous humor Cmax and AUC, and the effect of particle density on cornea concentration-time profile



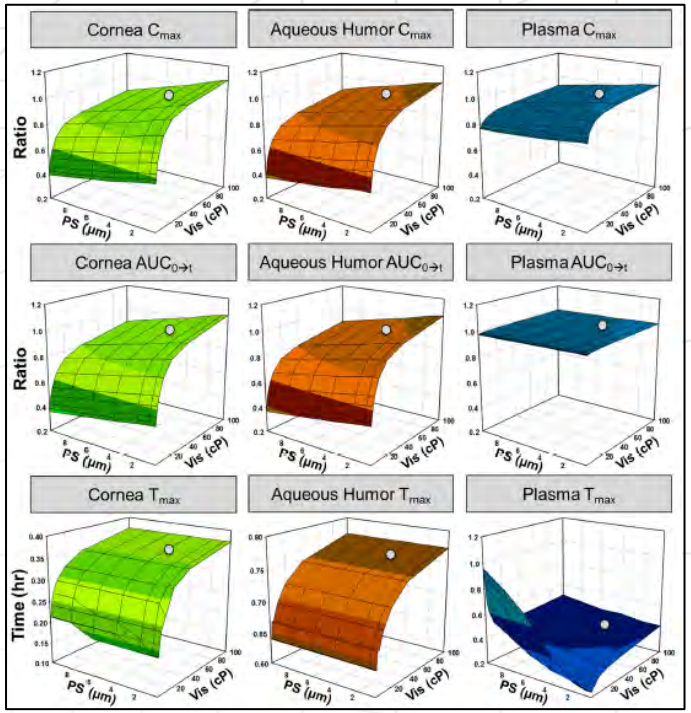
	C_{max} (µg/mL)		$AUC_{0\to3}$ (µg.h/mL)	
	Observed	Simulated	Observed	Simulated
TOBRADEX ST© 0.05%	0.106 ± 0.019	0.081	0.191 ± 0.01	0.13
TOBRADEX© 0.1%	0.069 ± 0.022	0.06	0.118± 0.006	0.095



Le Merdy et al, *AAPS J*, 2019

Parameter Sensitivity Analysis

- Parameter sensitivity analysis was performed to explore the effects of changes in particle size and viscosity in the cornea, aqueous humor, and plasma
- Analysis showed high sensitivity to formulation viscosity, but lower sensitivity to particle size
- Hypothetical formulations were developed with similar mean particle diameter and D10, but different D90 values
  - Simulation results showed little difference in aqueous humor C_{max} and AUC, suggesting this range of variation is acceptable for an ophthalmic formulation



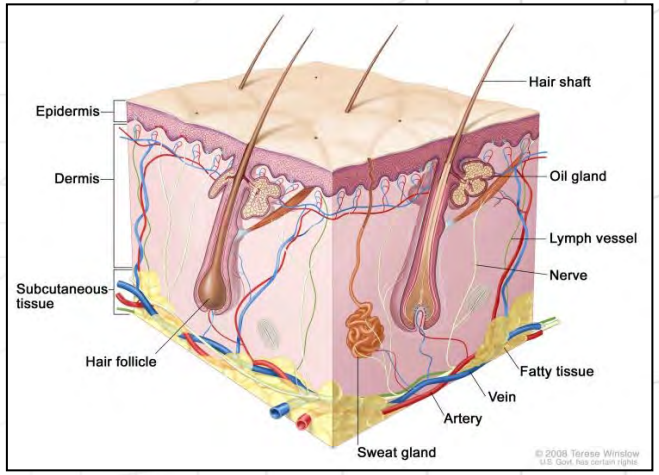
Formulations	D90	Aqueous humor T/R C_{max}	Aqueous humor T/R AUC
R	7.76	1.00	1.00
T1	8.76	1.01	1.01
T2	9.76	1.01	1.02
T3	10.8	1.03	1.02
T4	12.8	1.04	1.04
T5	14.8	1.05	1.05
T6	16.8	1.07	1.06

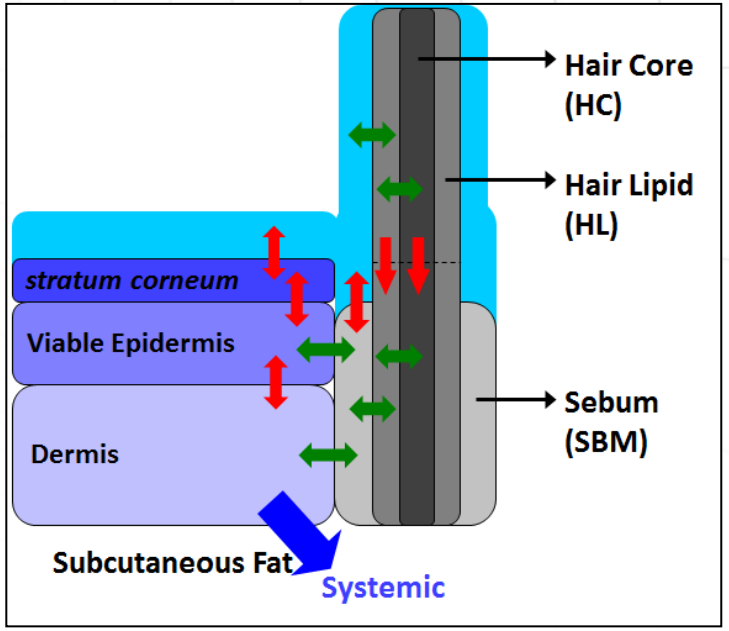
Le Merdy et al, *AAPS J*, 2019

Dermal Delivery

The Skin and the TCAT™ Model

- The Transdermal Compartmental Absorption and Transit™ (TCAT) Model is a physiologically-based mathematical model in GastroPlus™ that simulates the dermal and systemic ADME-PK of topically applied compounds
  - The TCAT Module comprises well-mixed compartments and material exchange pathways
  - Effects of formulation attributes such as solubility and diffusivity can be incorporated to understand and predict absorption
  - Skin permeation can be linked to systemic PBPK models via blood and lymph perfusion





Transdermal Compartmental Absorption and Transit (TCAT™)

Human physiology defined by region & scaled by age:

- Arm
- Leg
- Abdomen
- Back
- Face
- Scalp
- In Vitro Abdomen

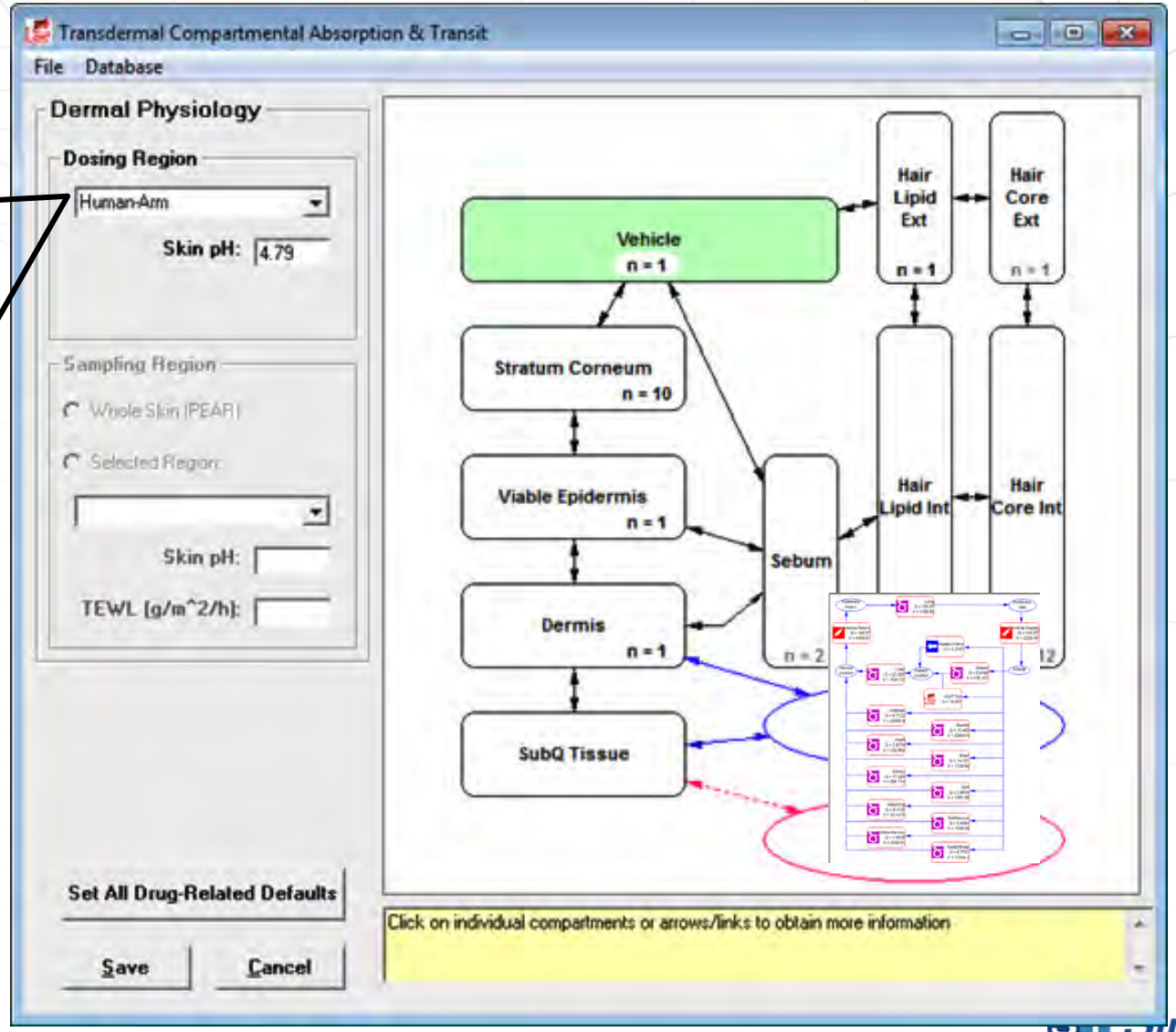
Minipig

- Ear
- Snout
- Neck
- Back
- Flank
- Abdomen

Rat

Mouse

Ability to create custom physiology

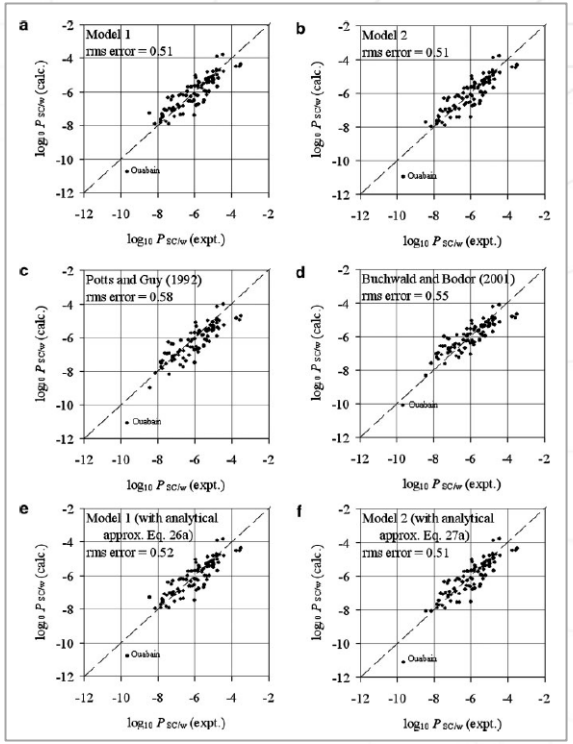


Transdermal Dosage Forms

Dosage form	Description
TD: Liq Soln	Homogeneous solution of API in a liquid solvent
TD: Liq Susp	Suspension of solid API particles in a liquid solvent
TD: Ointment/Paste	Suspension with <50% water/volatiles and >20% dispersed solid
TD: Lotion/Gel	Emulsion with both dispersed and continuous phase in liquid state
TD: Cream	Emulsion with > 20% water/volatiles and < 50% dispersed solid
TD: Reservoir Patch	API solution in a reservoir compartment

Estimating Permeability in Skin

- Equations to estimate drug partitioning between layers and drug diffusivity in each layer are included:
  - Stratum Corneum
    - Wang-Kasting-Nitsche (WKN) [2007]
    - Potts-Guy [1992]
    - Robinson [Wilschut et al, 1995]
  - Viable Epidermis and Dermis
    - Krestos [2008]
    - Bunge-Cleek [1995]
    - Robinson [Wilschut et al, 1995]
  - Sebum
    - Equations derived from Yang & Lian, 2018, 2019
    - Equation derived from Valiveti et al, 2008, 2009



Prediction of permeability through fully hydrated *stratum corneum*

J Pharm Sci. 2007 Nov;96(11):3024-51. **A multiphase microscopic diffusion model for stratum corneum permeability. II. Estimation of physicochemical parameters, and application to a large permeability database.** Wang TF[1], Kasting GB, Nitsche JM

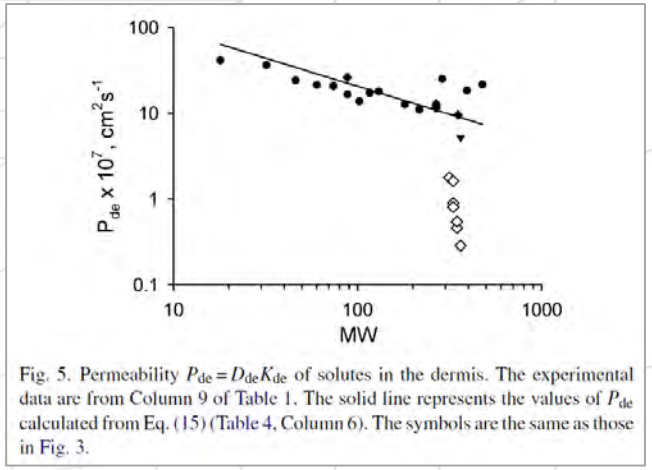


Fig. 5. Permeability $P_{de} = D_{de}K_{de}$ of solutes in the dermis. The experimental data are from Column 9 of Table 1. The solid line represents the values of P_{de} calculated from Eq. (15) (Table 4, Column 6). The symbols are the same as those in Fig. 3.

Prediction of dermis/buffer partition coefficient and diffusivity through dermis

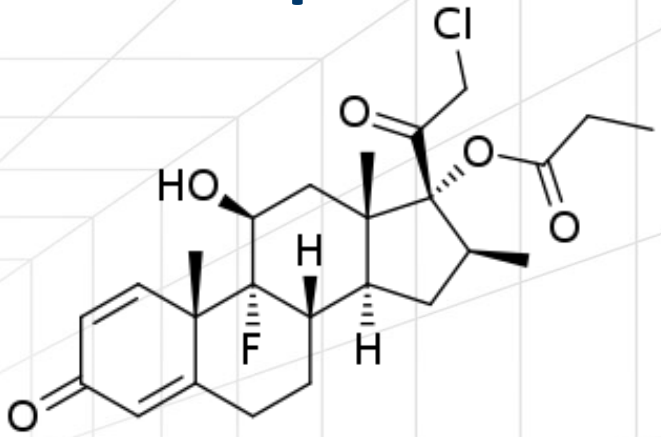
Int J Pharm. 2008 Jan 4;346(1-2):64-79. **Partitioning, diffusivity and clearance of skin permeants in mammalian dermis.** Kretsos K, Miller MA, Zamora-Estrada G, Kasting GB

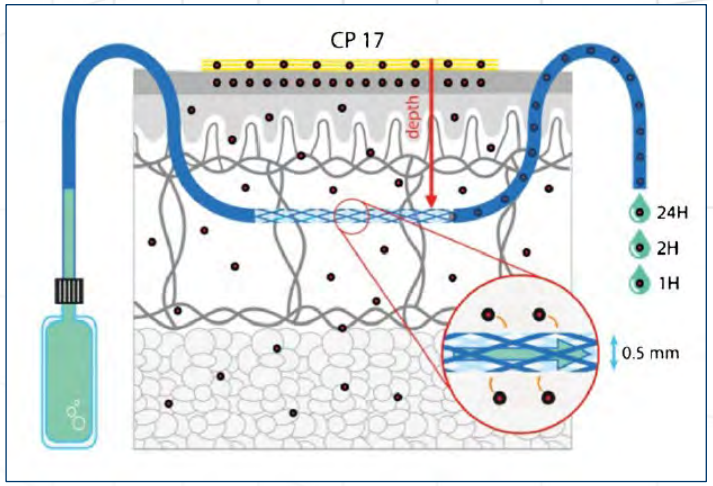
Cooperation Grant with the FDA Office of Generic Drugs (2021-2023)

2-year funded collaborative project with the FDA Office of Generic Drugs to improve the TCAT model by enhancing modeling of formulation mechanisms and skin physiology

Clobetasol-17 Propionate and Dermal Open-Flow Microperfusion

- Clobetasol-17 propionate (CP) is a highly potent glucocorticoid used topically to treat inflammatory skin conditions such as psoriasis
- When applied in formulations such as an oil-in-water microemulsion (O/W ME), dispersed phase droplets can act as a reservoir for CP to maintain its concentration in the aqueous continuous phase
- We developed a model for CP formulated as an O/W ME (Dermovate Cream®) and used it to explore the role of formulation attributes in CP skin permeation
- Bodenlenz, 2017 reported dermis concentrations of CP that were measured continuously via open-flow micro-perfusion (dOFM) over 24 hours
  - Geometric mean dOFM probe skin depth ~ 860 μm (95% CI ± 90 μm; range 535 - 1136 μm)





FDA OGD, Grants 1 U01 FD006526-01 & FD007320-01

The views expressed here do not reflect official policies of the US FDA or DHHS, nor does any mention of trade names imply endorsement by the US Government

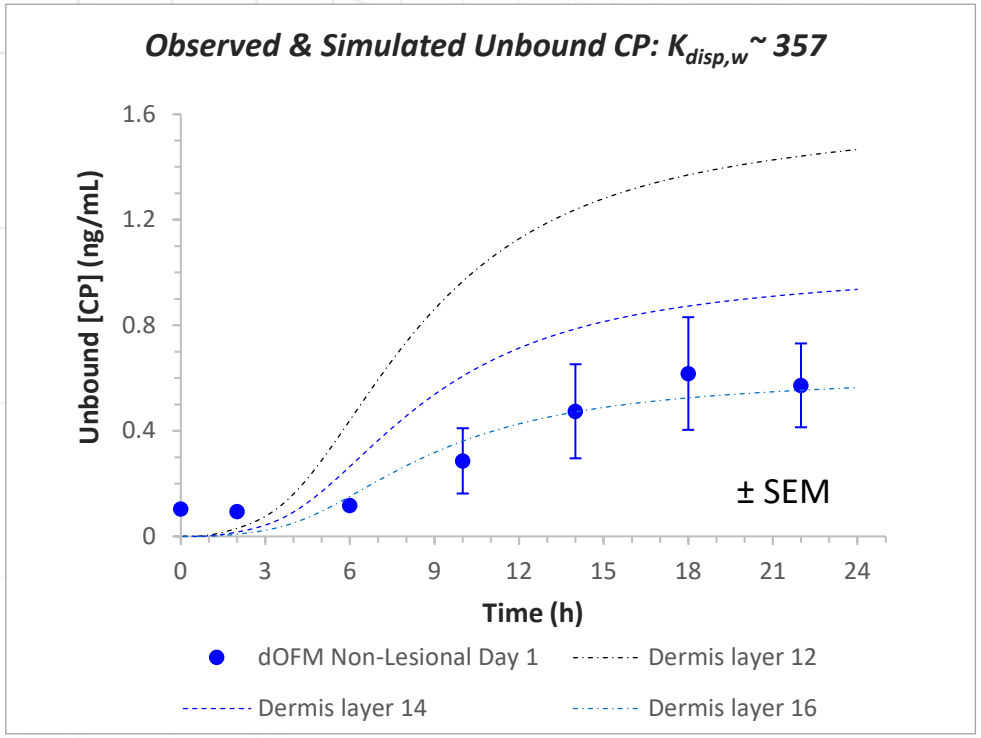
https://pubchem.ncbi.nlm.nih.gov/compound/32798

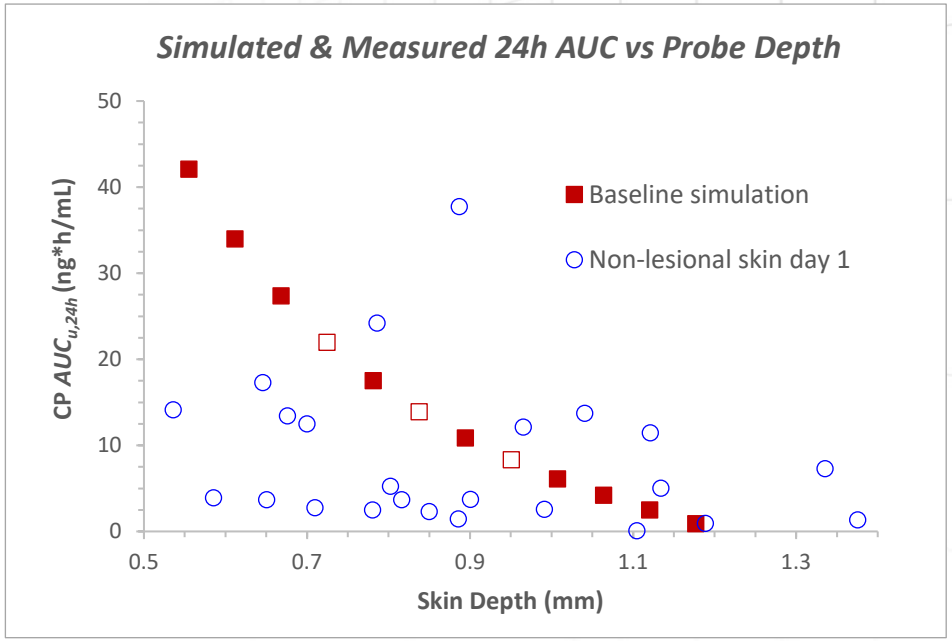
https://www.accessdata.fda.gov/drugsatfda_docs/label/2003/019322s018lbl.pdf

Bodenlenz, M, et al. *Pharm Res.* 33 (9); 2229–38, 2016

Validating the Baseline CP Model

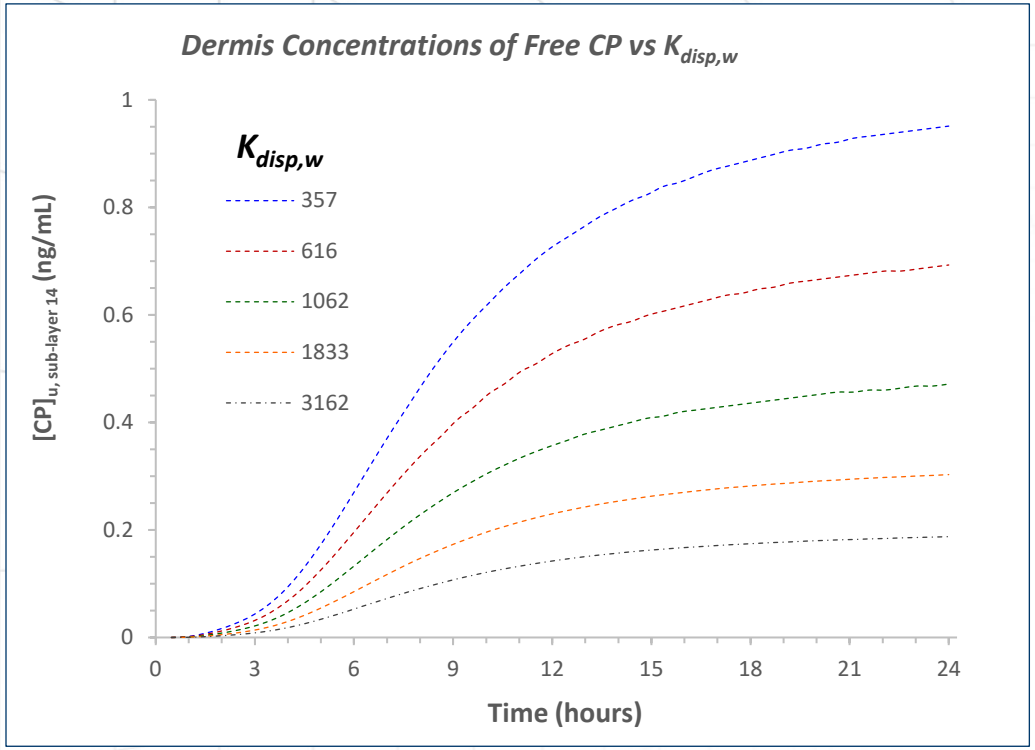
- Simulated concentrations of free CP in dermis at mean probe depth were within ~ 2-fold of the group average dOFM values and tracked the initial rise in mean dermis concentrations
- Simulated values of dermis CP $AUC_{0\text{-}24h}$ passed through the upper range of the observed values at each probe depth

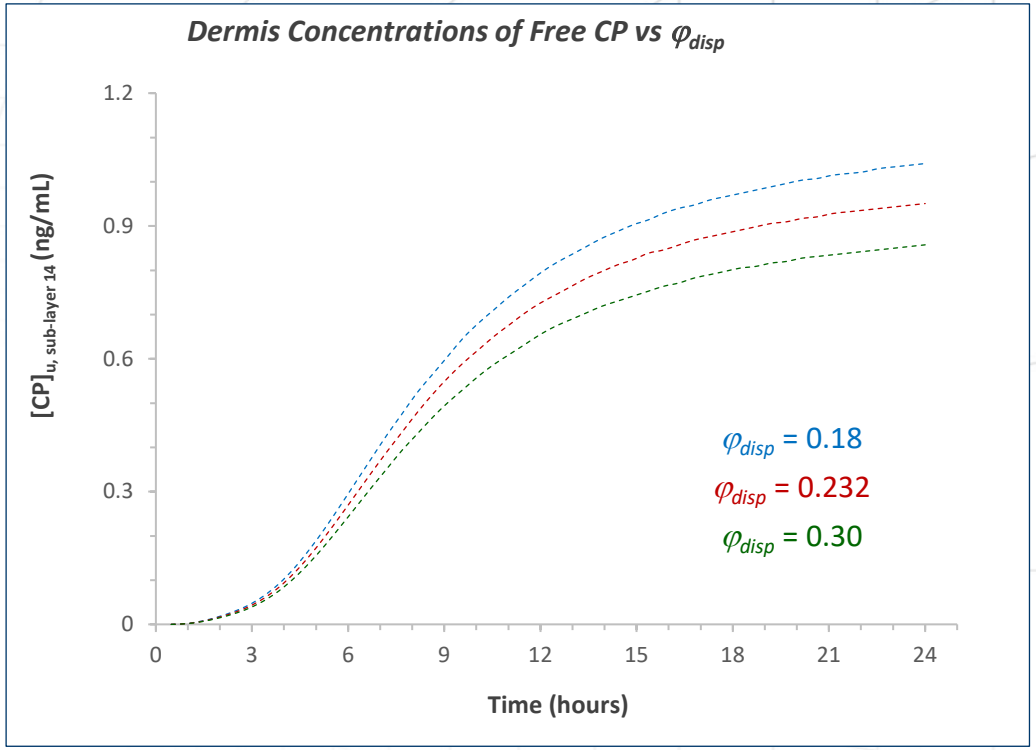




van Osdol, MIDD+, 2022

Exploring Sensitivity to Formulation Parameters



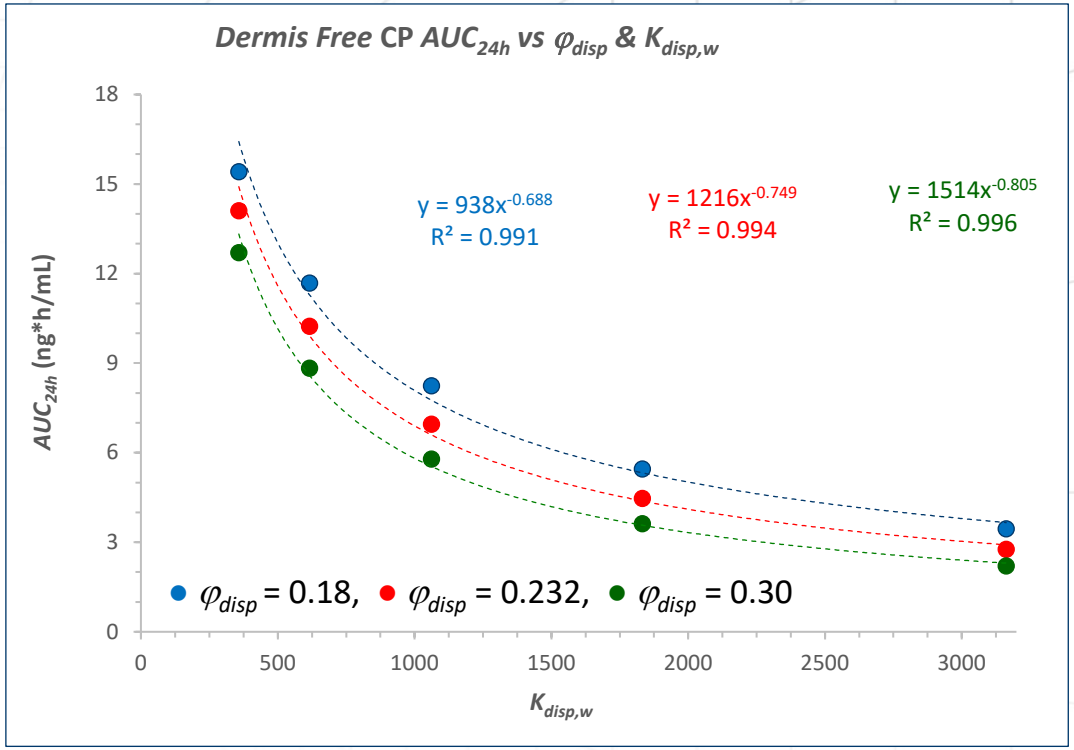


- We explored the effect of CP oil phase solubility (through the dispersed phase-water partition coefficient, $K_{disp,w}$) and volume fraction (φ_{disp}) separately
- As $K_{disp,w}$ increases, more CP partitions into the dispersed phase, lowering CP concentrations in the continuous phase, thus reducing the driving force for CP partitioning into stratum corneum (SC)
- Through a similar process, increases in φ_{disp} decrease partitioning into SC and concentration in the dermis, though the effect is less pronounced

van Osdol, MIDD+, 2022

Factorial Experimental Design: Simulation of $\varphi_{disp} \otimes K_{disp,w}$

- The combined effects of φ_{disp} and $K_{disp,w}$ on CP skin permeation can be quantified via a coupled (3D) PSA
- The simulation results allowed us to derive a response surface for the effects on AUC_{24h} and support predictions at interpolated values of (φ_{disp}, $K_{disp,w}$)
- c_1-c_4 are constants, and the adjusted $r^2 \sim 0.98$
- The response surface is non-linear in both parameters, and sensitivity to (φ_{disp}, $K_{disp,w}$) depends on their values

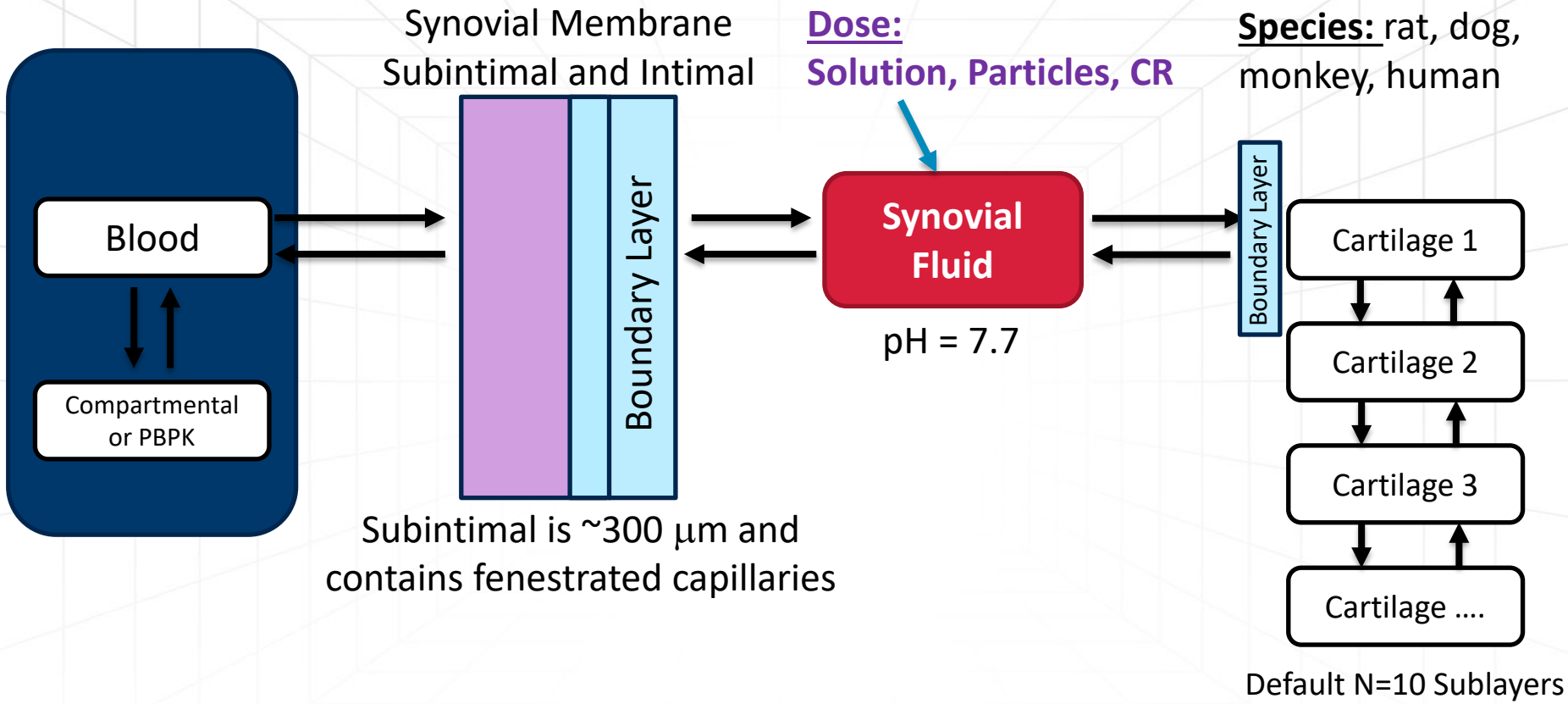


$$AUC_{24h}(\varphi_{disp}, K_{disp,w}) \sim (c_1\varphi_{disp} + c_2)K_{disp,w}^{-(c_3\varphi_{disp}+c_4)}$$

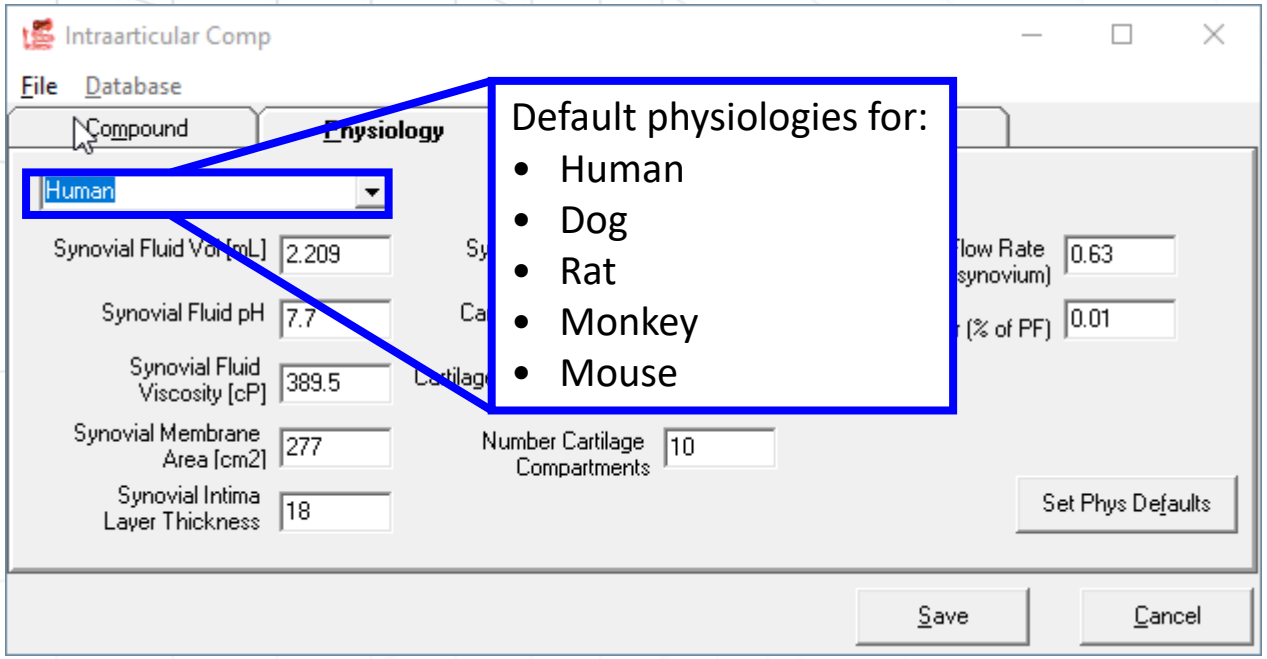
van Osdol, MIDD+, 2022

Intra-Articular Delivery

Intra-Articular Injections and the ICAT™ Model (version 1)

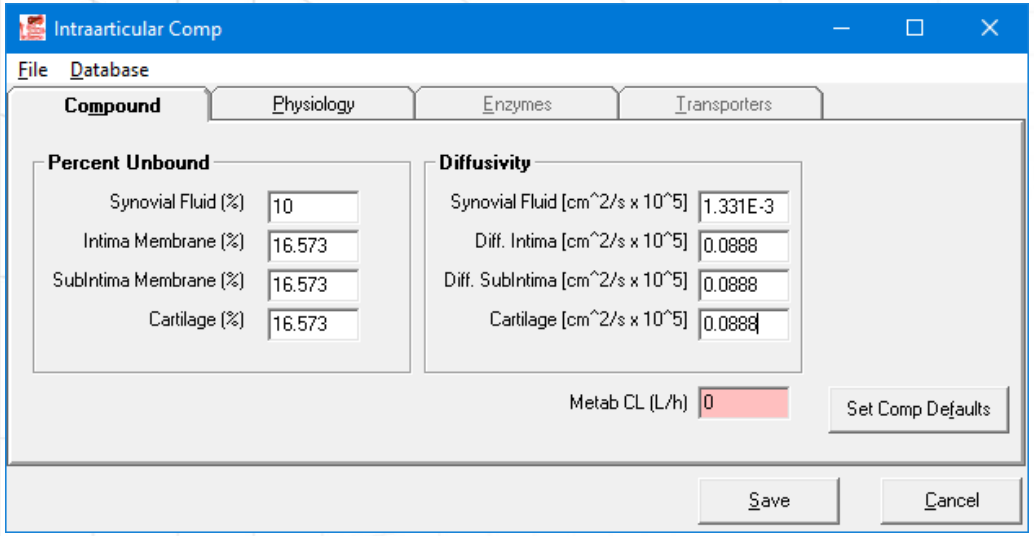


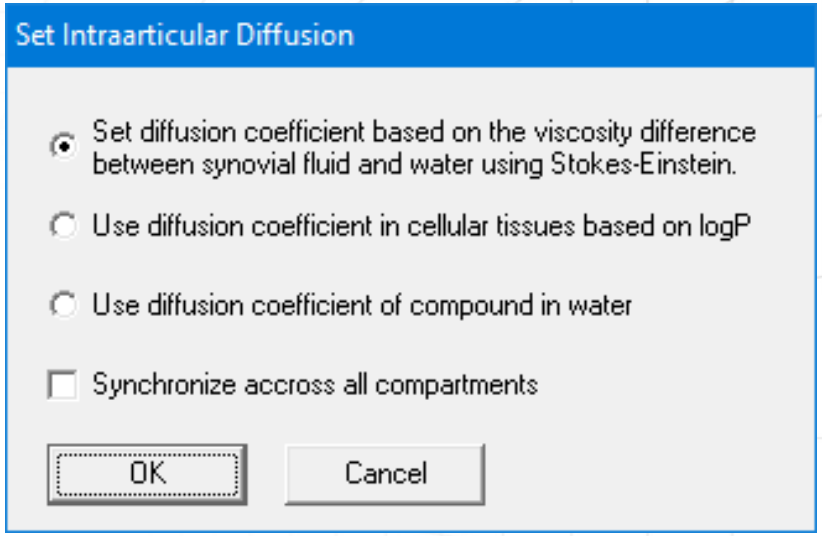
Intra-Articular Compartmental Absorption and Transit (ICAT™)



Dosage form	Description
IA: Solution	Solution injection
IA: Suspension	Suspension injection
IA: Cont Rel	Controlled release injection – dissolved drug released from formulation

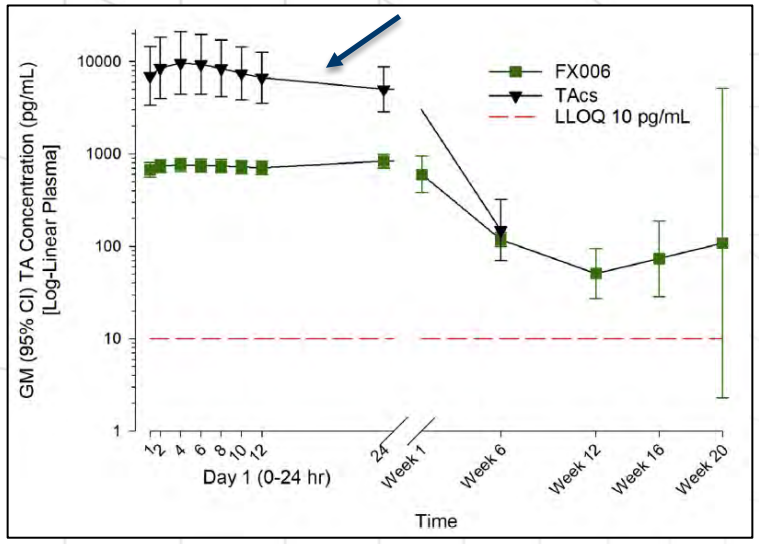
Compound Specific Input Parameters



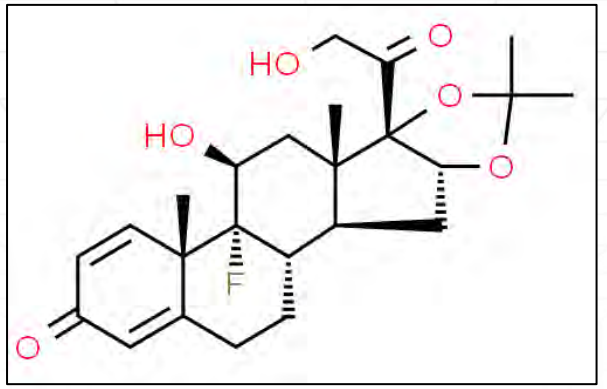


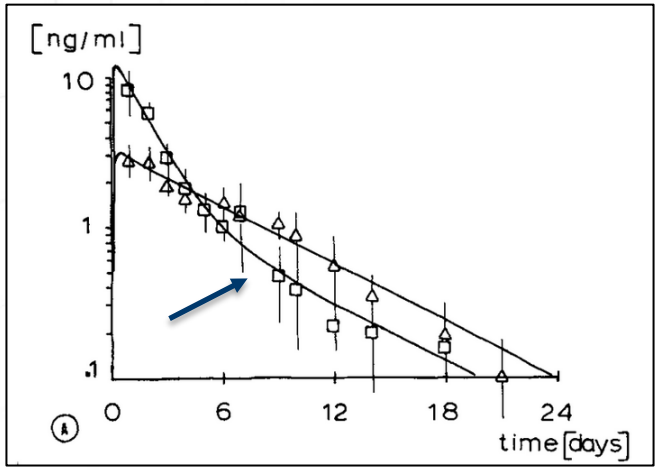
- Diffusion can be estimated in three different ways:
  - Stokes Einstein equation
  - Diffusion estimation in cellular tissues based on LogP (from Oral Cavity model)
  - Use diffusion coefficient in water

Triamcinolone Acetonide (TCA)



Krauss, Osteo Cart, 2018



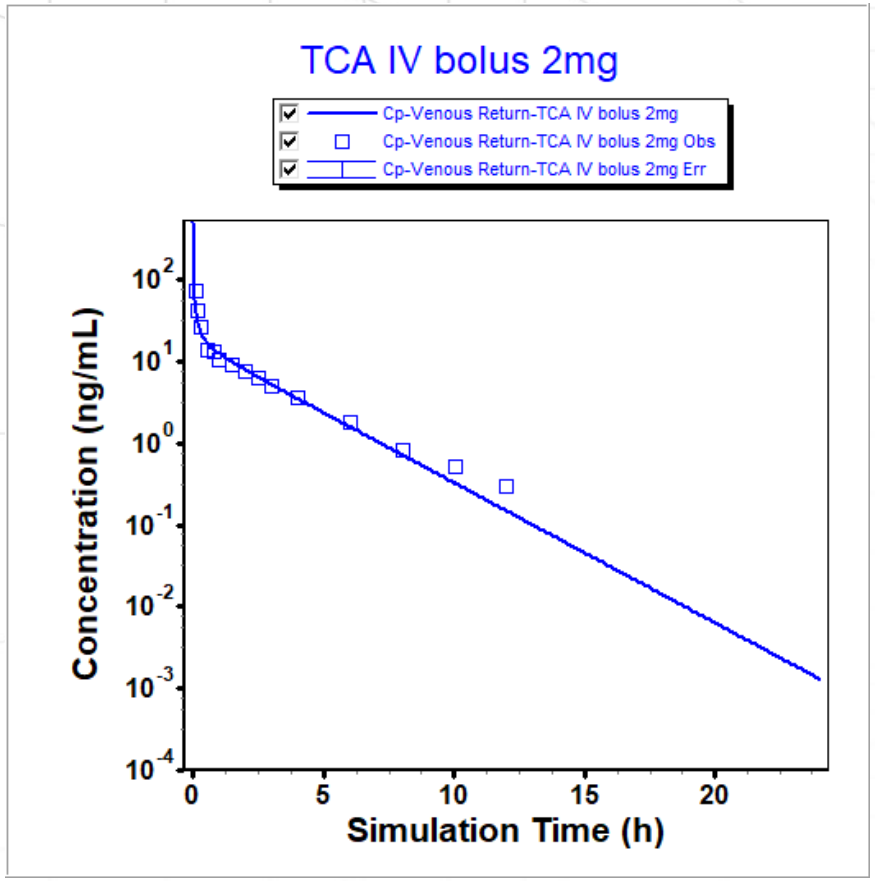


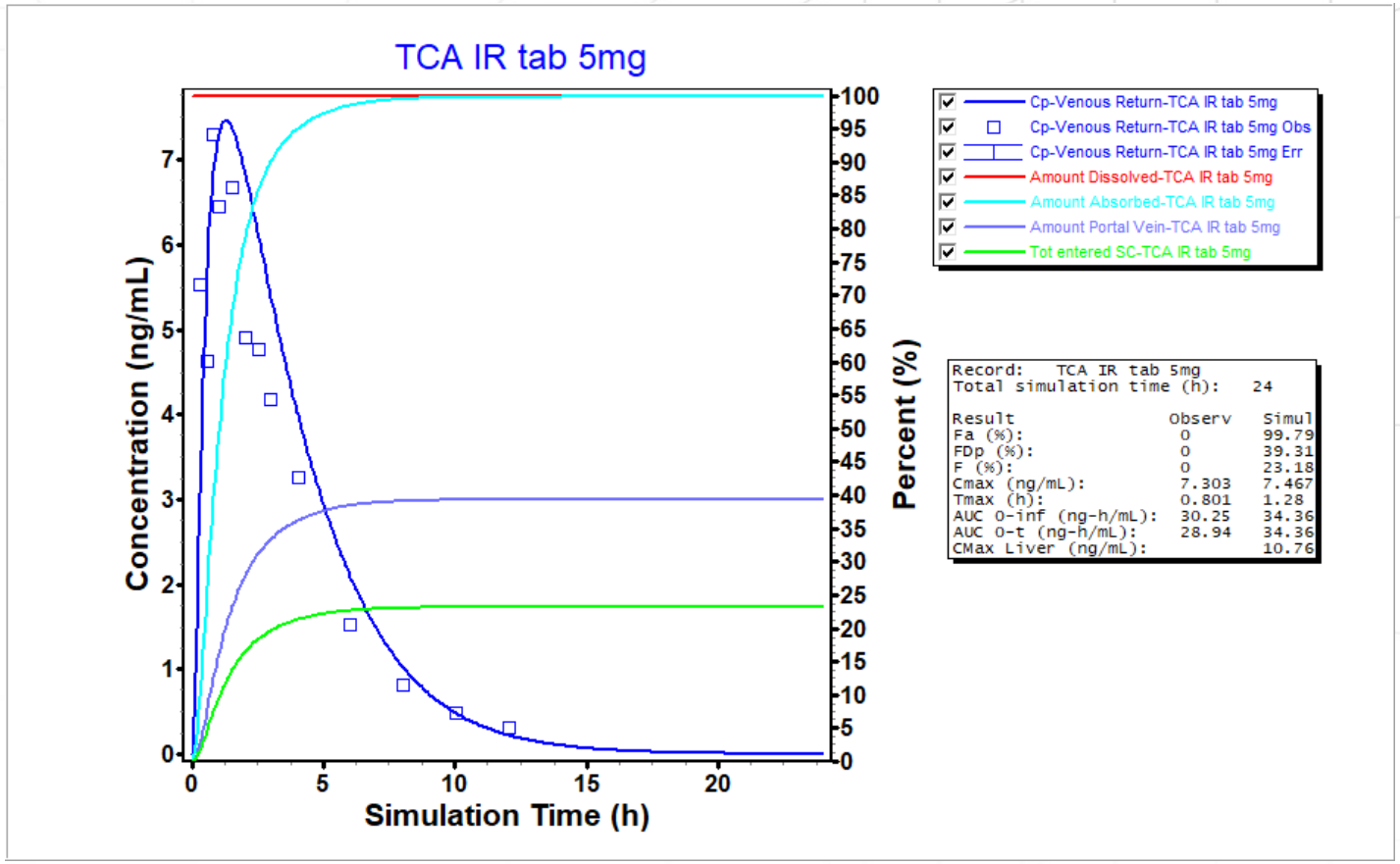
Derendorf, Clin Pharmacol Ther, 1986

- TCA is a corticosteroid injected intra-articularly to treat joint problems such as pain due to osteoarthritis
- To model TCA IA suspension injections, we pool data from two injections:
  - 0-24h: Krauss 2018 (Kenalog 40)
  - 24+h: Derendorf (Volon A)

AP refers to ADMET Predictor module version 9.0

PBPK Model of TCA

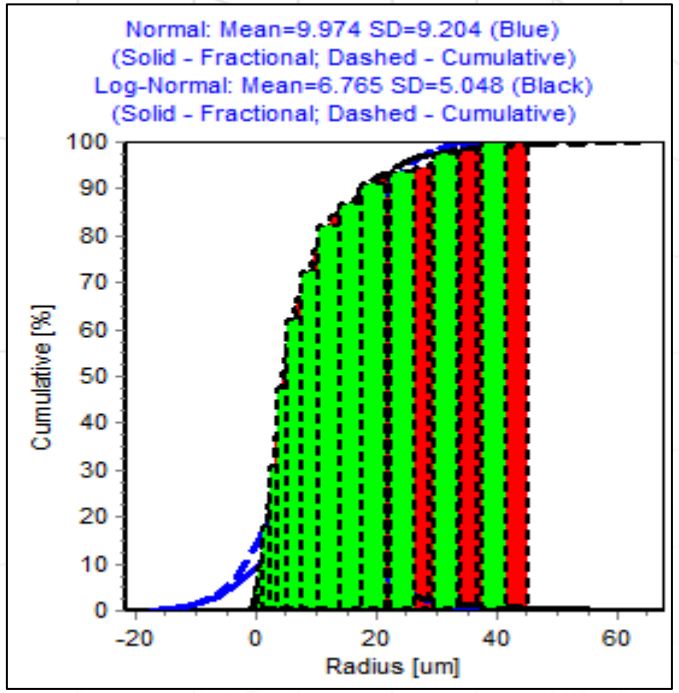




Derendorf, J Clin Pharm, 1995

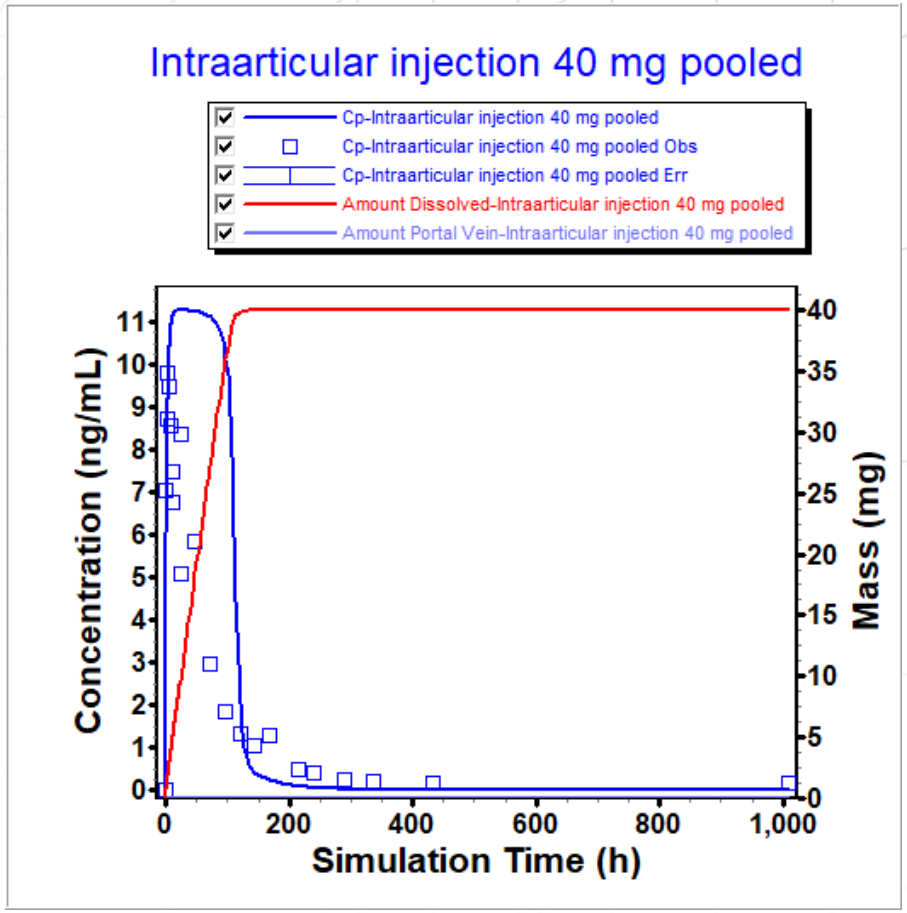
Initial Intra-articular Model: 40 mg IA Suspension

Particle size from Kenalog Injection



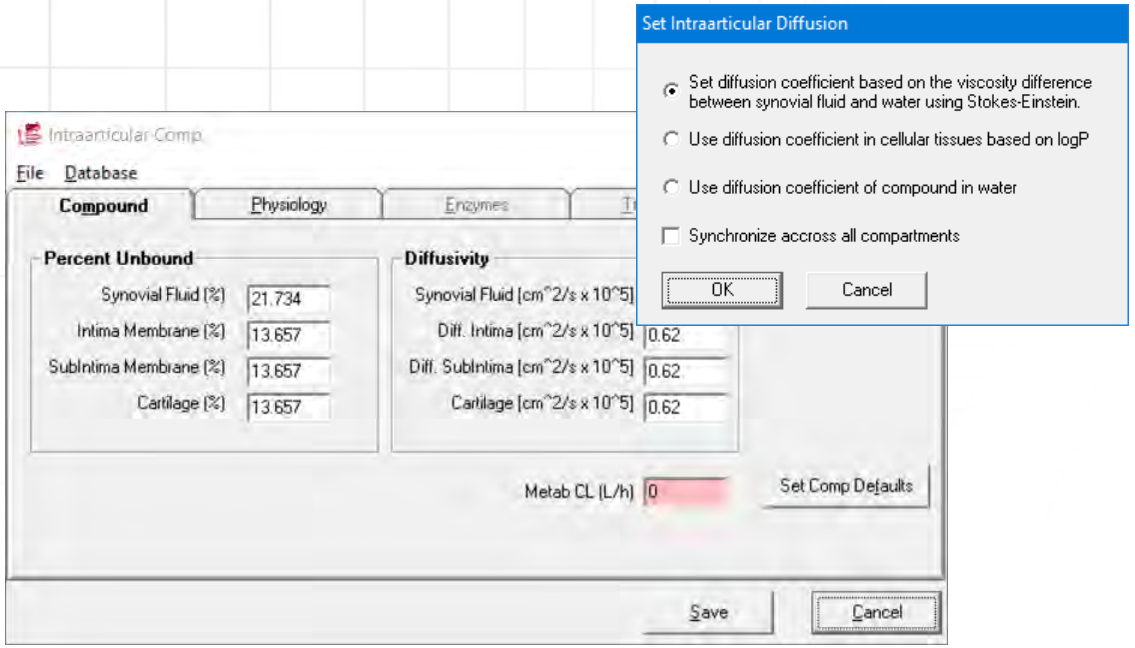
Dodwell, Clinical Ophthal, 2015.

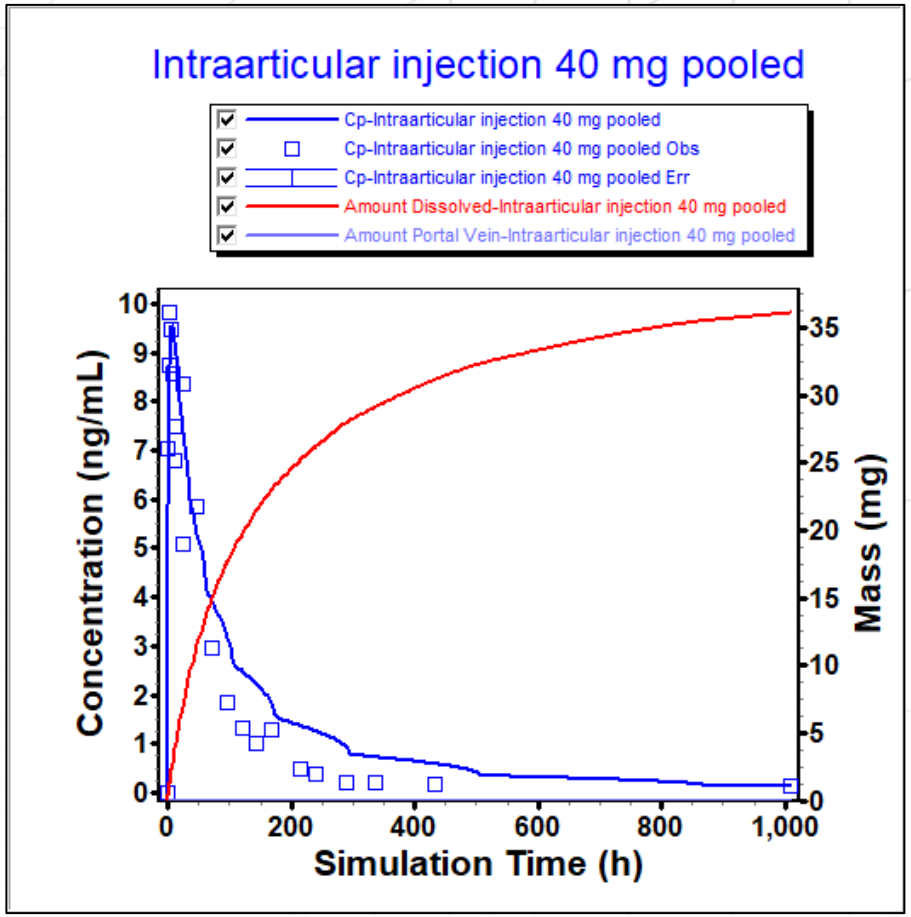
- Particle size of Kenalog injection used as the first 24 hr of the pooled data is from Kenalog product
- Diffusivity in water assumed for synovium
- Diffusion in tissue predicted from LogP based on diffusion in oral cavity epithelial tissue
- Dissolution is about the correct rate initially but synovial fluid becomes saturated and thus the profile becomes constant.



Adjustment based on formulation viscosity

- Assume Stokes-Einstein viscosity correction for diffusion coefficient in synovial fluid
- Diffusivity of water assumed for other tissues
- Measured particle size





Fate of Injection Particles in Solution

- Commercial TCA injections may agglomerate over time when sitting in saline even if diluted. When injected will these particles settle and agglomerate?
- Larger particles increased ~2X in number but that represents a large amount of mass.

Table 1. Particle Size Distribution of the Undiluted and Diluted Steroids

Preparation	Dilution	Diluent	No. of particles	Particle Distribution 0–20 μm	21–50 μm	51–1,000 μm	>1000 μm	*P* Value
Methylprednisolone acetate 80 mg/ml (MPA 80)	Undiluted		66	63	14	17	6	*
	1:1	Saline	164	73	11	12	4	0.03
	1:2	Saline	142	58	8	26	8	
	1:3	Saline	174	52	9	32	7	
	1:1	Lidocaine 1%	214	52	17	24	7	0.17
	1:2	Lidocaine 1%	226	63	11	22	4	
	1:3	Lidocaine 1%	224	55	15	28	2	
Methylprednisolone acetate 40 mg/ml (MPA 40)	Undiluted		298	64	8	27	1	*
	1:1	Saline	492	63	9	25	3	0.37
	1:2	Saline	415	67	15	16	2	
	1:3	Saline	281	67	15	17	1	
	1:1	Lidocaine 1%	311	51	20	28	1	0.28
	1:2	Lidocaine 1%	278	62	18	18	2	
	1:3	Lidocaine 1%	281	55	20	24	1	
Triamcinolone acetonide 40 mg/ml (TRA 40)	Undiluted		476	79	9	11	1	*
	1:1	Saline	324	66	10	23	1	0.15
	1:2	Saline	340	72	10	17	1	
	1:3	Saline	241	58	18	23	1	
	1:1	Lidocaine 1%	585	64	14	21	1	0.29
	1:2	Lidocaine 1%	580	63	14	23	0	
	1:3	Lidocaine 1%	376	68	15	17	0	
CLTN Betamethasone sodium phosphate/betamethasone acetate 6 mg/ml (Celestone Soluspan®)	Undiluted		1968	92	6	2	0	*
	1:1	Saline	519	93	5	2	0	0.29
	1:2	Saline	560	95	4	1	0	
	1:3	Saline	257	85	12	3	0	
	1:1	Lidocaine 1%	405	93	6	1	0	0.27
	1:2	Lidocaine 1%	588	91	8	1	0	
	1:3	Lidocaine 1%	270	83	15	2	0	
Betamethasone sodium phosphate/ betamethasone acetate 6 mg/ml (BTM Rep)	Undiluted		844	68	10	21	1	*
	1:1	Saline	517	82	8	10	0	0.12
	1:2	Saline	699	86	6	8	0	
	1:3	Saline	325	79	9	12	0	
	1:1	Lidocaine 1%	185	51	16	32	1	0.005
	1:2	Lidocaine 1%	108	51	20	29	0	
	1:3	Lidocaine 1%	217	76	11	13	0	

Both CLTN (Celestone Soluspan® [Schering-Plough, Kenilworth, NJ] [betamethasone sodium phosphate/betamethasone acetate, commercial betamethasone]) and BTM Rep (betamethasone repository [betamethasone sodium phosphate/betamethasone acetate, compounded betamethasone]) contain 3 mg/ml betamethasone sodium phosphate and 3 mg/ml betamethasone acetate. Dexamethasone and betamethasone sodium phosphate are liquid with no identifiable particles. Increased dilution of MPA 80 with saline increased the proportion of larger particles. Increased dilution of the BTM Rep with lidocaine decreased the particles.

(80 mg/ml methylprednisolone acetate), MPA 40 (40 mg/ml methylprednisolone acetate), and BTM Rep differ from CLTN, $P < 0.05$.

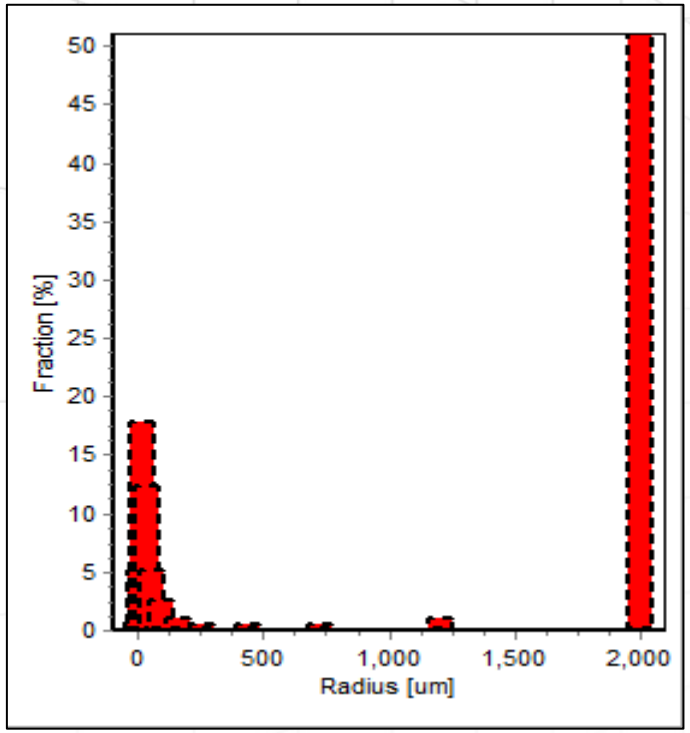
triamcinolone acetonide.

Triamcinolone acetonide 40 mg/ml (TRA 40)	Undiluted		476	79	9	11	1	*
	1:1	Saline	324	66	10	23	1	0.15
	1:2	Saline	340	72	10	17	1	
	1:3	Saline	241	58	18	23	1	
	1:1	Lidocaine 1%	585	64	14	21	1	0.29
	1:2	Lidocaine 1%	580	63	14	23	0	
	1:3	Lidocaine 1%	376	68	15	17	0	

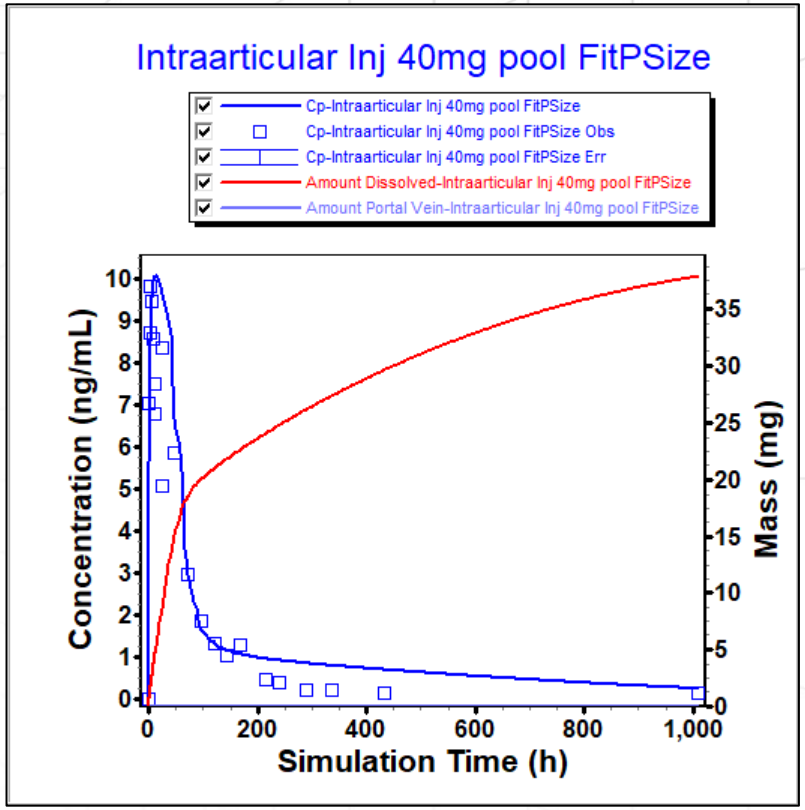
Benzon Anesthesiology 2007

IA 40 mg – Adjustment based on agglomoration

Particle size from Kenalog Injection



- Perhaps this is a little unrealistic
- Doesn't quite describe the curve as well as changing diffusion coefficient



Dodwell, Clinical Ophthal, 2015.

Distinguishing Potential IA Suspension Mechanisms

- The prediction of TCA was close in terms of Cmax but it seems either:
  - The dissolution is slower due to viscosity of synovial fluid
  - Agglomeration of particles

- Can other compounds prove one mechanism over the other?

PBBM/PBPK Modeling to Support Generic Drug Development

- PBBM/PBPK modeling can be used to build and validate models of locally acting drug products across a wide range of routes of administration
- PBBM/PBPK models of locally acting drug products are able to simulate and predict the effects of formulation attributes when those attributes are well understood
- Models of locally acting drug products can be used to identify key formulation attributes that are critical to determining local absorption
- These models can be used to predict effects of hypothetical formulation changes on local and systemic PK

SimulationsPlus

Cognigen | DILIsym Services | Lixoft

Thank You!