Application of Modeling and Simulation in Long Acting Injectable Product Development

October 18, 2022

Viera Lukacova

SimulationsPlus

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Session Description and Objectives

Description

- Discuss advances in mechanistic models to simulate *in vitro* and *in vivo* behavior of long acting injectables

Objectives:

- Identify processes that impact the drug release from PLGA particles
- Identify processes that impact the *in vivo* drug dissolution from long acting injectable crystalline suspensions
- Define areas for further development to increase the predictability of PBPK models

Biography and Contact Information

- **Viera Lukacova,** Chief Scientist – Lancaster Division, Simulations Plus
  viera@simulations-plus.com

- Ph.D. in Pharmaceutical Sciences
- 17+ years of experience in mechanistic absorption and PBPK modeling
- Development of GastroPlus®, DDDPlus™, MembranePlus™
- Application of mechanistic absorption and PBPK models throughout the drug development process
  - Mechanistic models for simulation of *in vitro* and *in vivo* studies with long acting injectables

Outline

- Mechanistic *in vitro* model for PLGA microspheres
  - Drug dissolution and diffusion
  - Polymer degradation
  - Intraparticle drug distribution

- Mechanistic *in vivo* model for crystalline suspensions
  - Particle aggregation
  - Drug diffusion limitation
  - Injection depot dynamics

Funding Support Provided in part by US FDA (grants 1U01FD005463 and contract 75F40121C00133) and a large pharmaceutical company

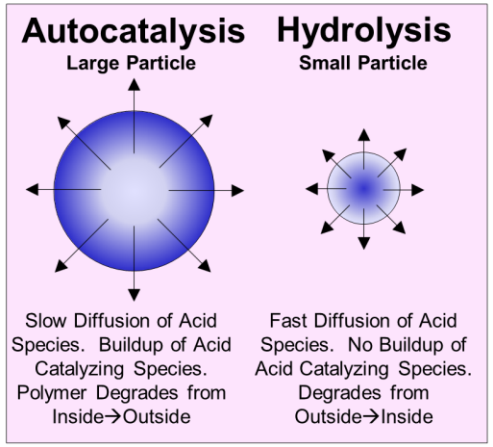
In Vitro Dissolution: Model Extension

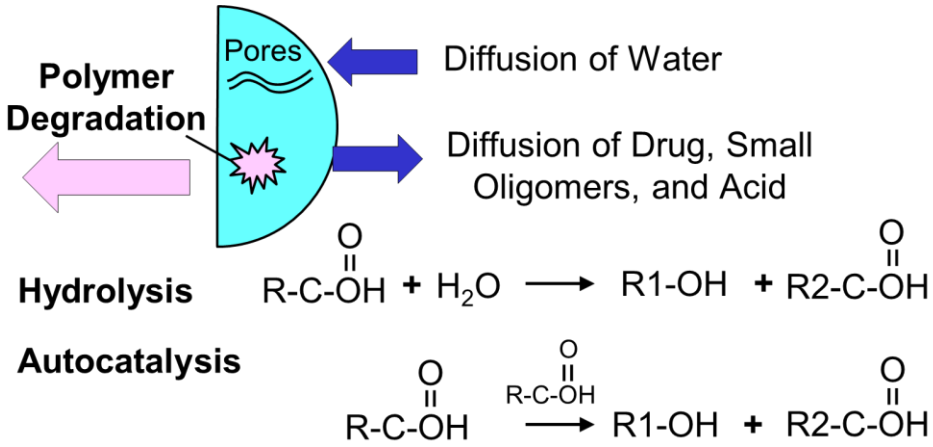
Model was based on previously published model (Rothstein 2009). The complete model includes:

- Diffusion of water and drug
- Dissolution of drug from polymer matrix
- Degradation of polymer microsphere
- Drug Diffusion coefficient is function of polymer molecular weight

New mechanisms:

- Autocatalytic degradation
- pH-dependent solubility of API within the particle
- Water diffusion and reaction





$$\frac{\partial C_i}{\partial t} = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 D(r)\frac{\partial C_i}{\partial r}\right) + R_i$$

$$\frac{\partial C_{ND}}{\partial t} = -k_{diss}\left(S - C_D\right)\left(\frac{C_{ND}}{C_{ND,o}}\right)$$

$$\frac{\partial C_D}{\partial t} = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 D(r)\frac{\partial C_D}{\partial r}\right) + k_{diss}\left(S - C_D\right)\left(\frac{C_{ND}}{C_{ND,o}}\right)$$

$$D(r,t) = D_o \times e^{-A\times\left(\frac{MW(r,t)}{MW_{ref}}-1\right)}$$

Where i = Drug, Small Oligomer, Water, and Free Acid

C_D	Concentration of free drug in matrix
C_{ND}	Concentration of undissolved drug in matrix
R	Rate of degradation
S	Solubility
$D(r,t)$	Diffusion coefficient – radial/time dependent
D_o, A	Initial diffusion coefficient and exponential diffusion constant
$MW(r,t), MW_{ref}$	Molecular weight in particle and reference

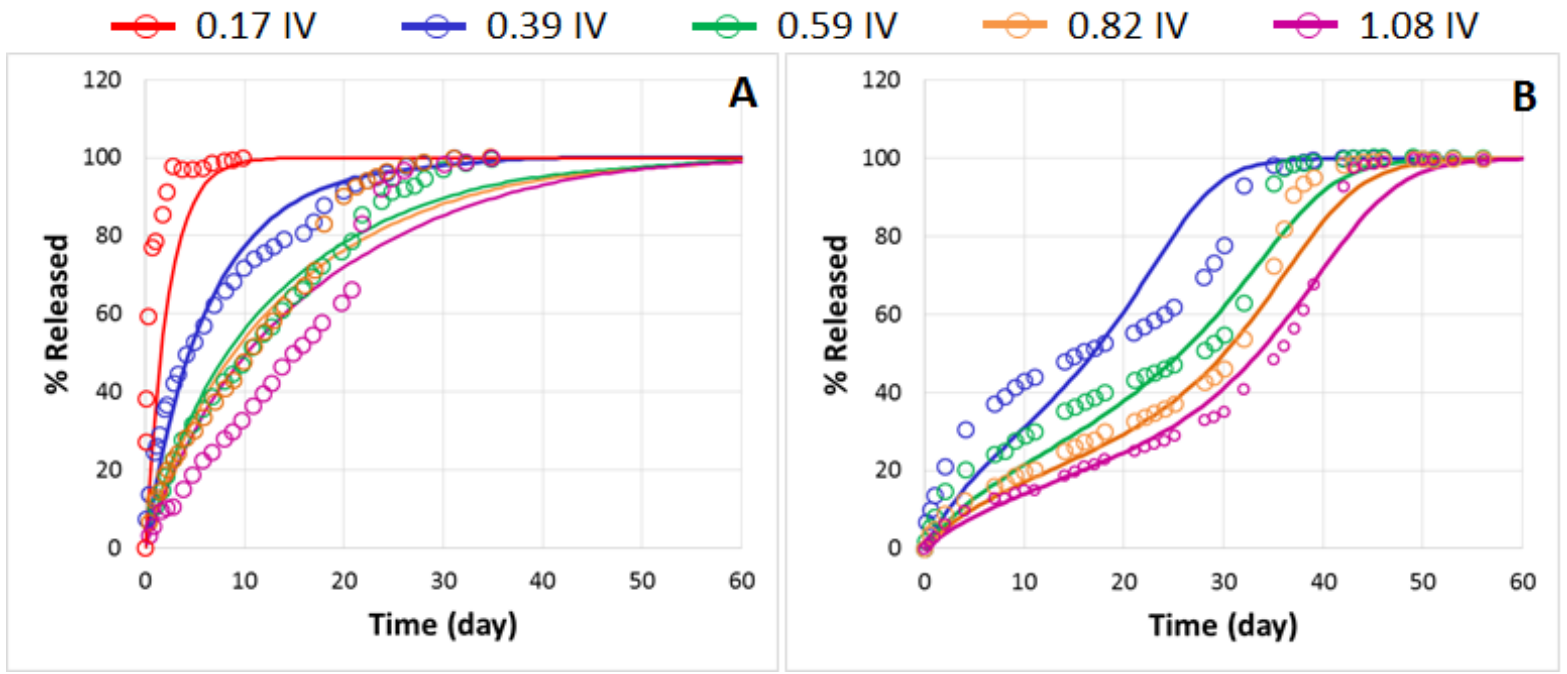
Rothstein et al, Biomaterials, 2009, 30: 1657-1664

Mullin J. CRS 2017 Annual Meeting, Poster presentation

In Vitro Dissolution: Model Extension

The expanded model showed potential to account for effect of particle size on API dissolution/release rate from LAI microsphere

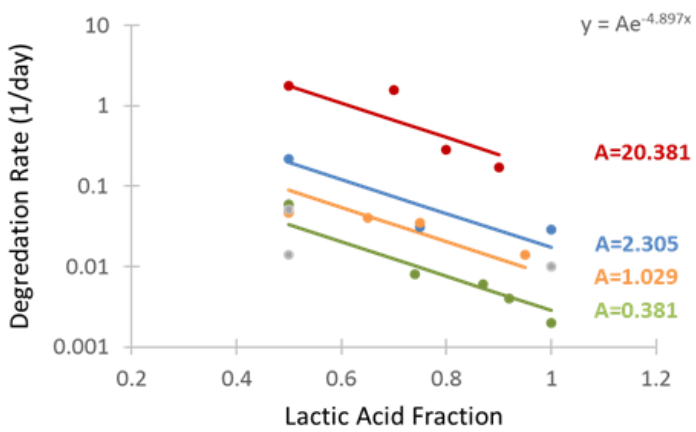
Observed (points) and simulated (lines) dissolution profiles of piroxicam from several formulations with 10 micron (A) and 50 micron (B) particles with varying polymer molecular weights using the expanded model. The same set of parameter values was used to simulate the dissolution profiles of all formulations.



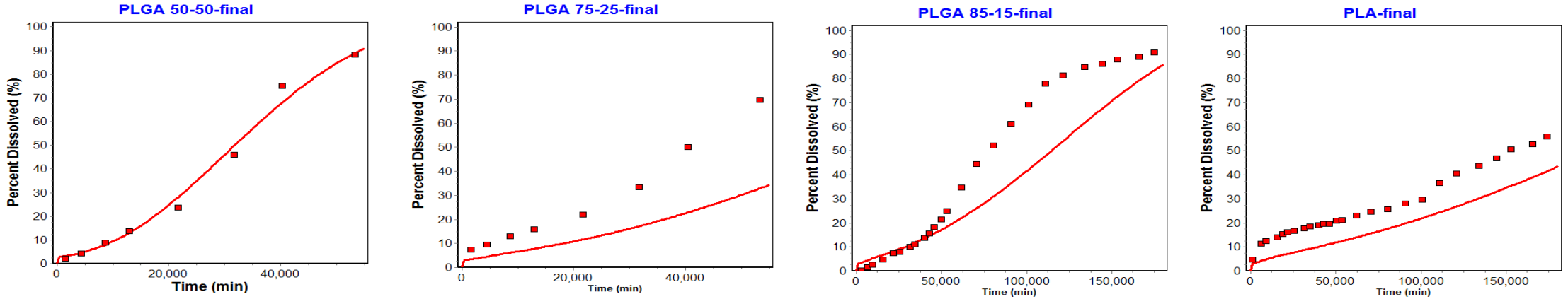
Observed data from: Raman et al. J Control Rel 2005, 103: 149-158

In Vitro Dissolution: Can we Predict PLGA Degradation?

Measured PLGA degradation rates vs. glycolate/lactate ration in PLGA polymers from several publications.



Observed (points) and simulated (lines) *in vitro* dissolution profiles of orntide from PLGA microspheres with varying L/G ratios (from left: L/G=50/50; L/G=75/25; L/G=85/15; L/G=100/0). The model fitted against the observed data for formulation with L/G=50/50 (first plot) was used to predict the remaining three formulations.

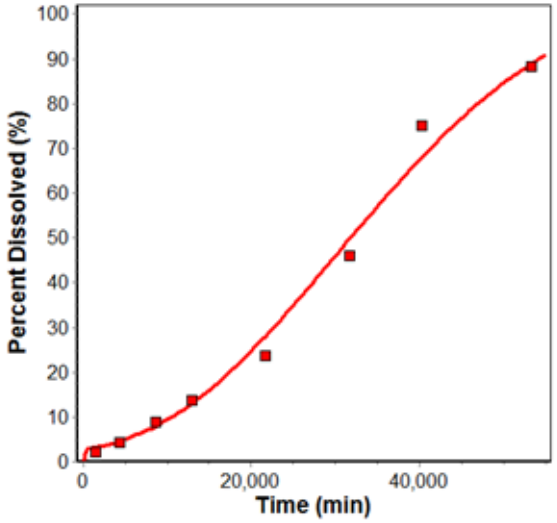


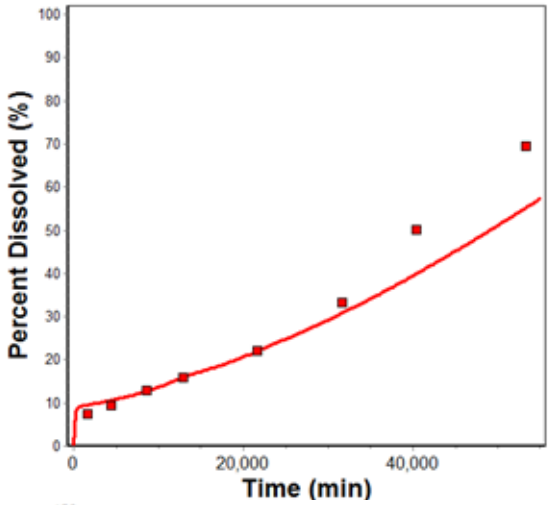
Observed data from: Kostanski et al. AAPS PharmSciTech 2000, 1(4): 4-16

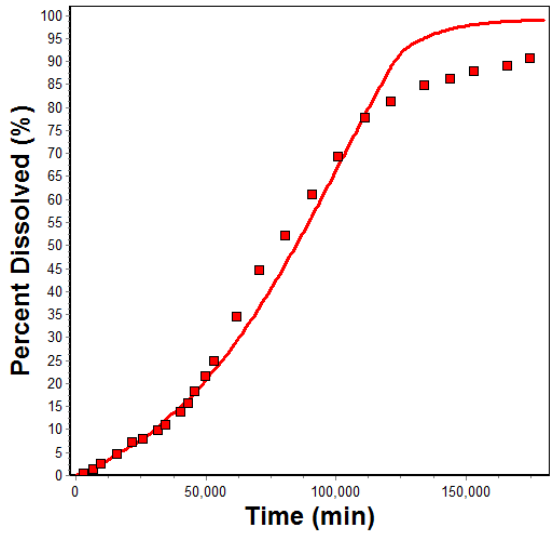
Mullin J. CRS 2017 Annual Meeting, Poster presentation

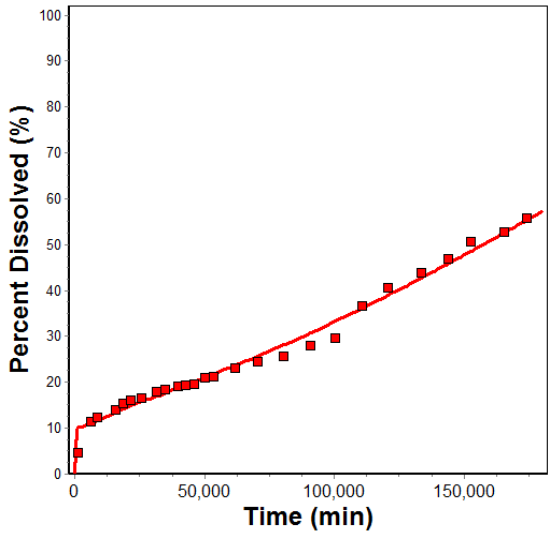
In Vitro Dissolution: Intraparticle Drug Distribution?

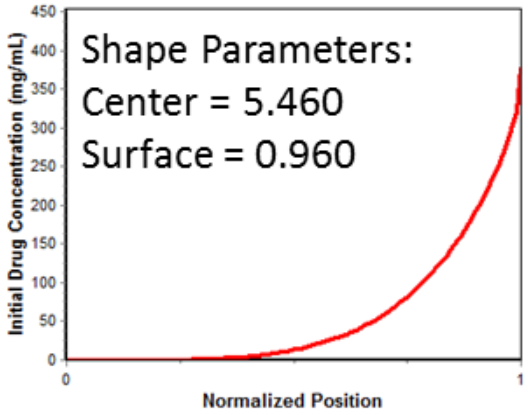
The intraparticle API distribution (shown in the bottom row) that would explain the observed release profile was fitted to each of these three formulations.

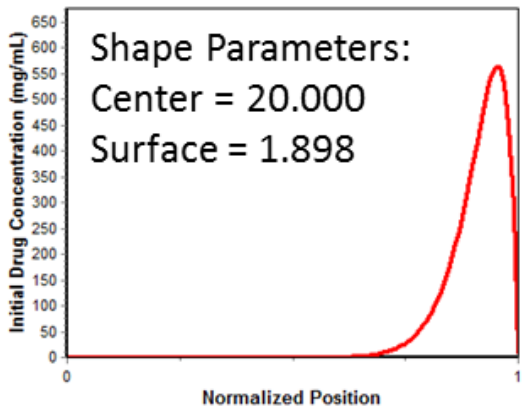


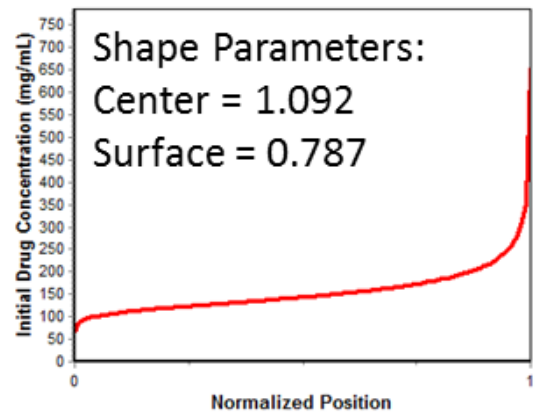












Observed data from: Kostanski et al. AAPS PharmSciTech 2000, 1(4): 4-16

Summary I

- Mechanistic in vitro dissolution model allows investigating mechanisms/processes affecting drug release from the formulation
  - API dissolution
  - Polymer degradation
  - Diffusion of API and water
  - API distribution throughout the particle
- The model showed potential of scaling the release across the formulation with varying composition (L/G ratio)

Outline

- Mechanistic *in vitro* model for PLGA microspheres
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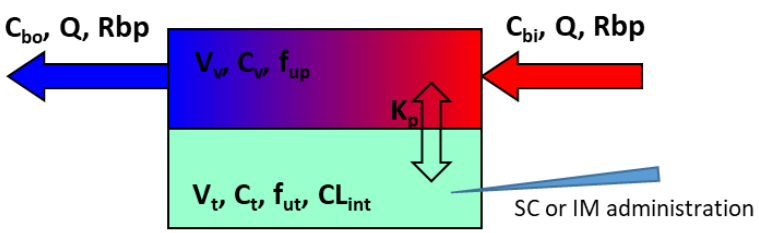
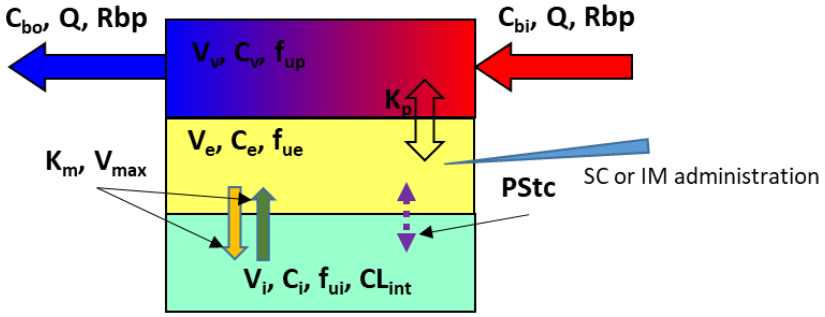
IM and SC Administration Model

Perfusion Limited:

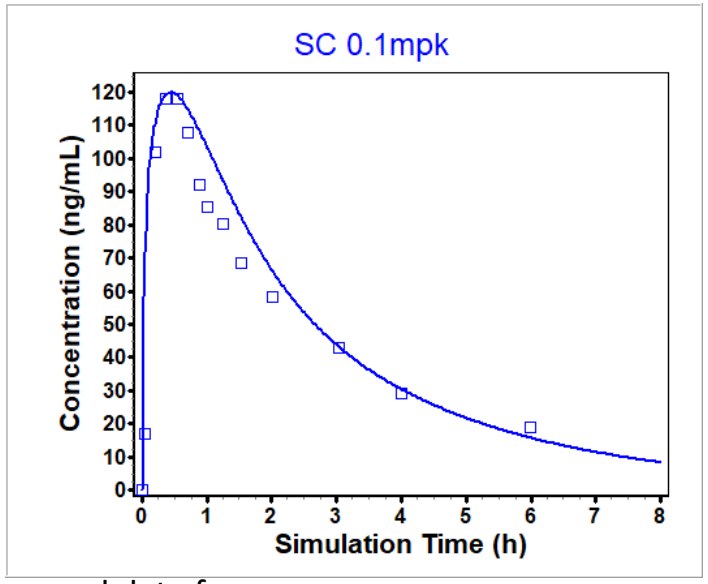


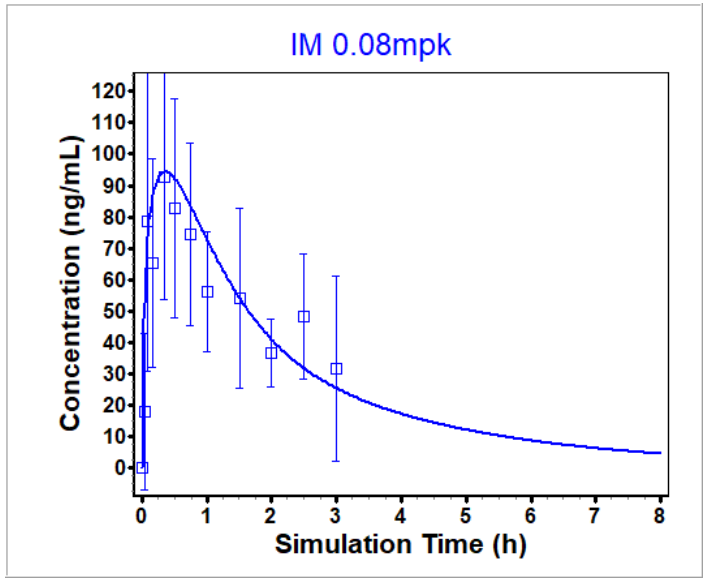
Permeability Limited:

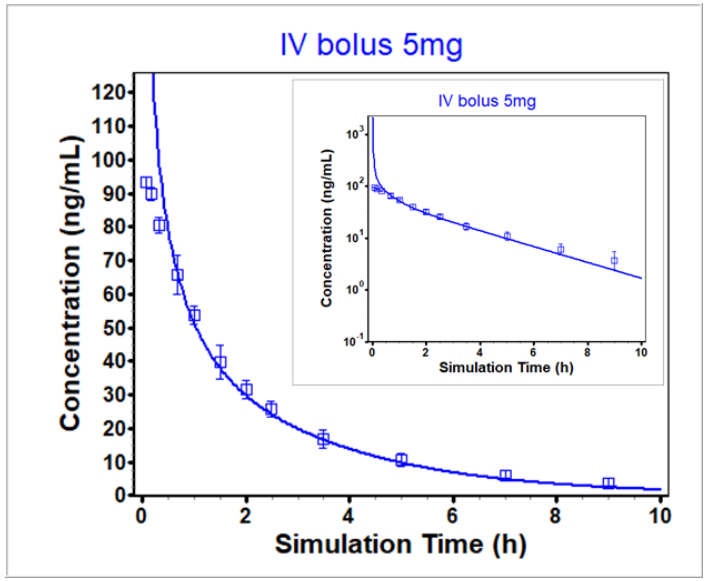


Midazolam administration in healthy volunteers

- The same model correctly described PK after IV, SC solution and IM solution administration





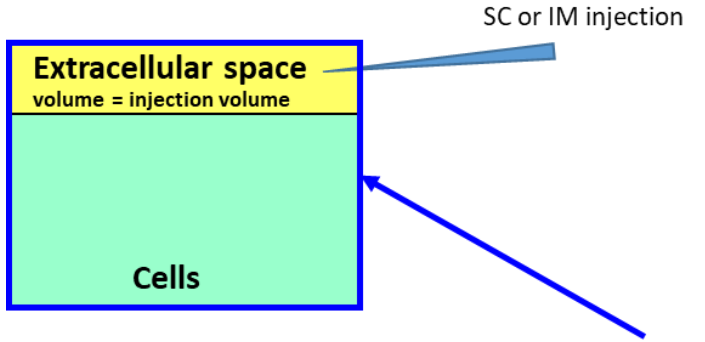


Observed data from:

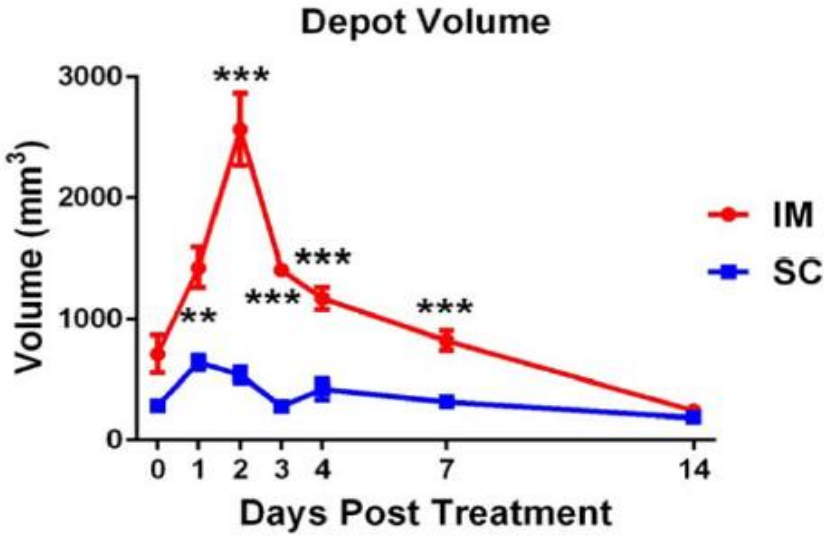
Pecking – Br J Clin Pharmacol 2002, 54:357; Alfonzo Echeverri – Anesth Prog – 1990, 37:277; Kupferschmidt – Clin Pharmacol Ther 1995, 58:20

Effective Depot Volume

- Effective depot volume affects:
  - Volume for compound dissolution
  - Absorption rate through changes in total blood flow
- Initial assumption is that injection goes into the extracellular tissue space
- However, the effective volume may be significantly lower if the vehicle is absorbed quickly
- Inflammation may cause temporal changes in the effective depot volume



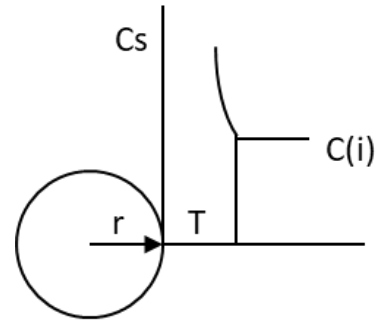
Effective Depot Volume =
[injection volume]/[extracellular water fraction]



Jucker – J Contr Rel 2017, 268: 102-112

Dissolution

$$\frac{dM_D}{dt} = \frac{D_w}{\rho h r_t}\frac{(1+2s)}{s}(C_s - C_l)M_{u,t}$$



$T = r_{0j}$

Oral administration:

- Particles well separated – total surface area of each particle plays a role in dissolution
- Reasonably well stirred environment keeps diffusion layer thickness small

Injection in tissue:

- Restricted tissue environment causes packing/aggregation of particles affecting effective dissolution surface area
- Static environment – the effective diffusion layer thickness may be significantly higher

Example: Cabotegravir

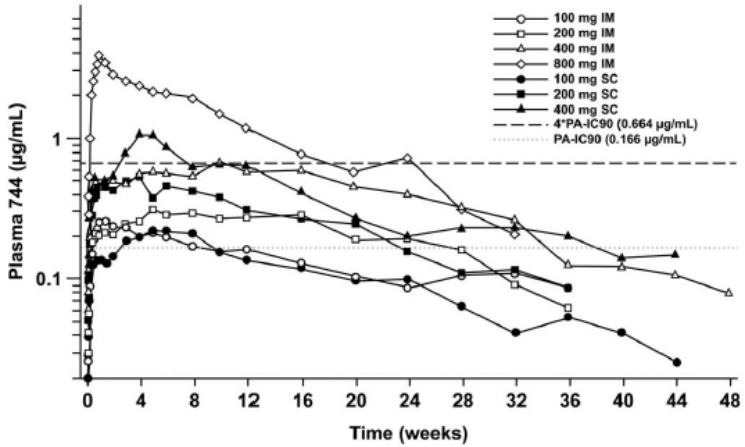
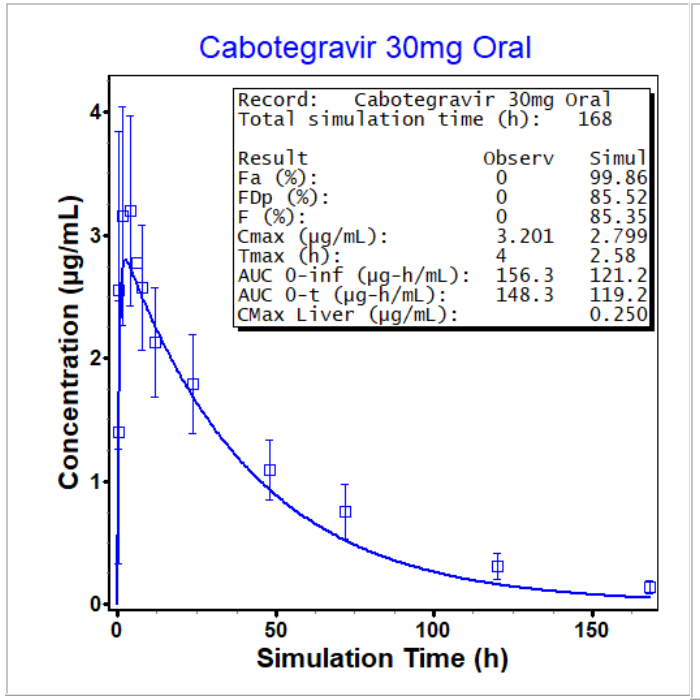


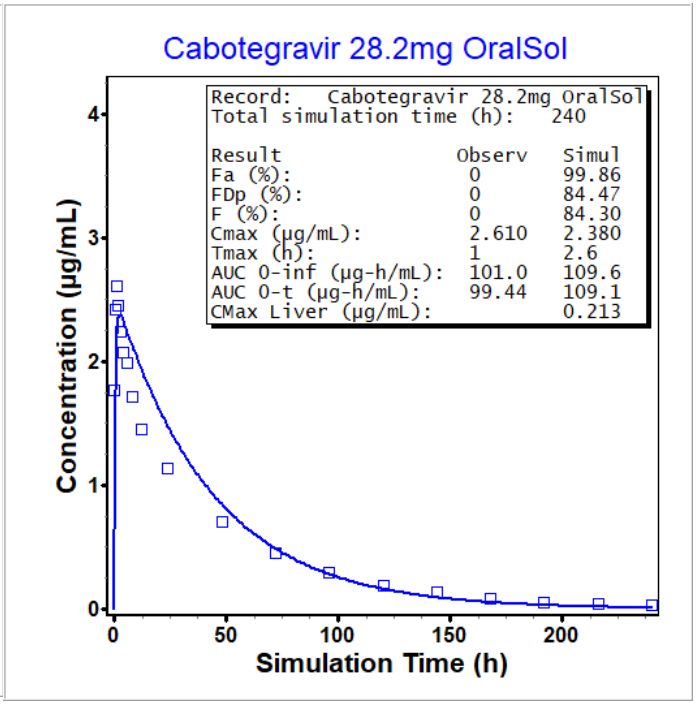
FIGURE 1. Mean plasma 744 concentration–time profiles after single-dose LA injections in healthy subjects (cohorts 1–7). PA-IC90 is the protein-adjusted concentration that inhibits viral replication by 90%. Figure reproduced with permission from Ref. 3. Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

Spreen - J Acquir Immune Defic Syndr, 2014, 67(5):481

- 100-800 mg IM suspension injection in gluteal muscle
- 100-400 mg SC suspension injection in abdominal region
- Nanosuspension 200 mg/mL injected at maximum volume 2 mL/injection IM and 1mL/injection SC

Systemic disposition described with PBPK model built using oral data: Kps estimated from drug- and tissue properties using default method; Elimination via UGT1A1 and UGT1A9 parameterized based on *in vitro* data



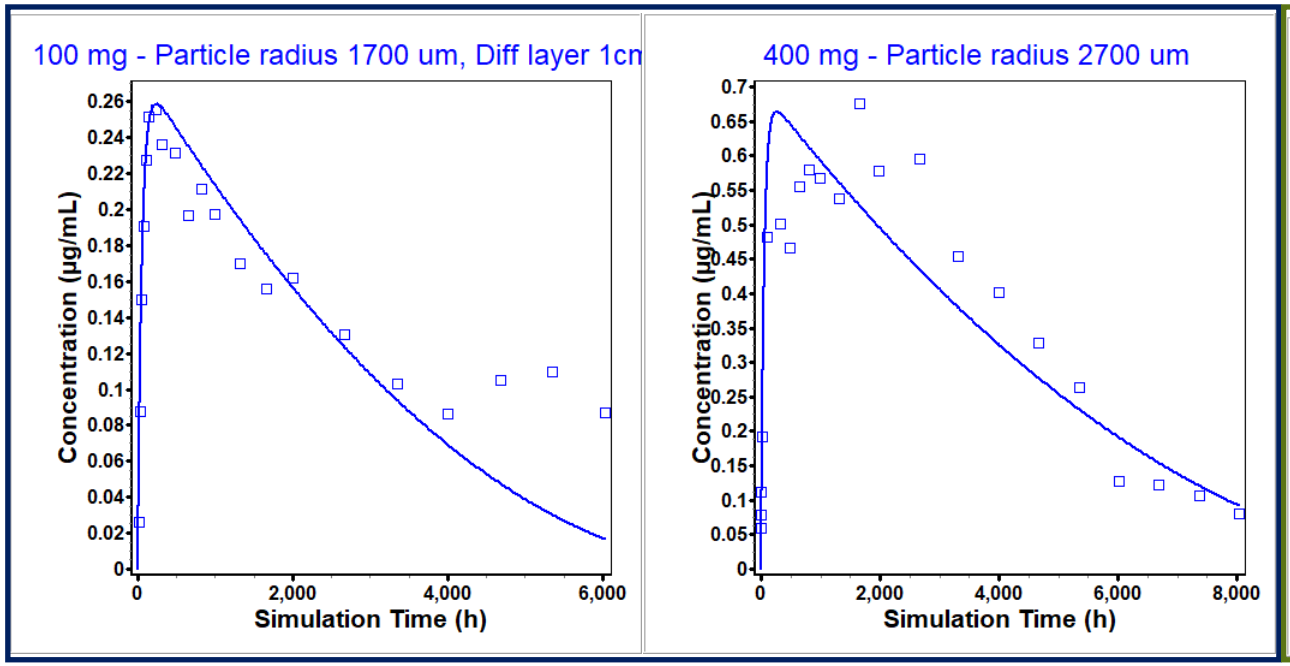


Observed data from:
Bowers – Xenobiotica 2016, 46(2): 147; Ford, 17th Inter. Workshop on Clin. Pharmacol. of HIV & Hepatitis Therapy, June 8-10, 2016.

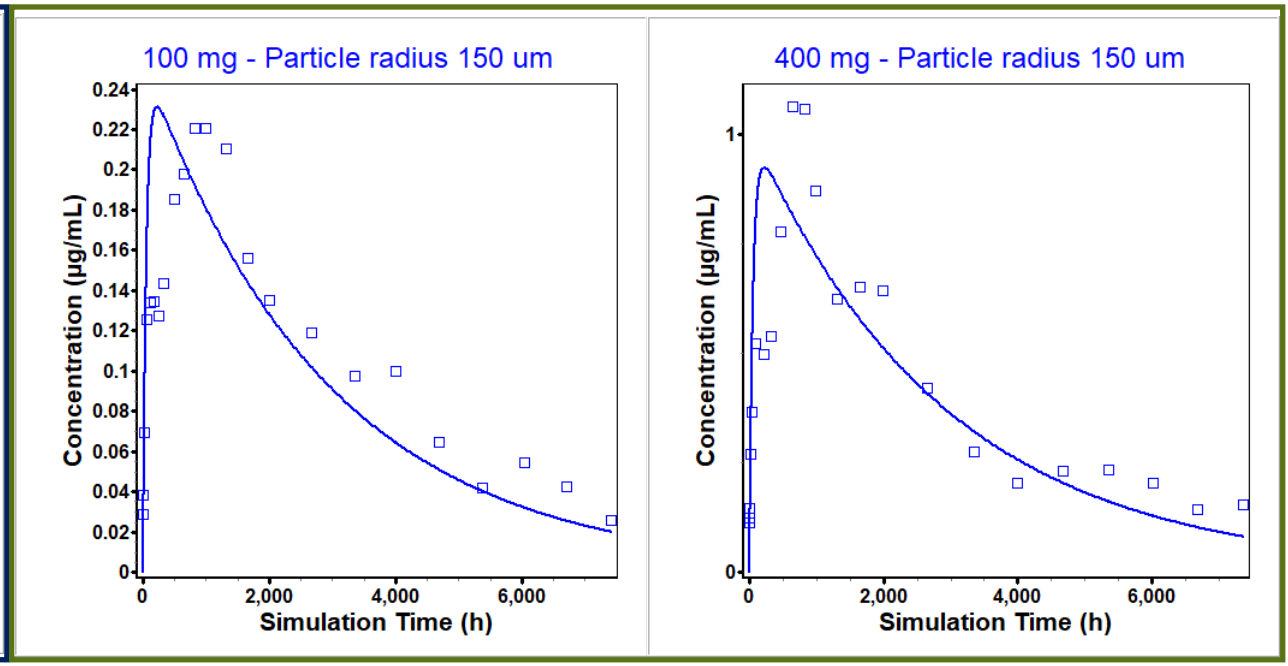
Effect of Particle Size and Diffusion Layer Thickness

Significant increase in either Particle Size **or** Diffusion Layer Thickness did not explain the observed PK data
Combination of both effects resulted in reasonable match to the shape of the profile for all IM dose levels

Intramuscular



Subcutaneous



All simulations with diffusion layer thickness 1 cm

Example: Paliperidone/Paliperidone Palmitate

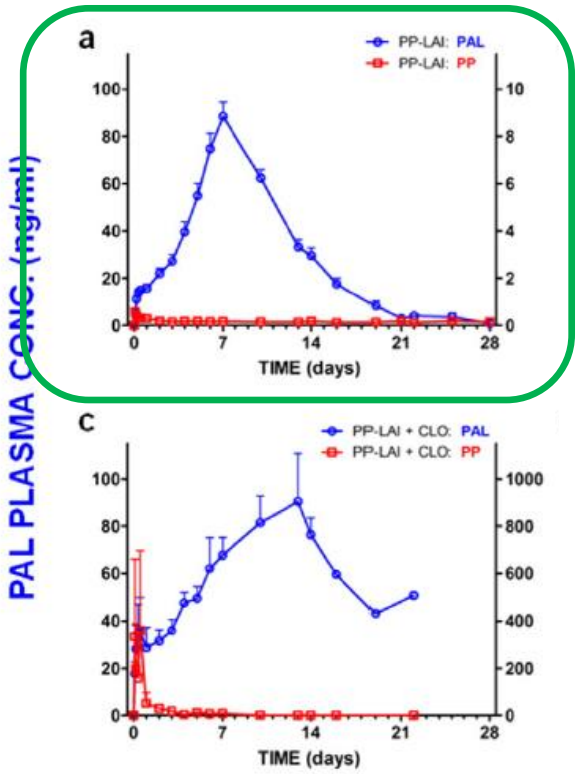
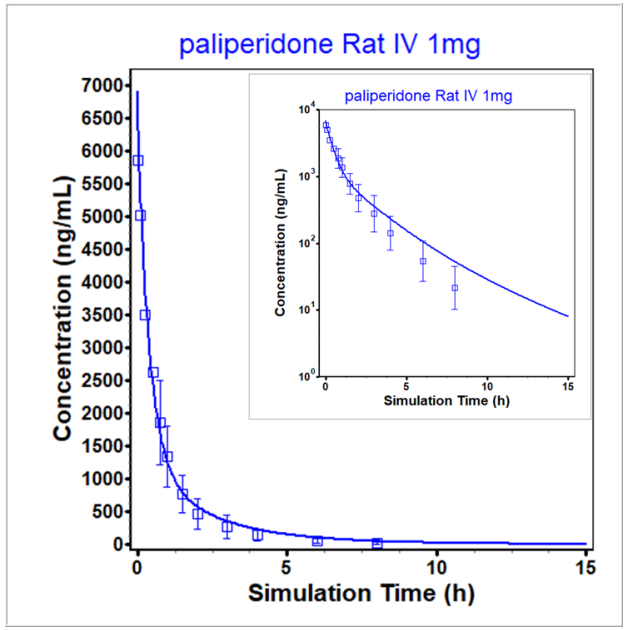


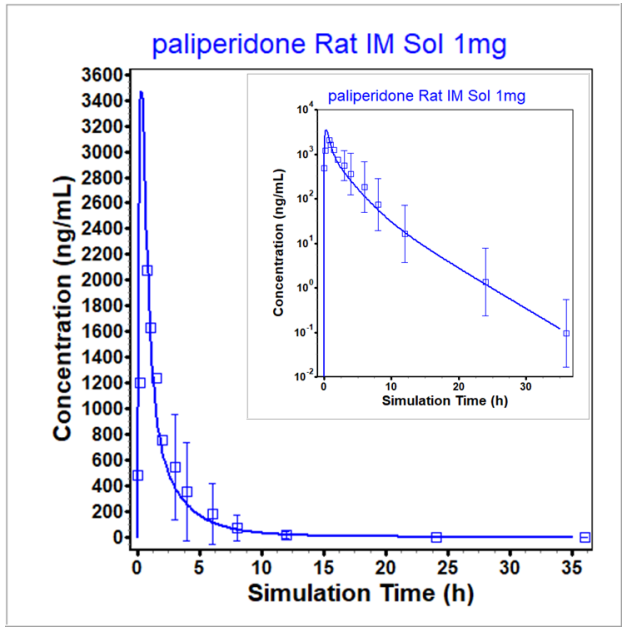
Fig. 4. Observed mean plasma concentration–time profiles of paliperidone palmitate (PP, red □ PP-LAI: a) PP-LAI only (control group); b) PP-LAI with intermittent IV doses of phosphate buf liposomes (CLO); d) PP-LAI with daily oral doses of 20 mg/kg sunitinib (SNT). Data represent

Darville – J Cont Rel – 2016, 230:95

- 20 mgEq/kg IM suspension of Paliperidone Palmitate (PP) injection in rats
- PP properties drive initial dissolution but once dissolved it appears to break down quickly to paliperidone as only negligible amounts of PP were measured in plasma

Systemic disposition described by a Compartmental PK model fitted to *in vivo* data; default settings for IM solution administration





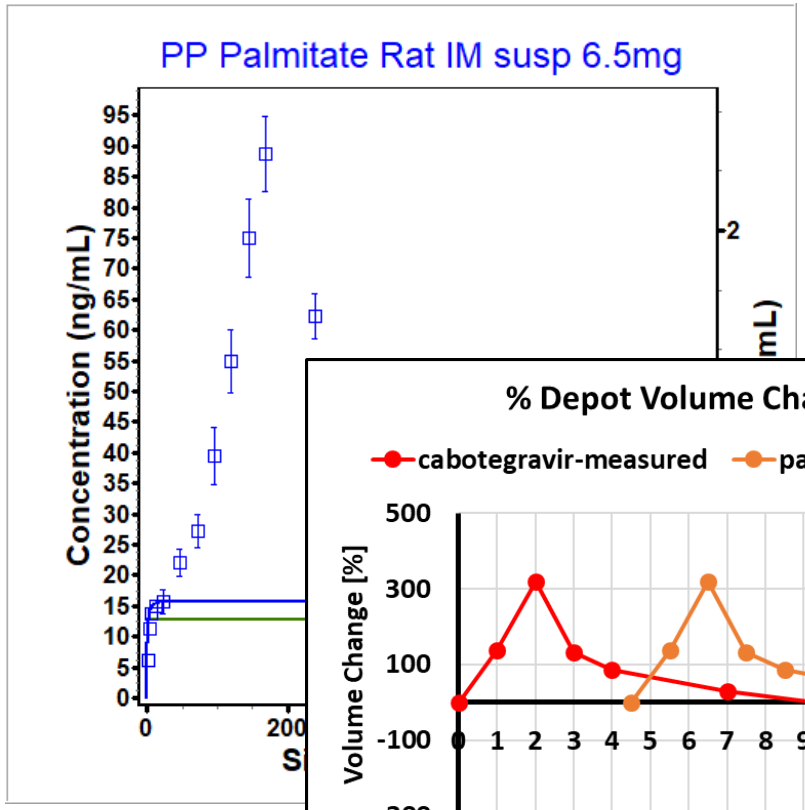
Effect of Inflammation on Paliperidone PK

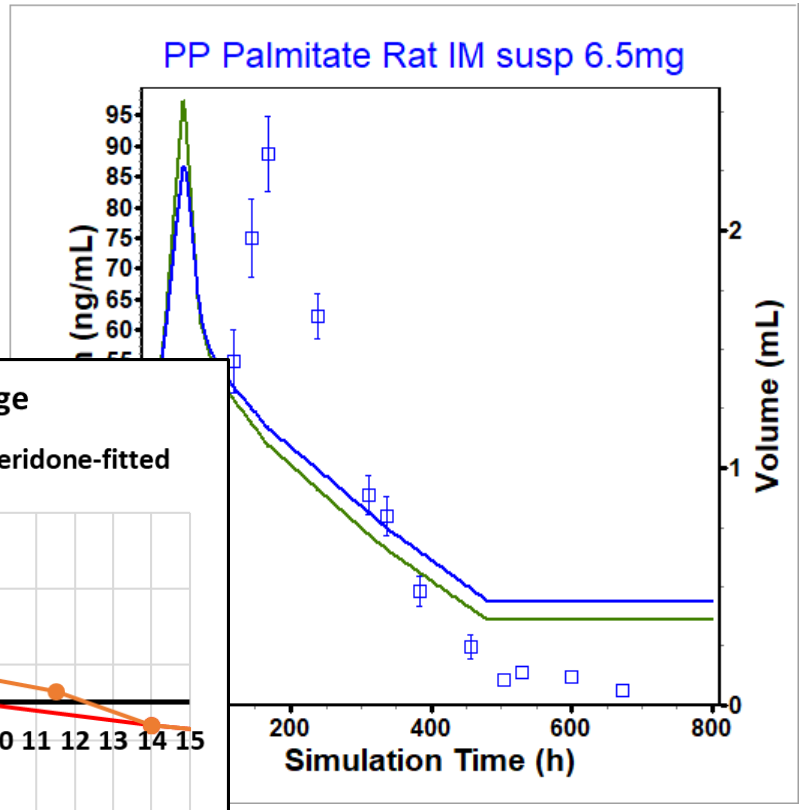
All simulations used solubility 80ng/mL; Particle size 1.04 um, standard diffusion layer thickness

Fixed depot volume = 0.336 mL (volume at the end point)

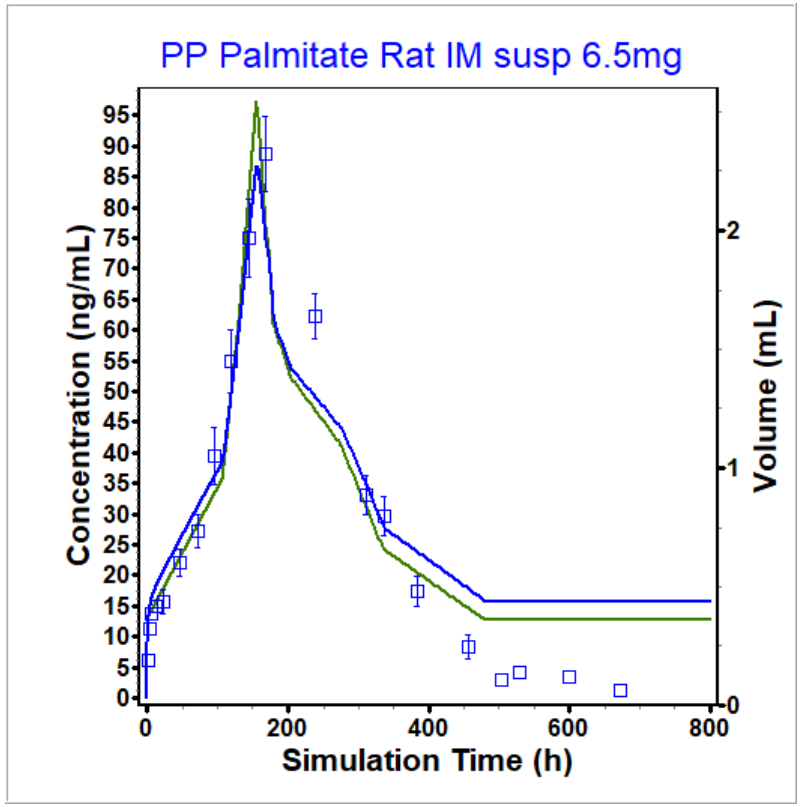
Depot volume changes as measured for cabotegravir

Depot volume changes measured for cabotegravir shifted by 4.5 days





Green – depot volume



Blue – plasma concentration

Case Study

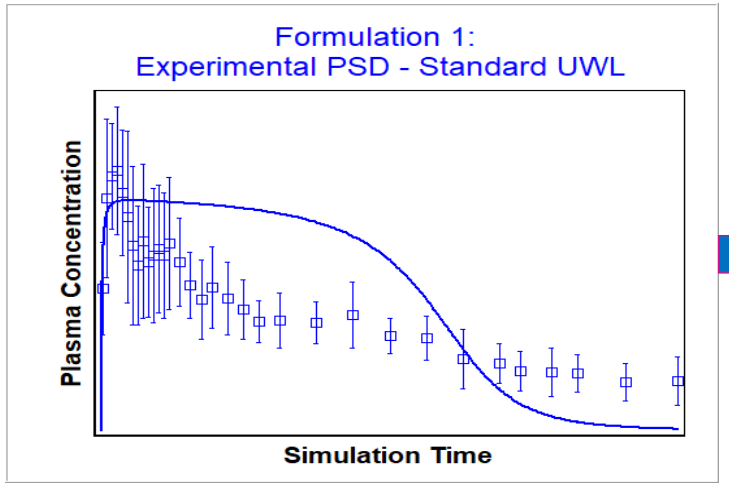
- Subcutaneous injection of low solubility compound suspensions in rabbit
- Five different formulations were tested (difference in particle size and dissolution)
- The baseline PBPK model was calibrated against IV Cp-time profile

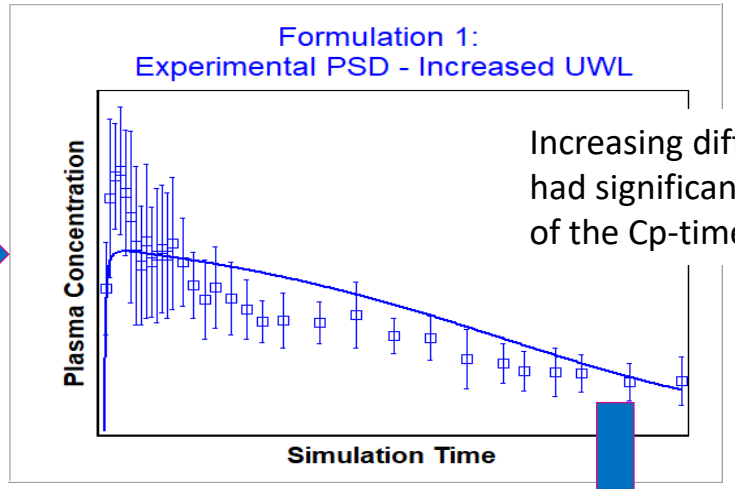
Can the PBPK model link the formulation parameters to *in vivo* exposure for these formulations?

All *in vitro* and *in vivo* data for this case study were generated in the lab of Dr. Burgess at University of Connecticut.

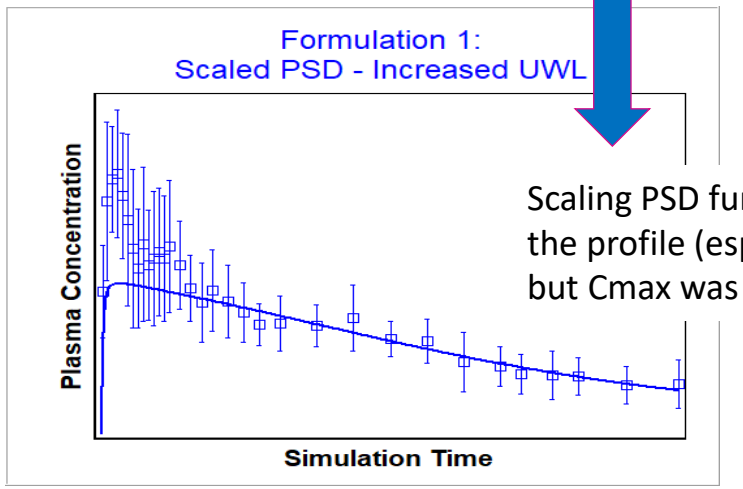
Disclaimer: This research was funded through the FDA Office of Generic Drugs: contract 75F40121C00133. The views expressed here do not reflect official policies of the US FDA or the Department of Health and Human Services, nor does any mention of trade names imply endorsement by the US Government.

Model Development & Results

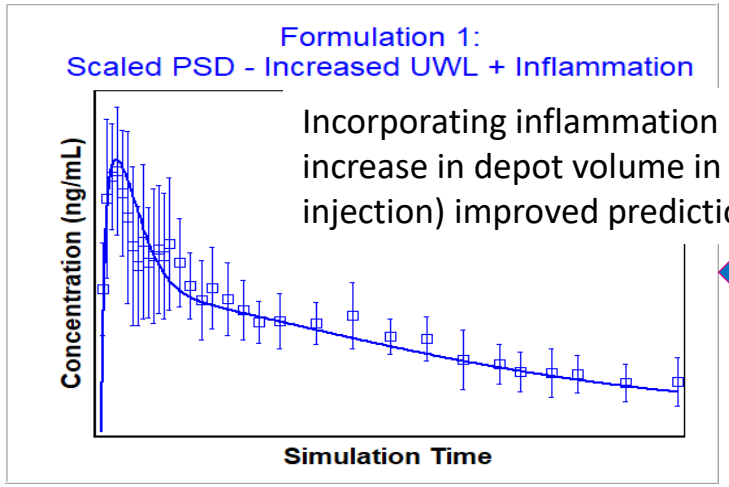




Increasing diffusion layer thickness had significant impact on the shape of the Cp-time profile

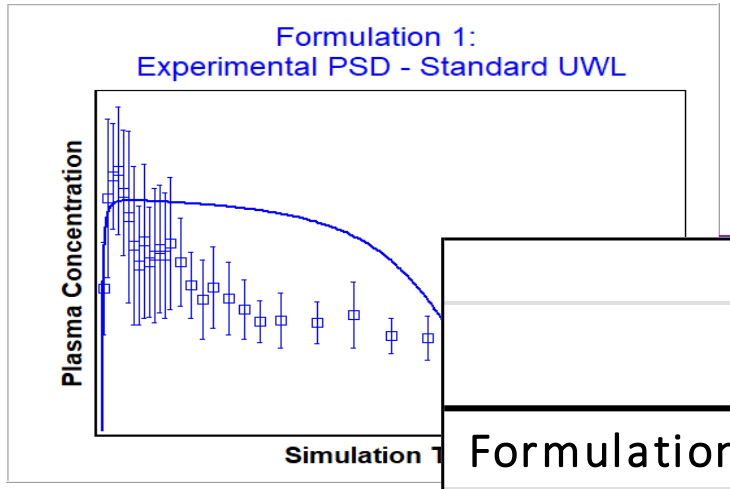


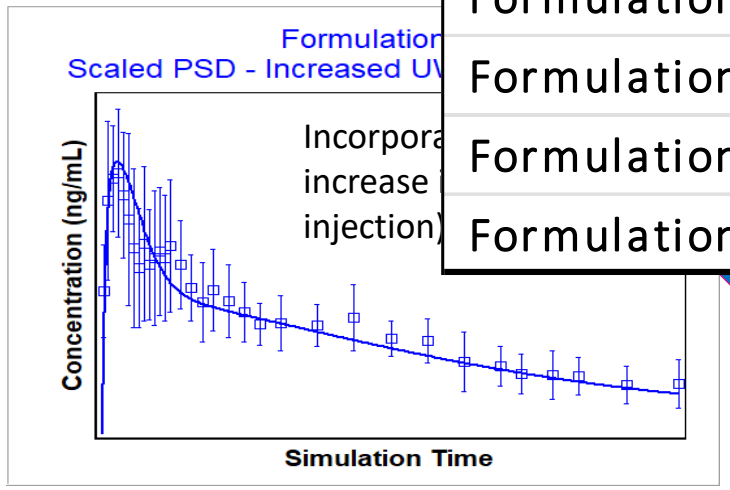
Scaling PSD further improved shape of the profile (especially terminal phase) but Cmax was still underpredicted

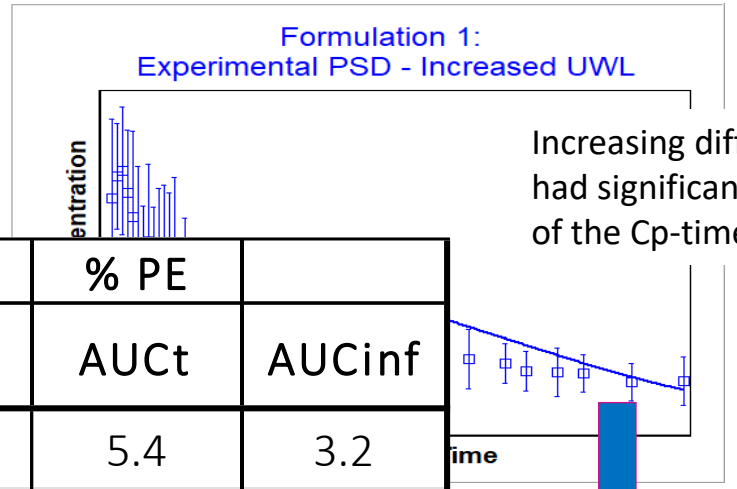


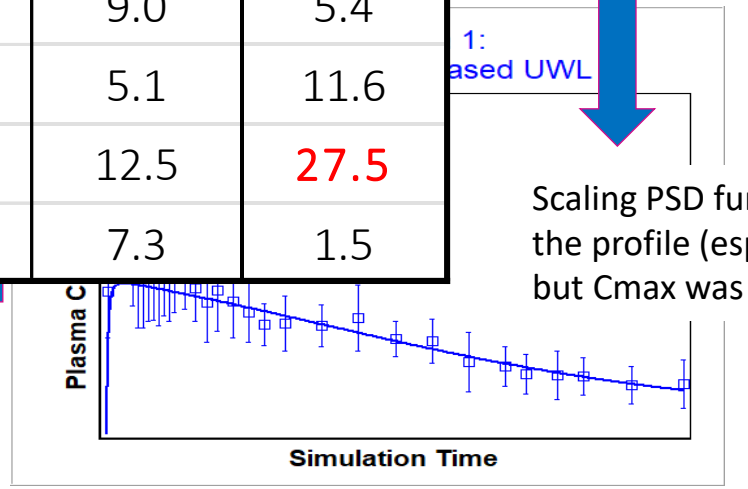
Incorporating inflammation (~3-fold increase in depot volume in 2-3 days after injection) improved prediction of Cmax

Model Development & Results









	% PE		
	Cmax	AUCt	AUCinf
Formulation 1	4.5	5.4	3.2
Formulation 2	10.2	9.0	5.4
Formulation 3	12.4	5.1	11.6
Formulation 4	16.9	12.5	27.5
Formulation 5	34.9	7.3	1.5

Increasing diffusion layer thickness had significant impact on the shape of the Cp-time profile

Scaling PSD further improved shape of the profile (especially terminal phase) but Cmax was still underpredicted

Summary II

- Several possible mechanisms affecting the dissolution of low-solubility drugs from nanosuspensions after IM or SC injection were explored:
  - Possible packing/aggregation of particles affecting effective dissolution surface area
  - Static environment affecting the diffusion of dissolved molecules
  - Possible effect of inflammation on transient changes in injection depot volume
- The model was able to distinguish differences in exposure for formulations with different API particle sizes
  - The scaling of particle size distribution suggests that aggregation happens slowly over time

Acknowledgements

Simulation Technologies Team
at Simulations Plus, Inc.

University of Connecticut

Diane Burgess

Quanying Bao

Collaborators:

FDA

Scientists from pharmaceutical company

Questions and Contact Information

viera.lukacova@simulations-plus.com

https://www.simulations-plus.com/

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