What does it take to develop a PBPK model that mimics *in vivo* behavior of LAIs? Part II

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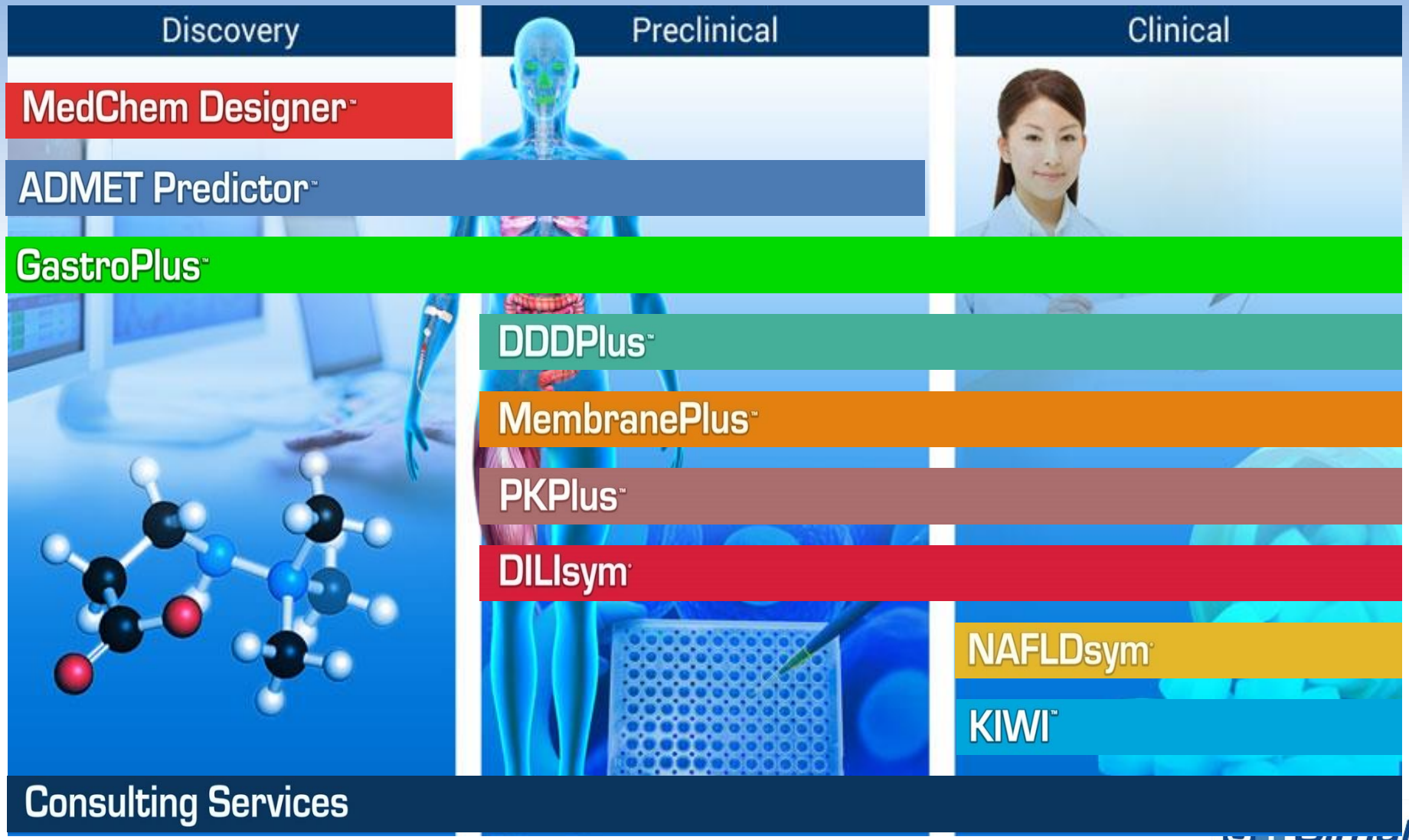

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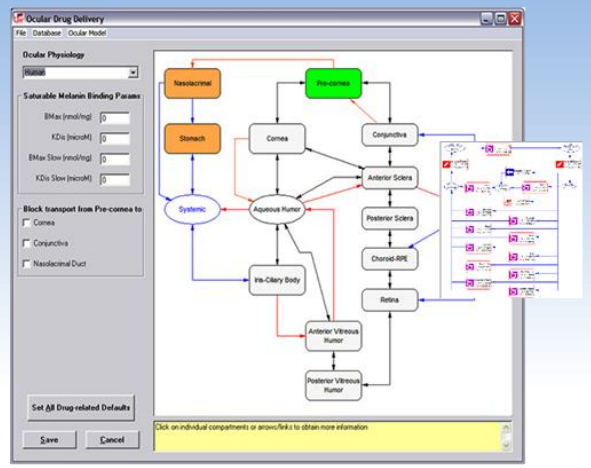
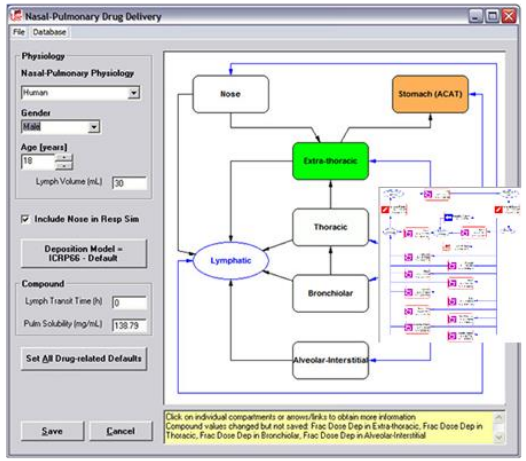
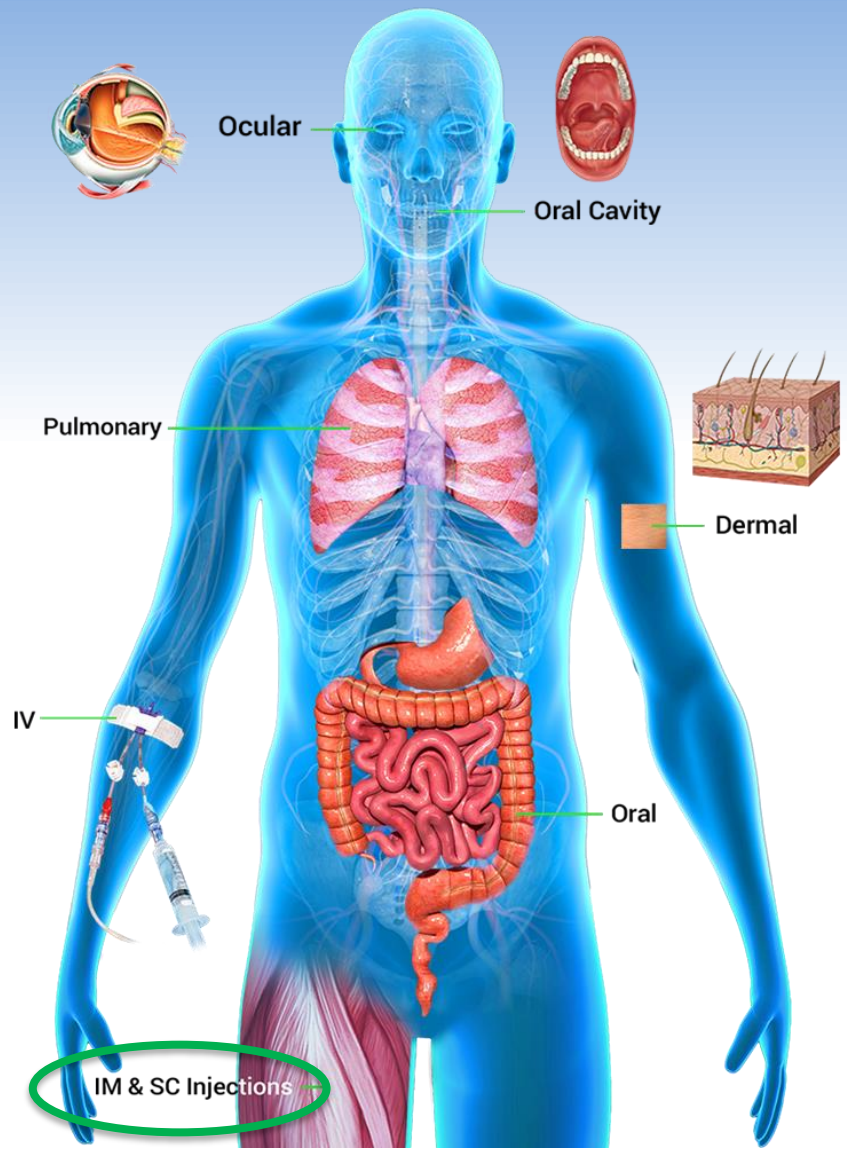
Pathways beyond oral absorption…

Ocular (OCAT™)

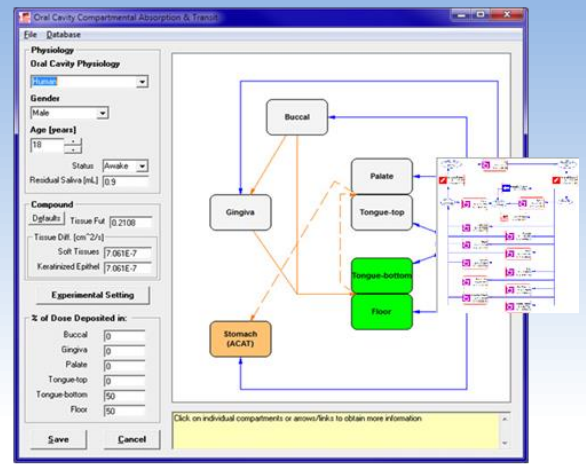


Pulmonary (PCAT™)

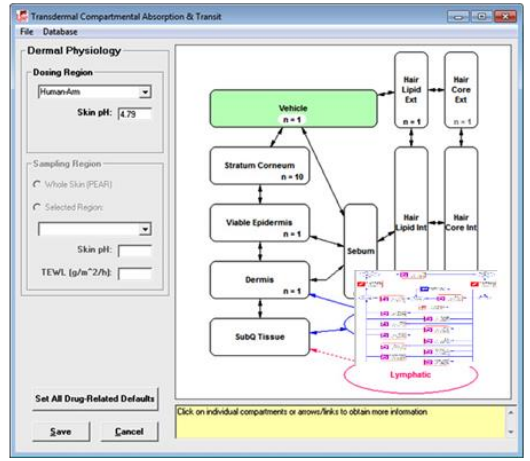




Oral Cavity (OCCAT™)



Dermal (TCAT™)



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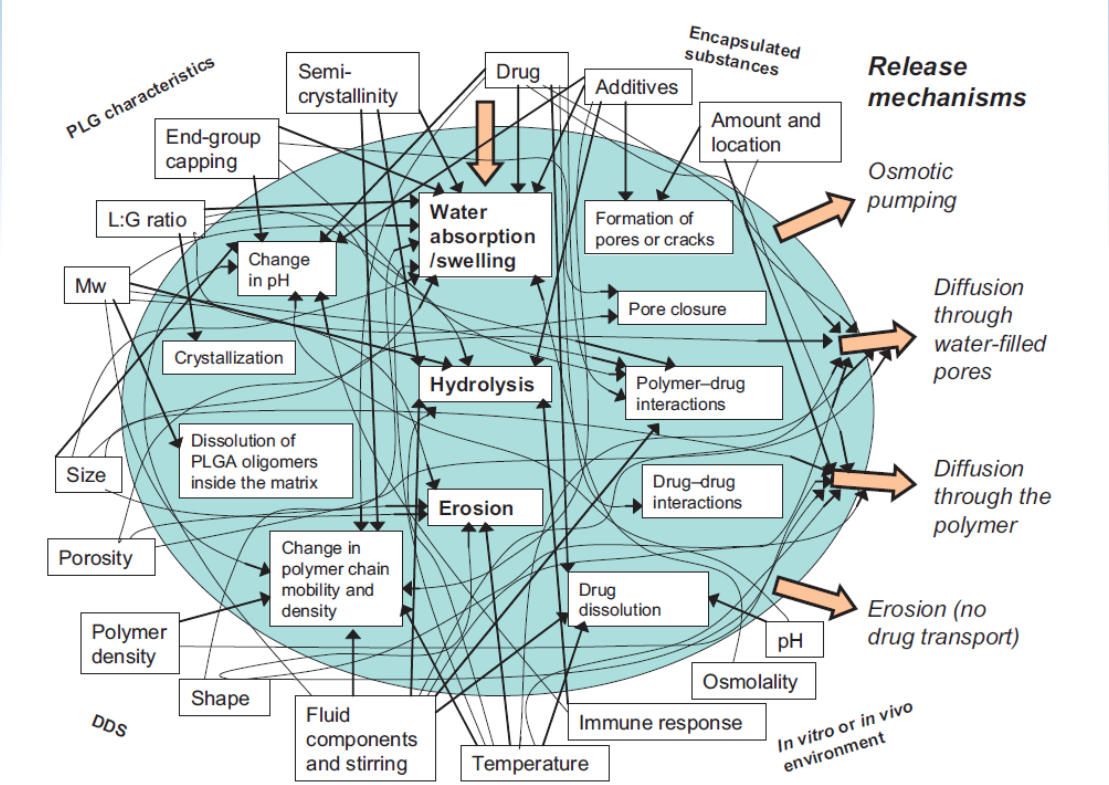
Recap of Part I

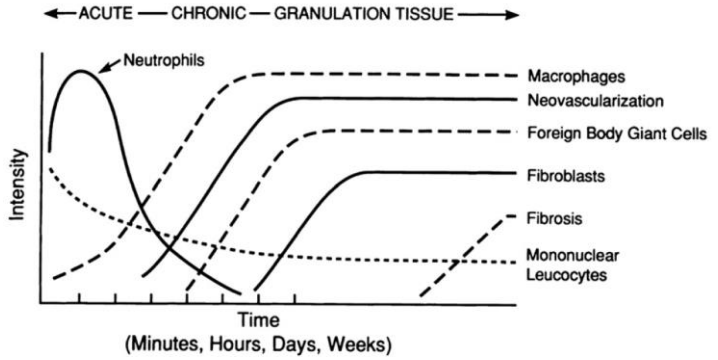
The complex nature of how different factors may affect drug release from PLGA matrices



Fredenberg, International Journal of Pharmaceutics 415 (2011)

The discussion was focused on LAIs based on PLGA matrices:

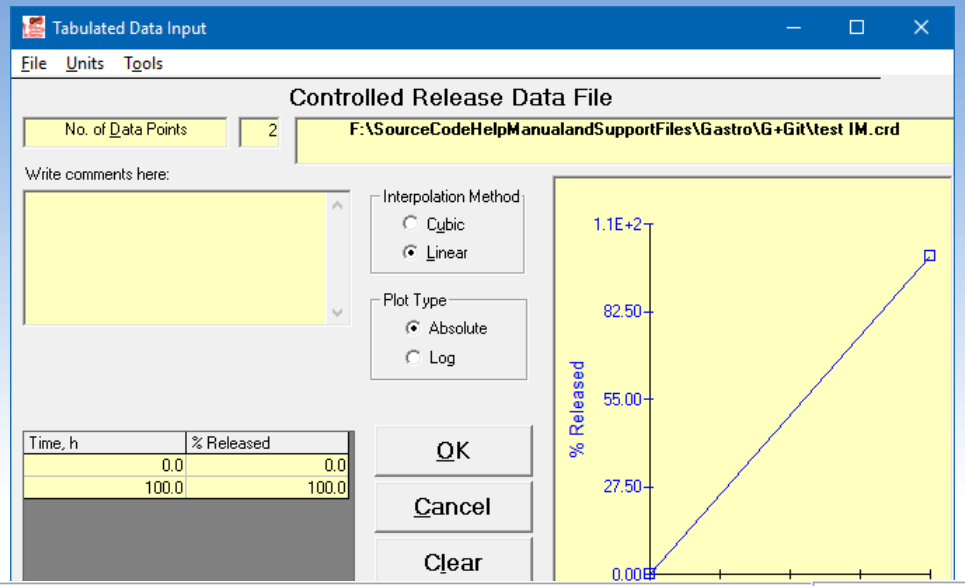
- *in vitro* model for drug release from PLGA microspheres
- Empirical IVIVC – lessons learned about important aspects for deconvolution
- Effect of tissue response to PLGA administration – possible effects of immune cell layer (preliminary results discussed)

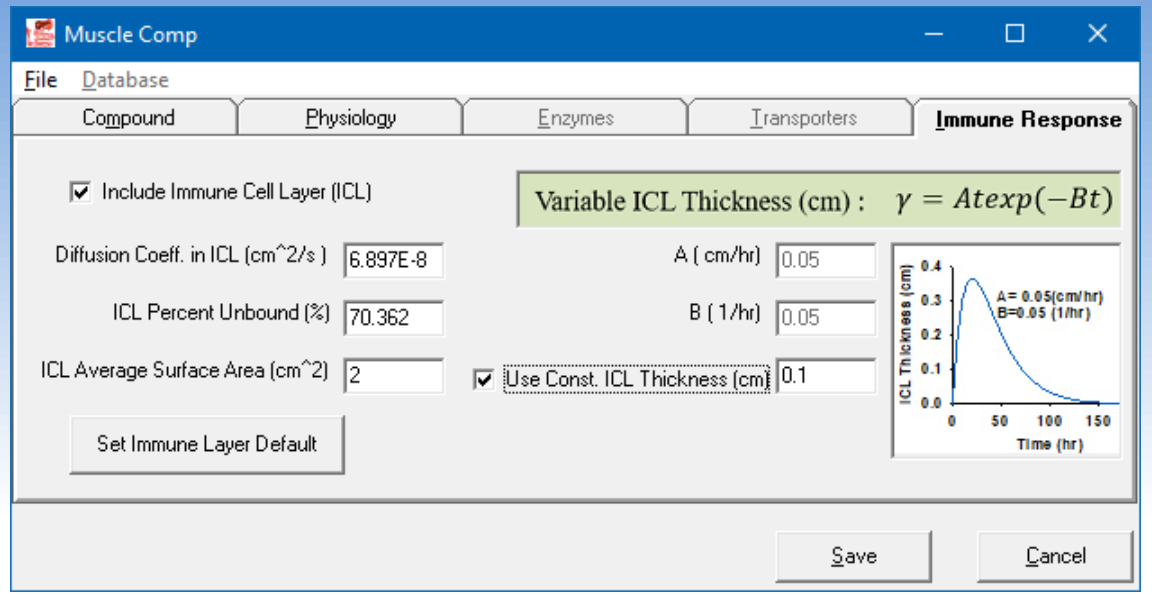


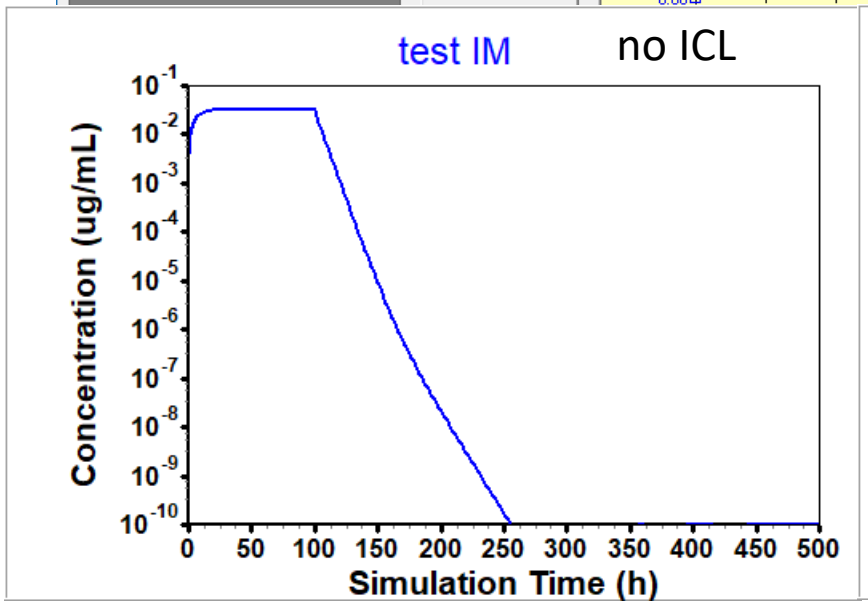
The temporal variation in the three phases of inflammatory response resulting from administration of biodegradable microspheres

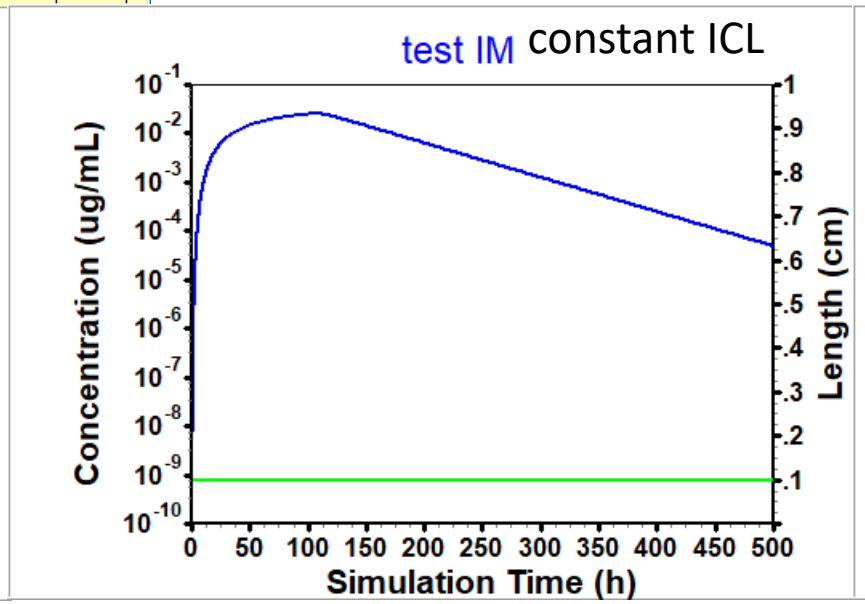
Anderson et. al., Advanced Drug Delivery Reviews 64 (2012), 2012

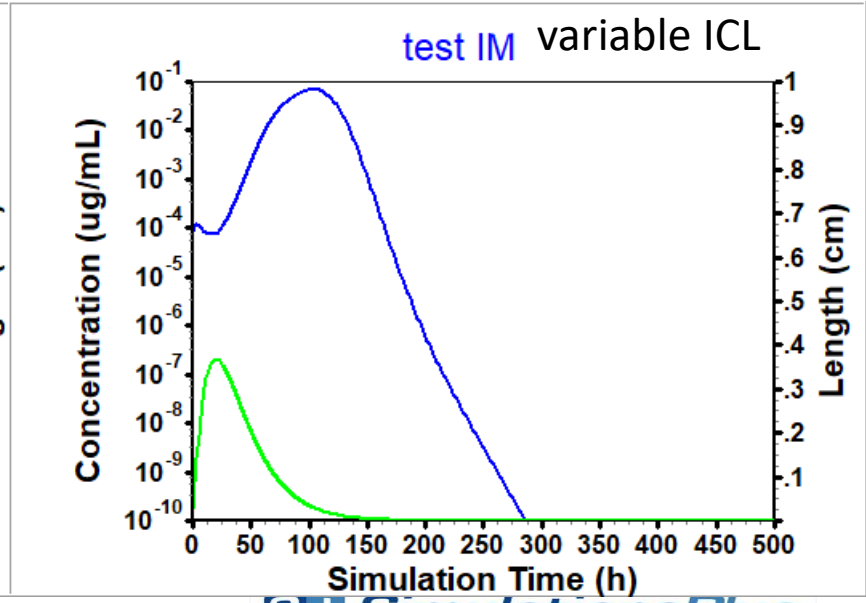
Recap of Part I











blue – plasma concentration, green – ICL thickness

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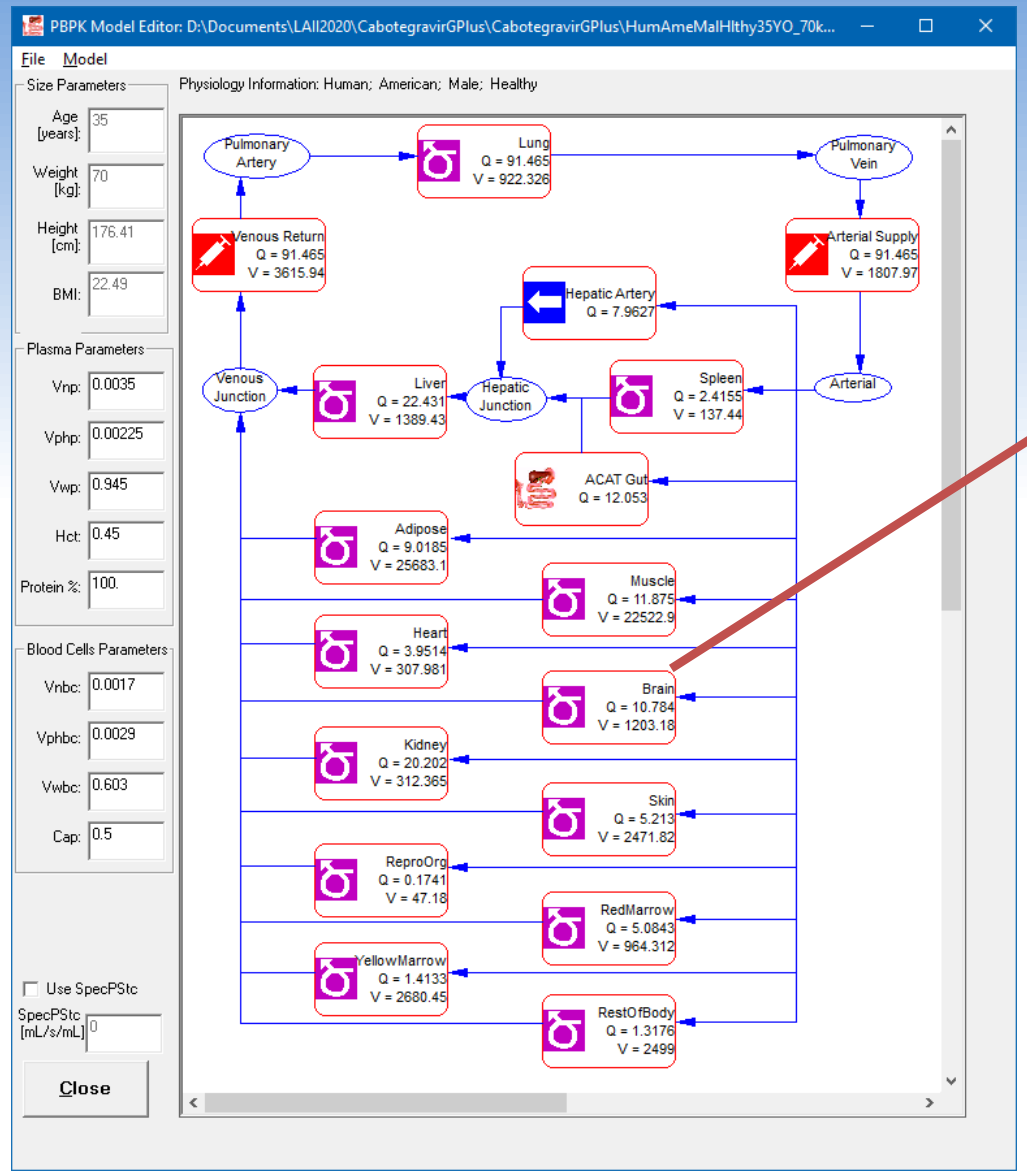
Outline

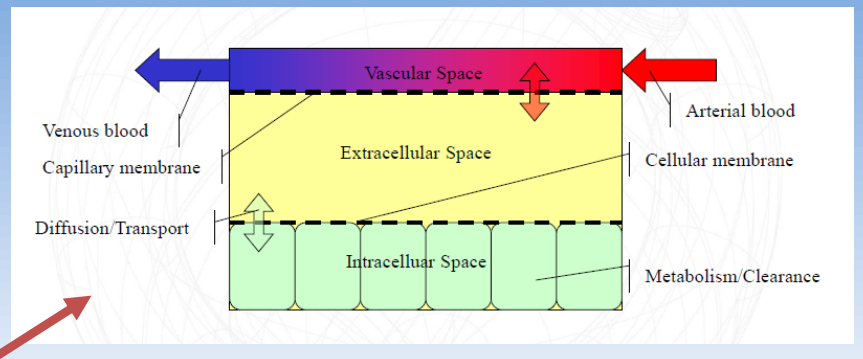
This presentation will take a closer look at possible mechanisms affecting behavior of suspensions of low solubility drugs

- PBPK model description
- Effect of dissolution rate – Example Cabotegravir
- Effect of changing depot volume – Example Paliperidone Palmitate

Funding Support Provided in part by US FDA (grant 1U01FD005463) and a large pharmaceutical company

What is Defined in a PBPK Model





$$Vt\frac{dCt}{dt} = \left(Q \times Cbi - \frac{Q \times Ct \times R_{bp}}{Kp} - CL_{int,u}\left(\frac{Ct \times fu_p}{Kp}\right)\right)$$

- Each compartment represents a tissue:
  - Specific volume(s) *
  - Blood perfusion rate *
  - Enzyme/transporter expression levels *
  - Volume fractions of lipids & proteins *
  - Tissue:plasma partition coefficient (K_p)
    - Estimated from drug properties:
      - logD vs. pH
      - pKa(s)
      - Plasma protein binding
      - Blood:plasma concentration ratio

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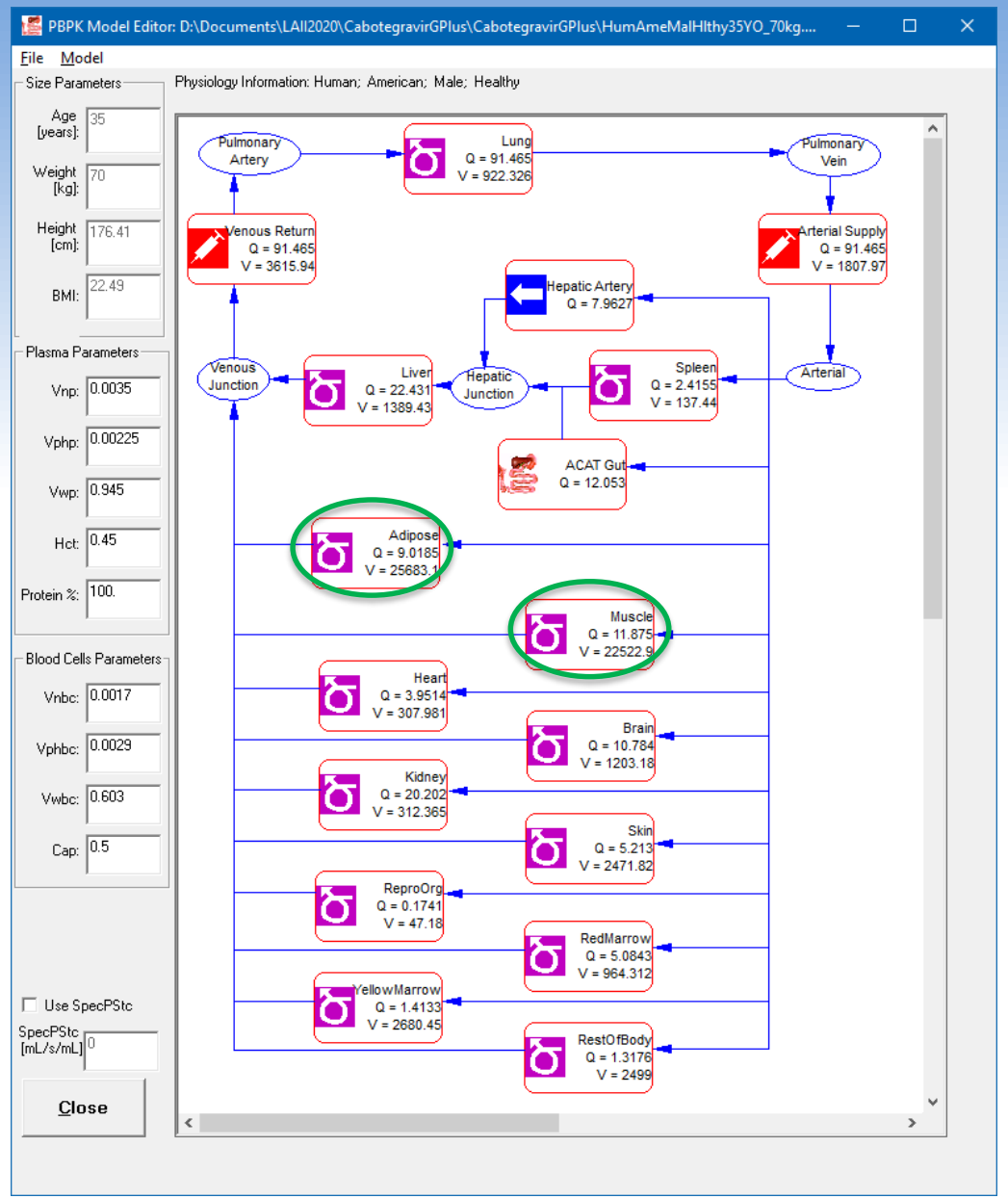
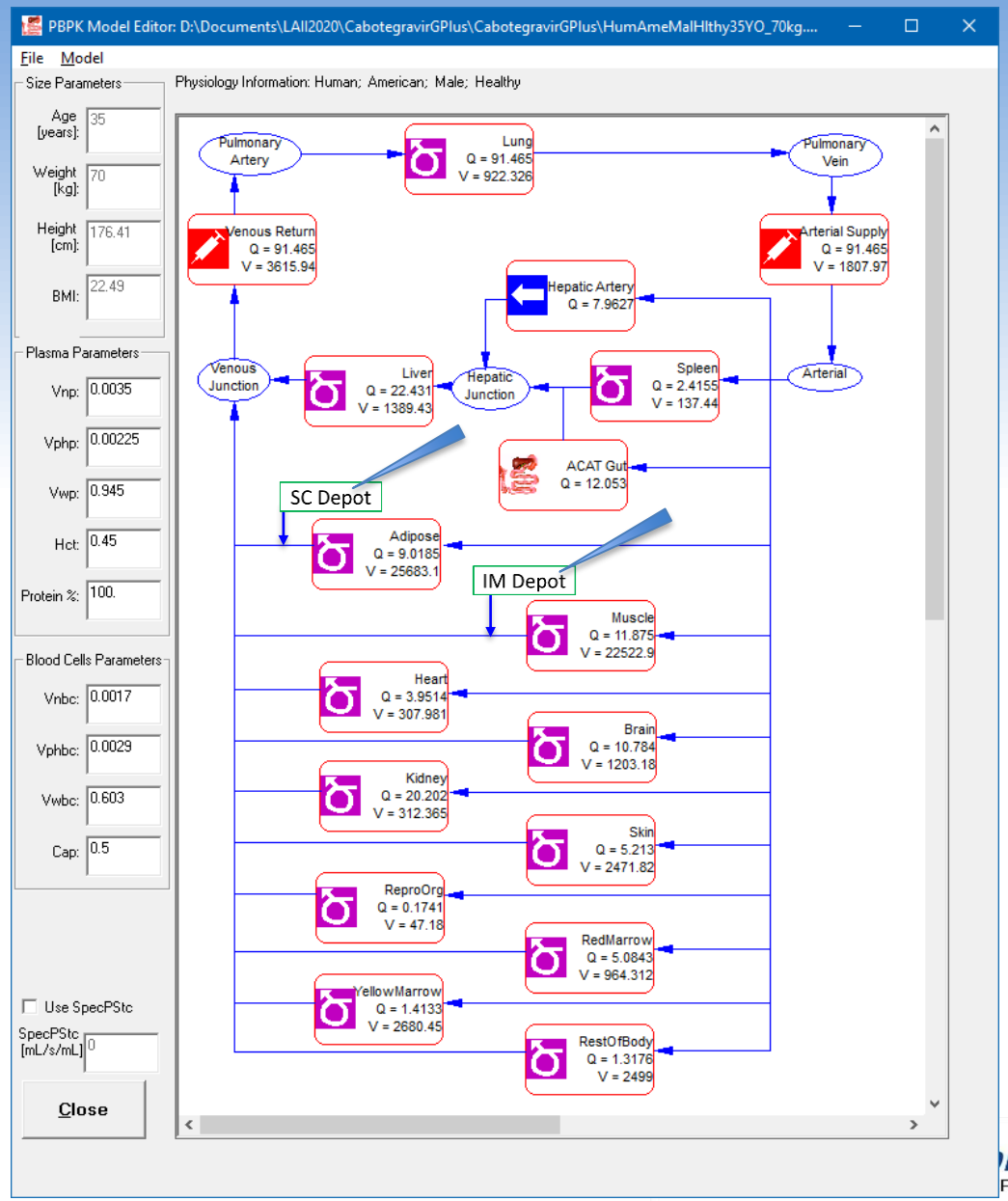
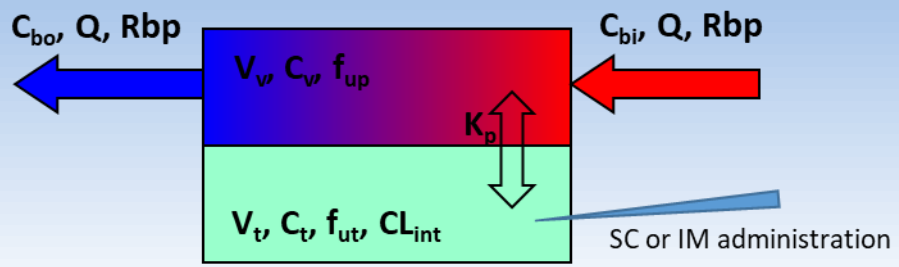
IM and SC Administration Model



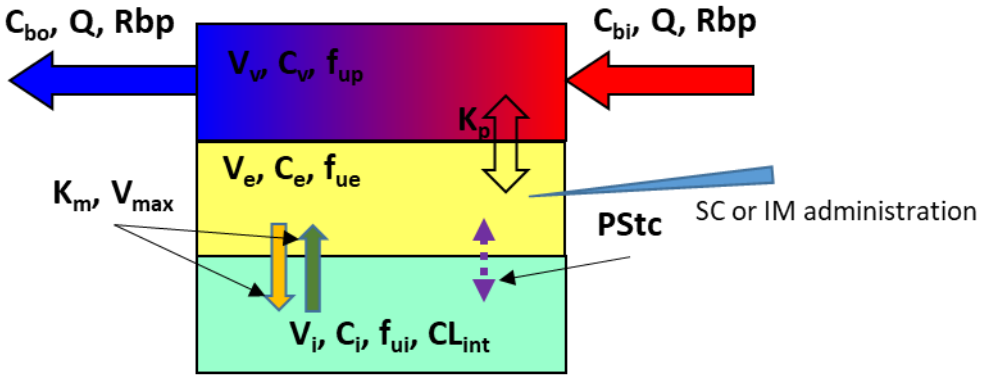


IM and SC Administration Model

Perfusion Limited:



Permeability Limited:



Existing PBPK model features are used to account for systemic uptake and distribution of the compound released from formulation after subcutaneous or intramuscular injection

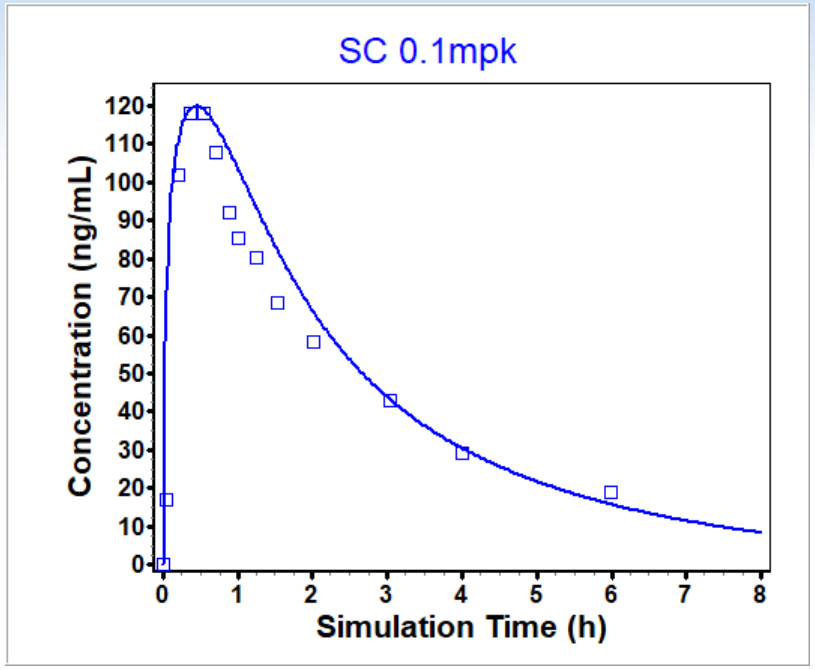
$$\frac{dm_{free}^{M}}{dt} = QC_{bi} - QC_{u}^{M}\frac{R_{bp}}{K^{M/p}}\left(1-(1-Hct)\cdot\frac{LymFlowFr}{100}\right) - QC_{u}^{M}\frac{Kpect}{K^{M/p}}\left((1-Hct)\cdot\frac{LymFlowFr}{100}\right) - CL_{M}$$

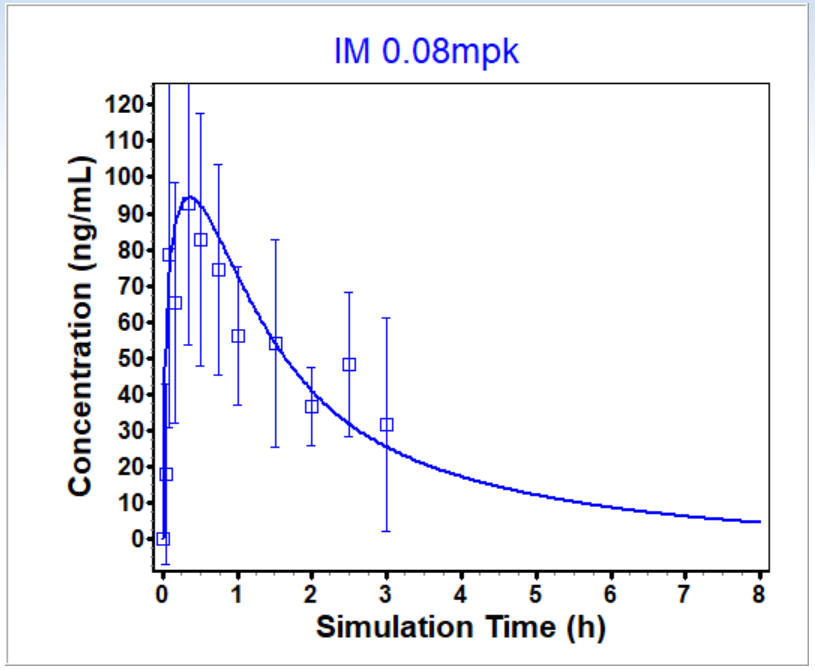
Permeability-limited tissue model includes additional terms for drug exchange between extracellular and cellular space via passive diffusion and/or carrier-mediated transport

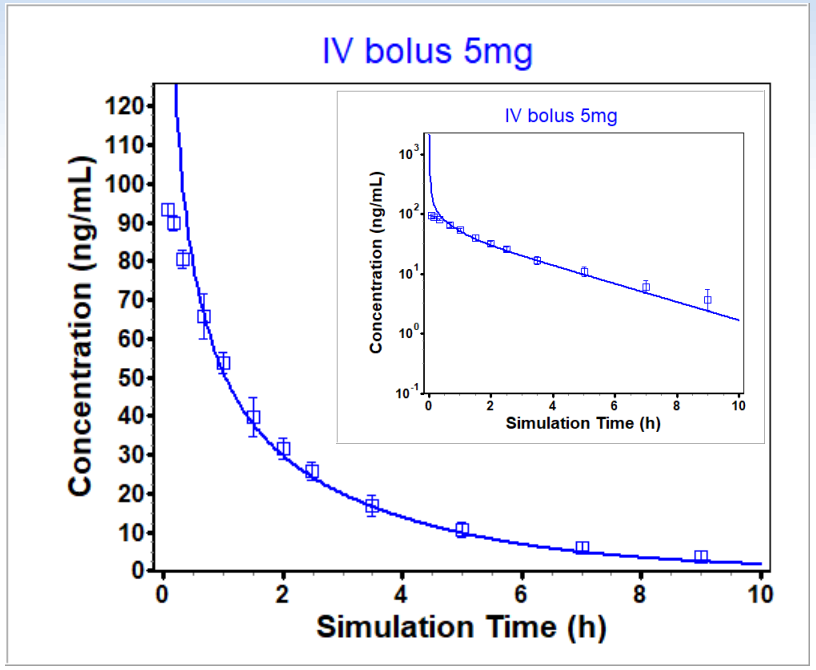
Validation of IM and SC Model: Solution Admin

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

Example: Cabotegravir

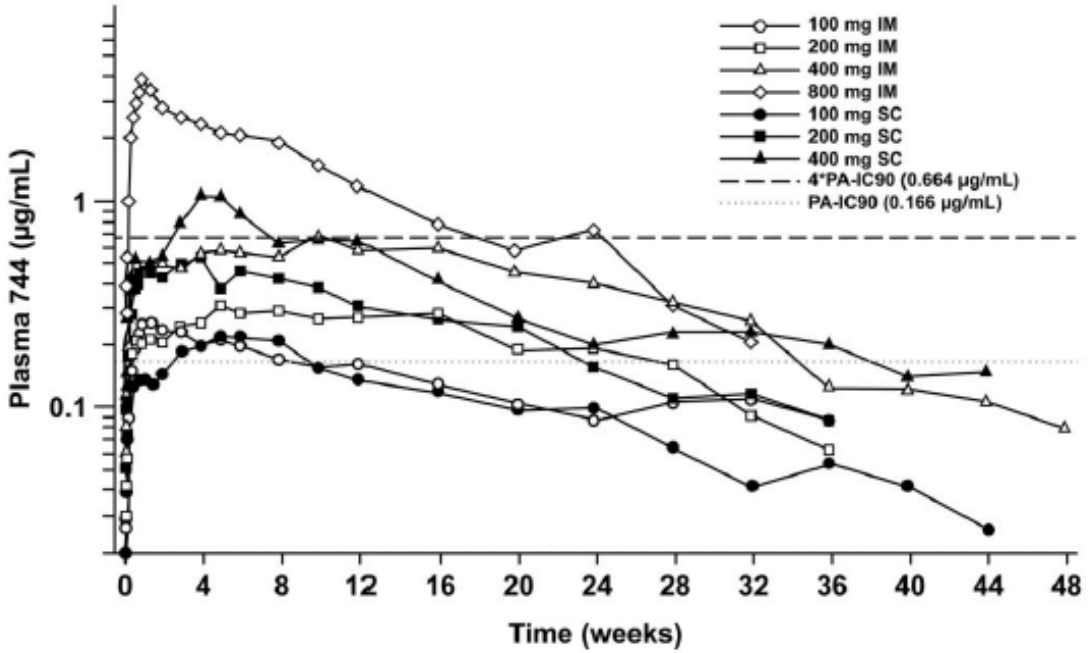


FIGURE 1. Mean plasma 744 concentration–time profiles after single-dose LA injections in healthy subjects (cohorts 1–7). PA-IC90 is the protein-adjusted concentration that inhibits viral replication by 90%. Figure reproduced with permission from Ref. 3. Adaptations are themselves works protected by copyright. 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

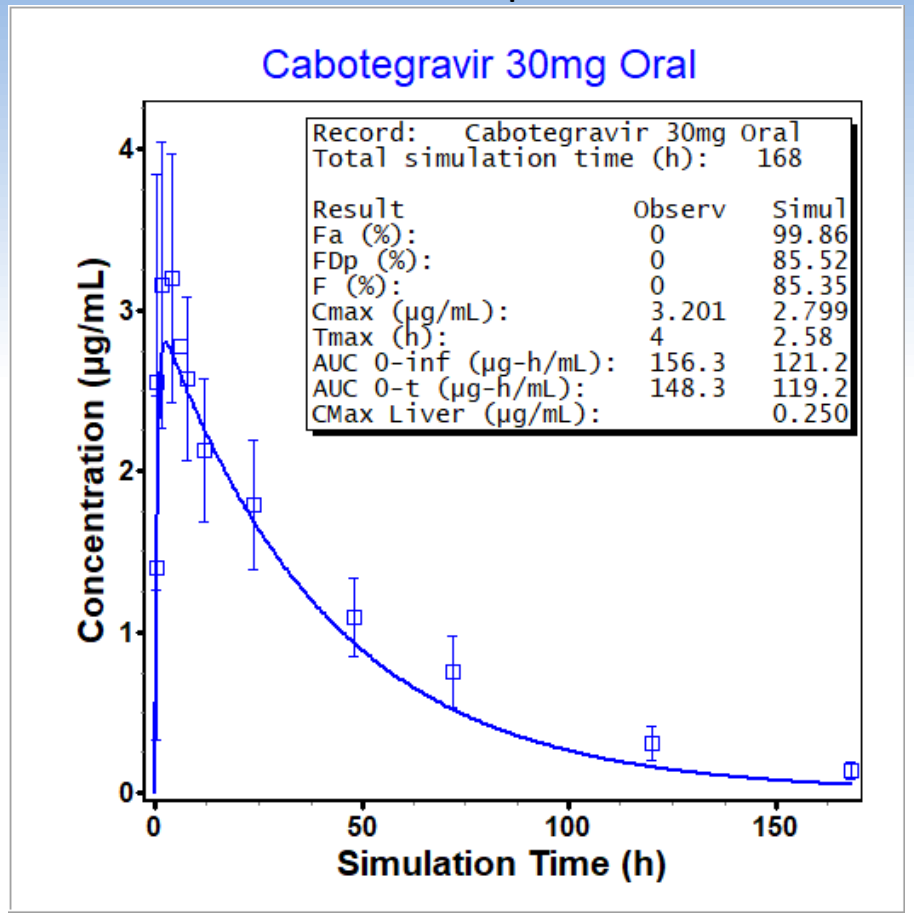
Cabotegravir Properties

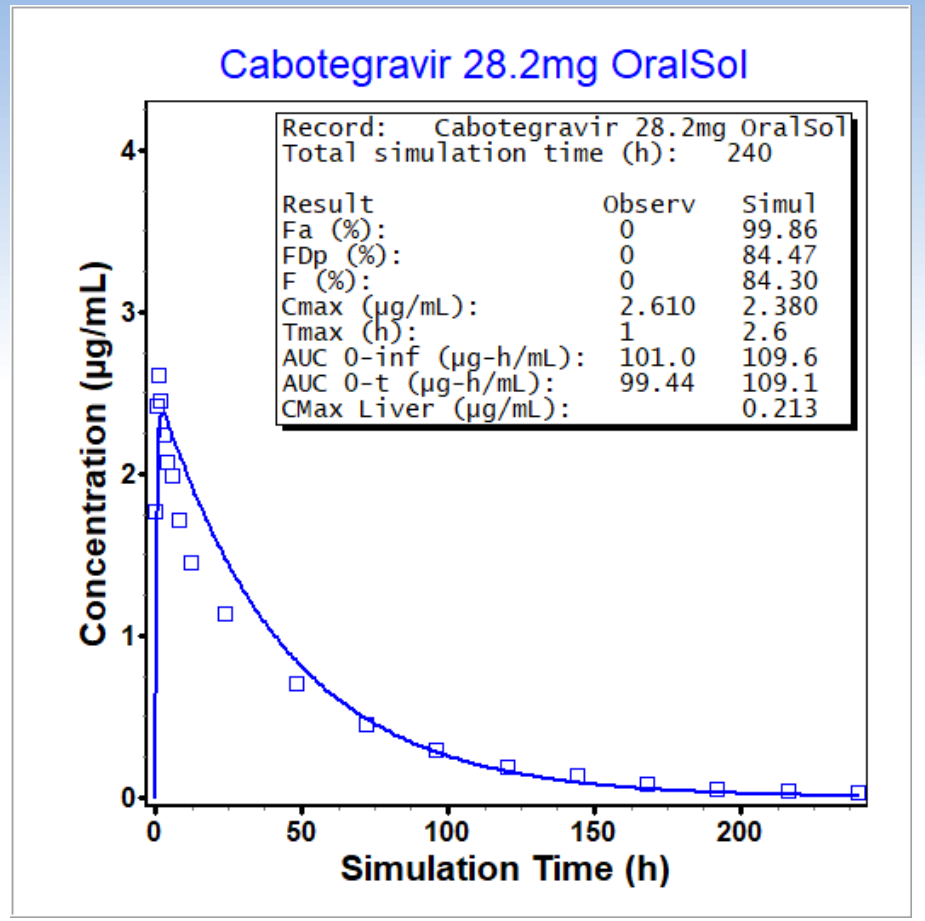
Parameter	Value	Source
Solubility (ug/mL) FaSSIF FeSSIF	<10ug/mL 2.3 ug/mL 1.24 mg/mL 0.61 mg/mL	(1) Yalkowski AP 8.1 AP 8.1
Solubility Factor (SF)	118.67	AP 8.1
logP	2.16	Estimated from dolutegravir (2)
pKa	4.52,10.51 Acid	AP 8.1
Peff (10^4 cm/s)	2.54	AP 8.1
Rbp	0.58	(3)
Fup	1 0.7	(1) (4)
Km/Vmax UGT1A1 (uM ,pmol/min/mg) Km/Vmax UGT1A9 (uM ,pmol/min/mg)	148 / 660 90 / 200	(1)

(1) Bowers, Xenobiotica, 2016; 46(2): 147–162
(2) (2) US FDA/CDER. Clinical Pharmacology Review: Dolutegravir, GSK 1349572. NDA 204,790. 2012.
(3) Estimated from pK source (1)
(4) Rajoli, pHd. Thesis, Univ. of Liverpool, 2017

Cabotegravir Baseline PK Model: PO Sol Admin

PBPK model with all perfusion-limited tissues; Kps estimated from drug- and tissue properties using default method; Elimination via UGT1A1 and UGT1A9 parameterized based on *in vitro* data





Observed data from:

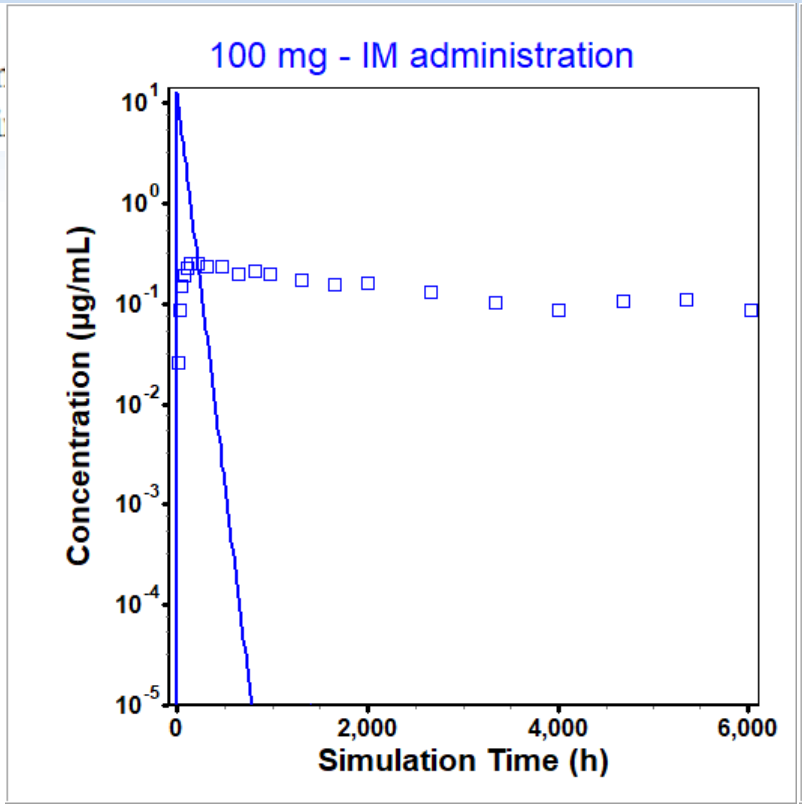
Bowers – Xenobiotica 2016, 46(2): 147; Ford, 17th Inter. Workshop on Clin. Pharmacol. of HIV & Hepatitis Therapy, June 8-10, 2016.

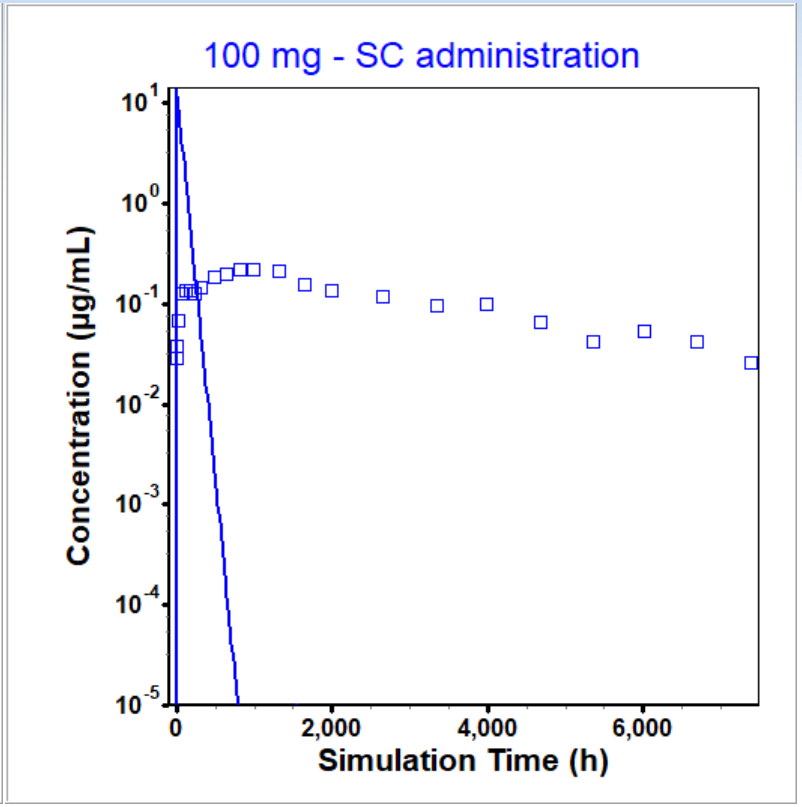
Cabotegravir: IM and SC Suspension Admin

GSK1265744 (GSK744), an analogue of dolutegravir, is a potent integrase strand transfer inhibitor with physiochemical properties that permit nanomilling of the crystalline free acid to a median particle size of 200 nm in the presence of surfactant, polymer, mannitol, and water for injection (*8*). The resulting nanoparticles are essentially 100% active drug and formulated as a GSK744 LA (200 mg/ml) pension. The same formulation is under evaluation in m studies (*8*). In healthy volunteers, single GSK744 LA i

Andrews – Sci Trans Med 2015, 270: 270ra4

Based on this information we assumed 100 nm particle radius for suspensions in the clinical study





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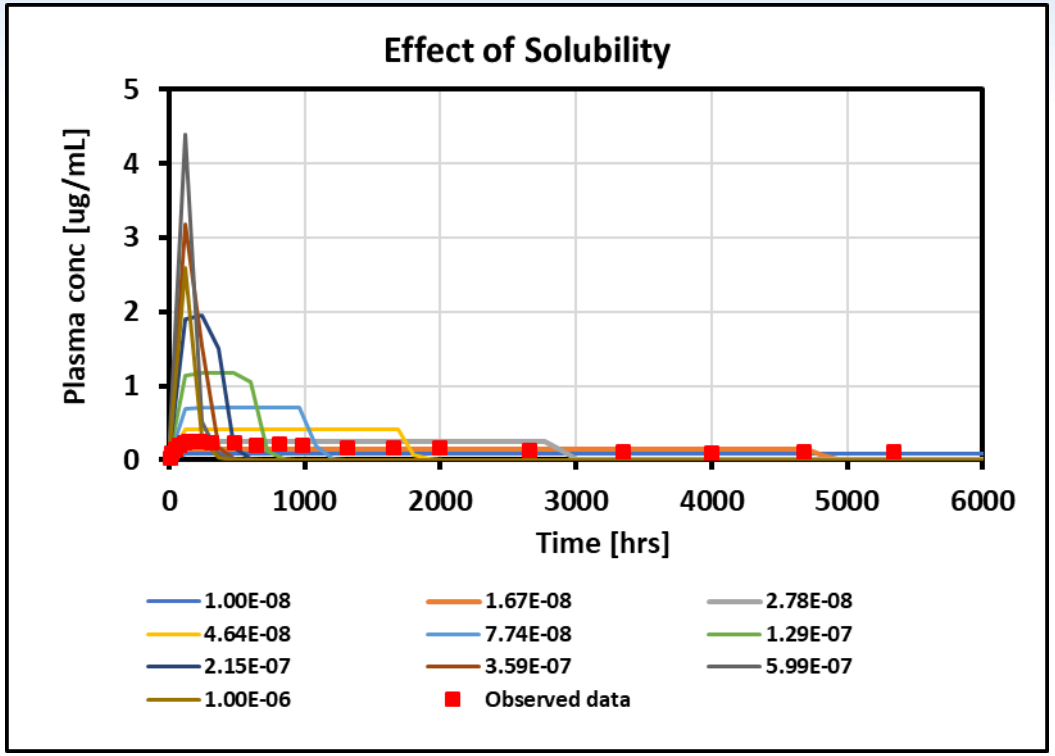
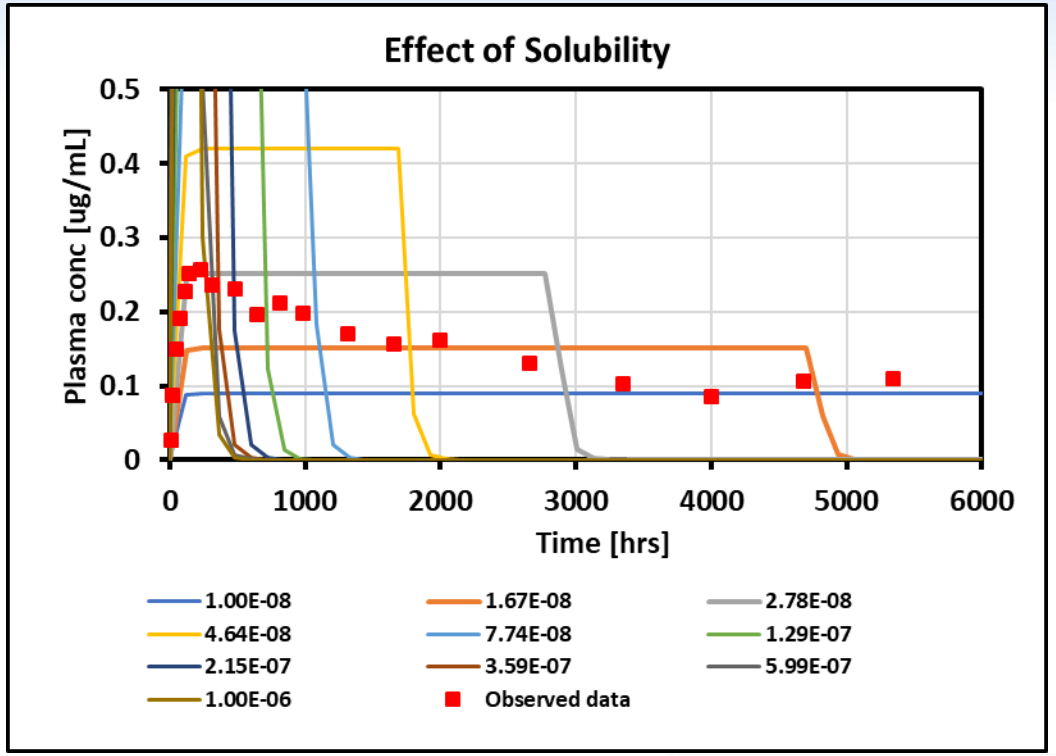
Cabotegravir 100 mg IM Susp: Effect of Solubility

Parameter sensitivity analysis was performed to evaluate the effect of solubility on PK after IM suspension administration:

- Significant decrease in solubility (in range ~20 pg/mL) would help to match the overall exposure (AUC)
- Change in solubility alone would not allow matching the shape of the observed Cp-time profile





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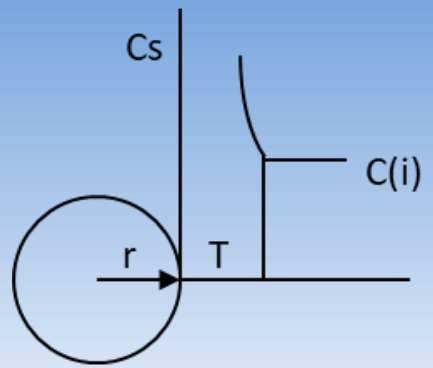
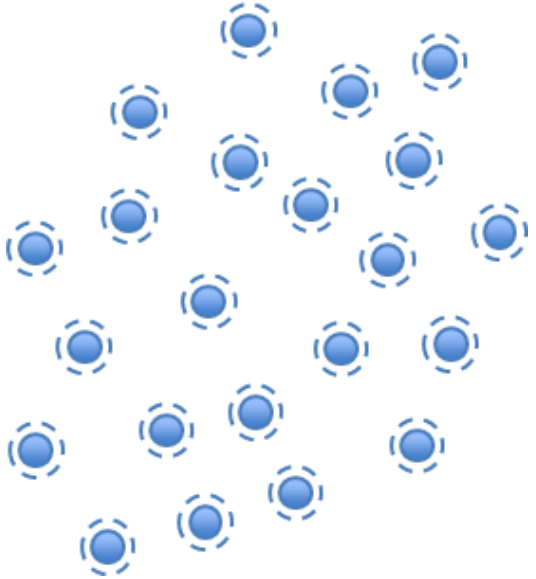
Dissolution

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



$T = r_{0j}$

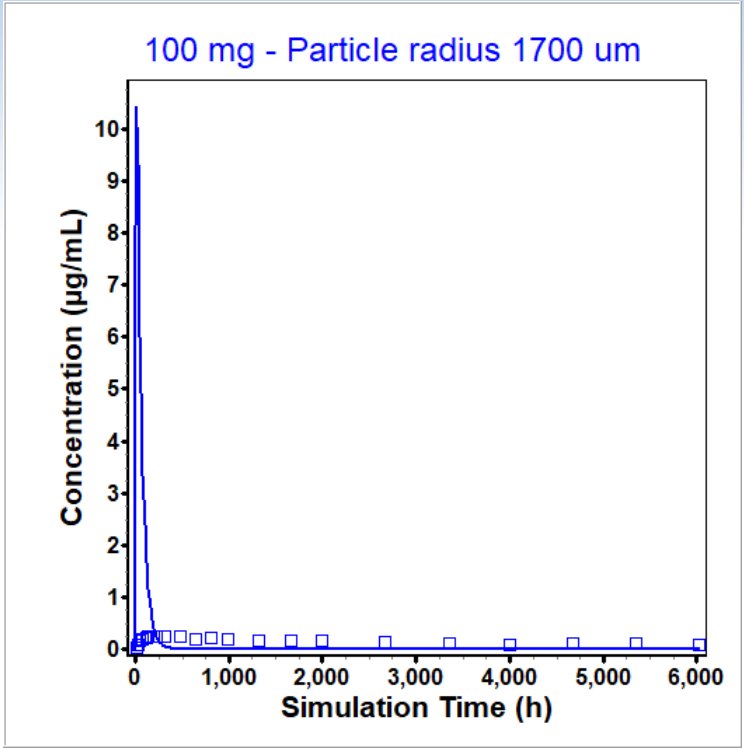


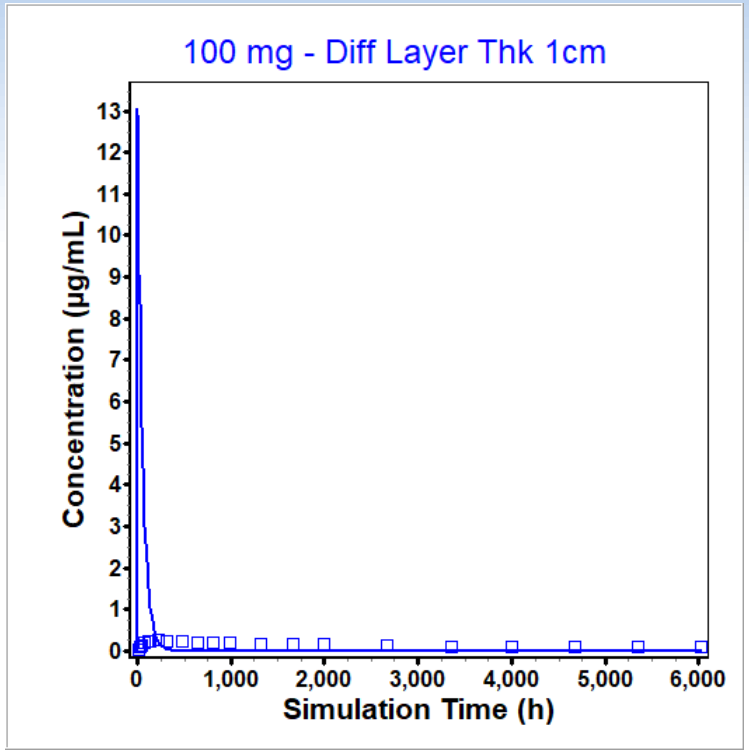
- Particles well separated – total surface area of each particle plays a role in dissolution
- Reasonably well stirred environment keeps diffusion layer thickness small

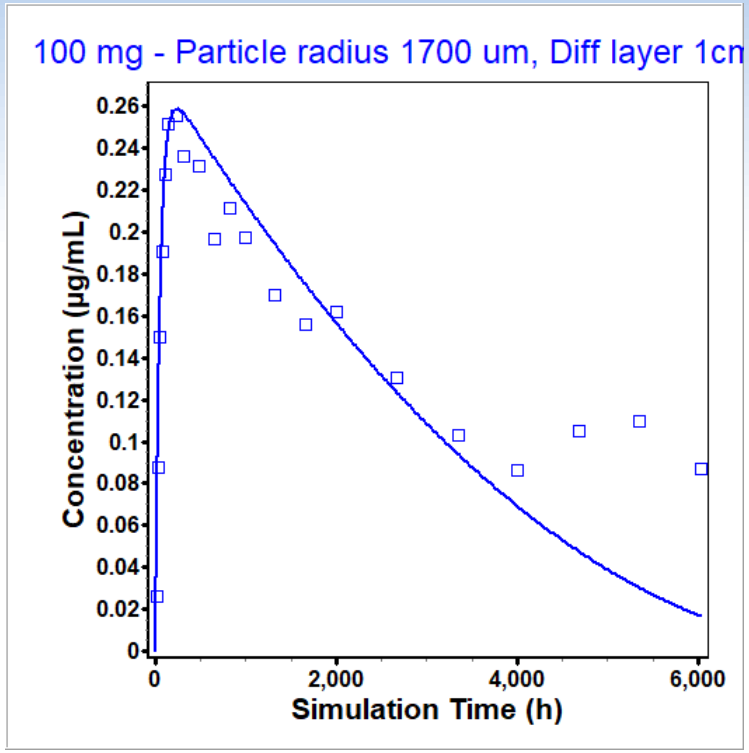
- Restricted tissue environment causes packing/aggregation of particles affecting effective dissolution surface area
- Static environment – the effective diffusion layer thickness may be significantly higher

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 accurate simulation of PK after 100 mg IM suspension injection







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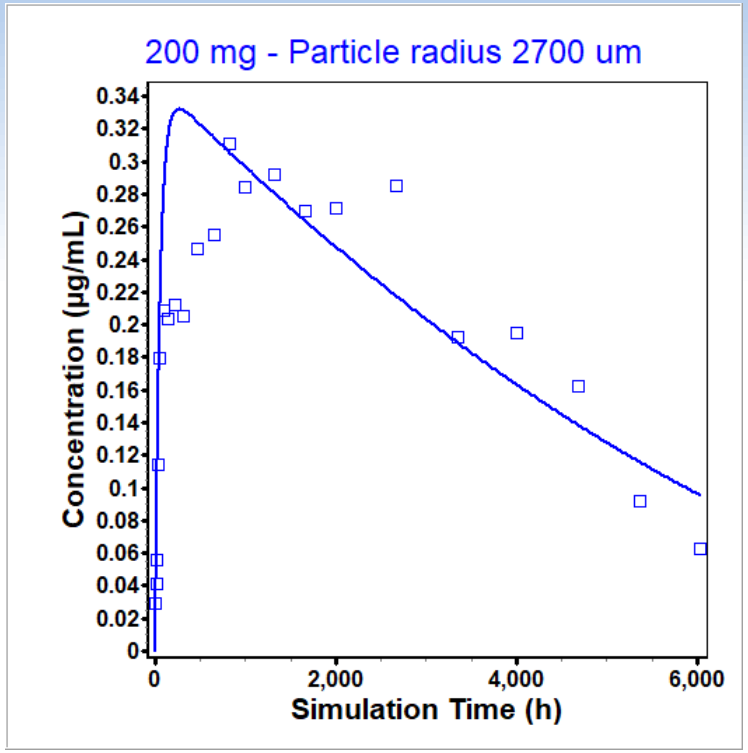
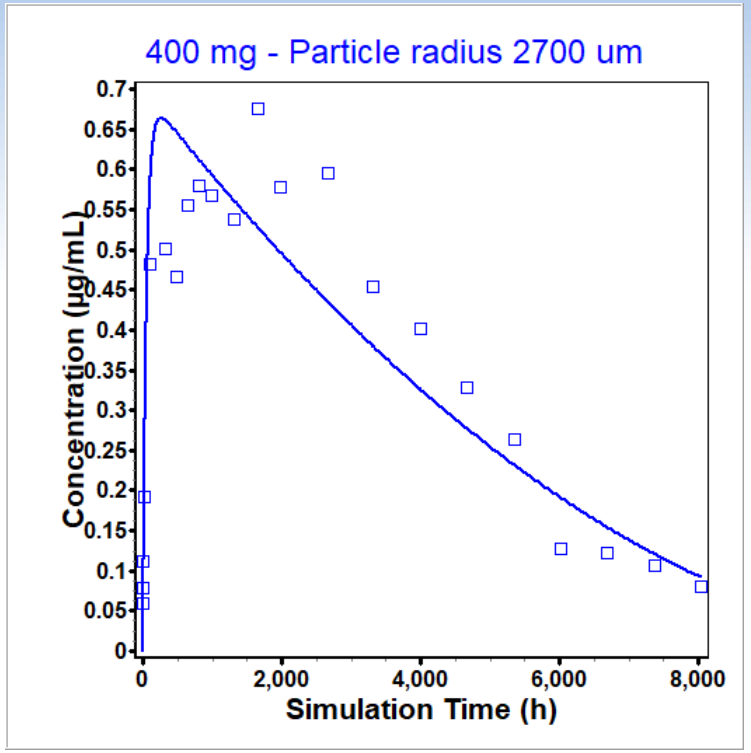
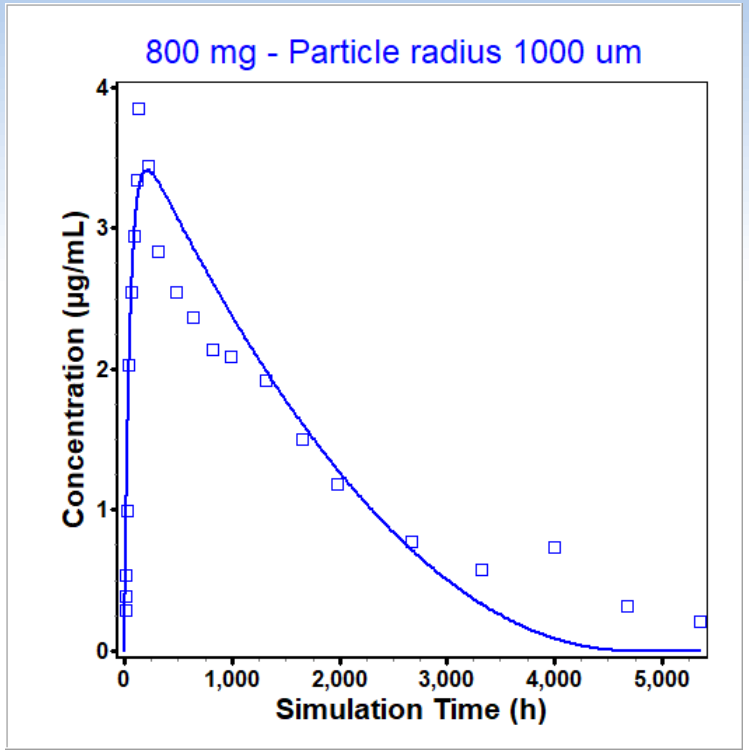
Effect of Particle Size and Diffusion Layer Thickness

Higher Doses of IM Suspension Administration

All simulations with diffusion layer thickness 1 cm







NOTE: 800 mg dose was administered as 2 injections of 400 mg which might explain the lower ‘effective’ particle radius

Effect of Particle Size and Diffusion Layer Thickness

Injection split

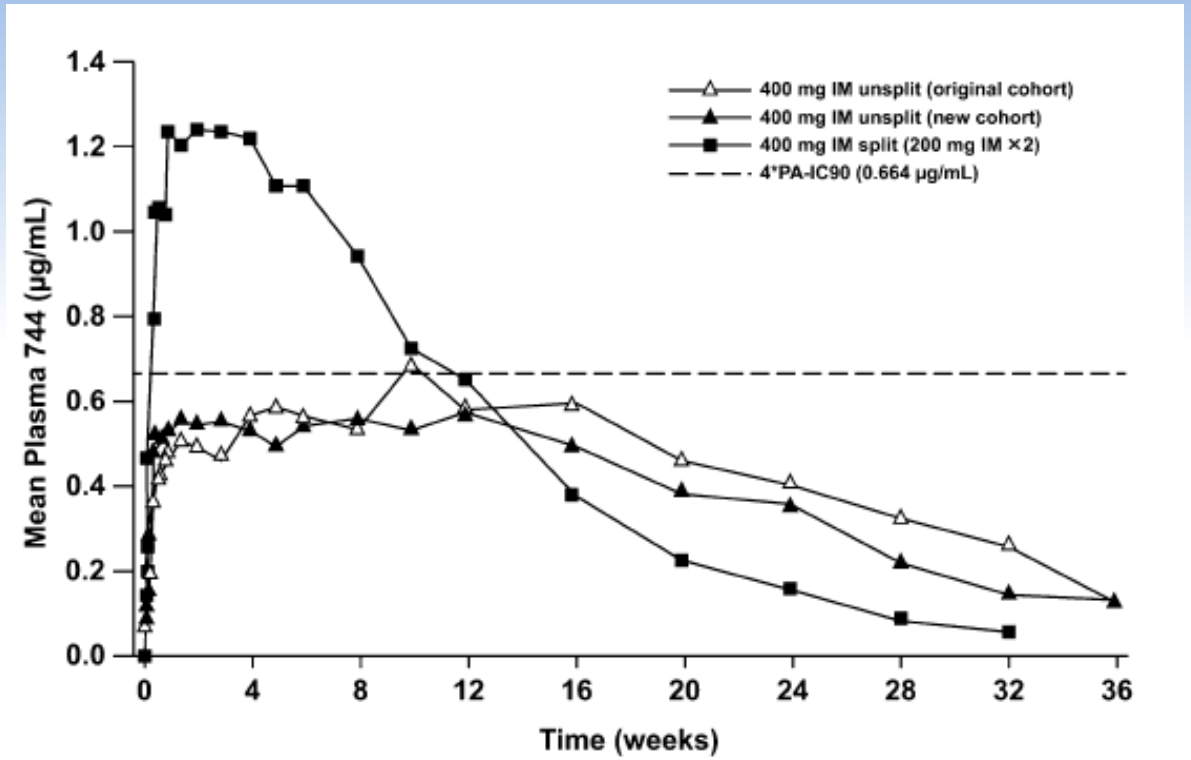


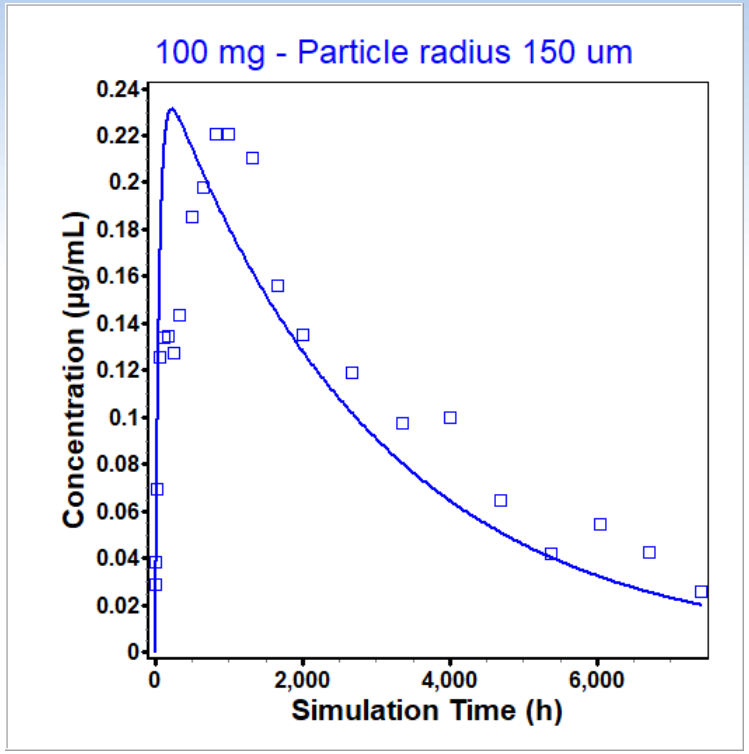
FIGURE 2. Comparison of mean 744 concentration–time profiles after 400 mg IM unsplit (cohorts 3 and 8) and split (cohort 9). PA-IC90 is the protein-adjusted concentration that inhibits viral replication by 90%.

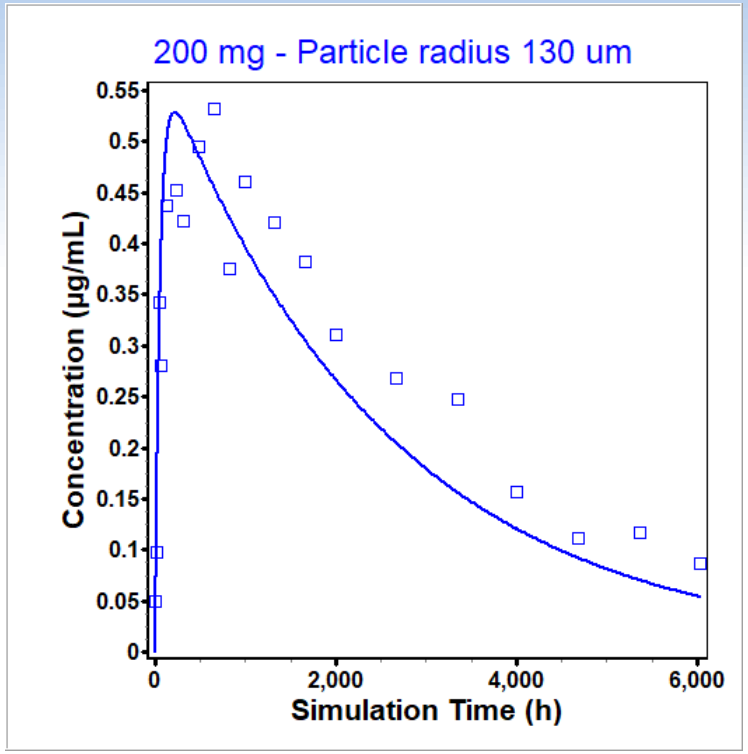
The clinical study also investigated the effect of splitting the dose into multiple injections and the Cmax was significantly higher when 400mg dose was split into 2 injections vs. when it was administered as single injection (AUC(0-inf) was unaffected)

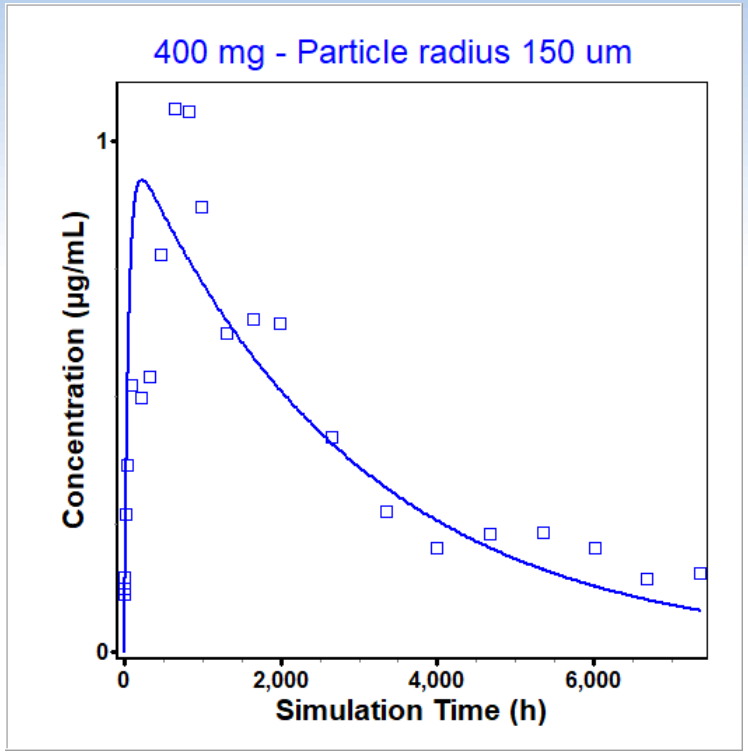
Effect of Particle Size and Diffusion Layer Thickness

Subcutaneous Administration

All simulations with diffusion layer thickness 1 cm







'Effective' particle radius more than 10-times smaller would explain PK data after subcutaneous administration

Unlike with IM suspension administration, the 'effective' particle radius remained the same for doses 100 – 400 mg

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Example: Paliperidone/Paliperidone Palmitate

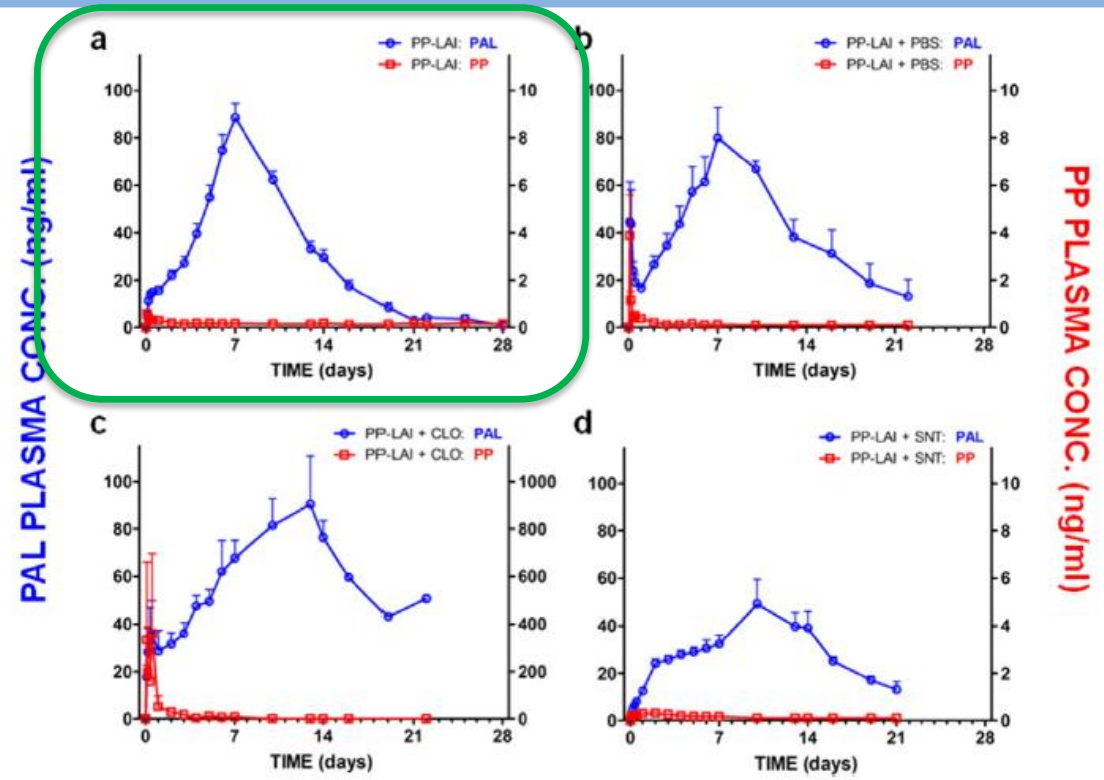


Fig. 4. Observed mean plasma concentration–time profiles of paliperidone palmitate (PP, red □) and paliperidone (PAL, blue ○) in rats following a single bolus IM injection of 20 mgEq./kg PP-LAI: a) PP-LAI only (control group); b) PP-LAI with intermittent IV doses of phosphate buffered saline liposomes (PBS); c) PP-LAI with intermittent IV doses of 50 mg/kg clodronate liposomes (CLO); d) PP-LAI with daily oral doses of 20 mg/kg sunitinib (SNT). Data represent mean concentrations ± SE ($n \geq 3$; except for CLO from day 16 onward ($n = 1$)).

- 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

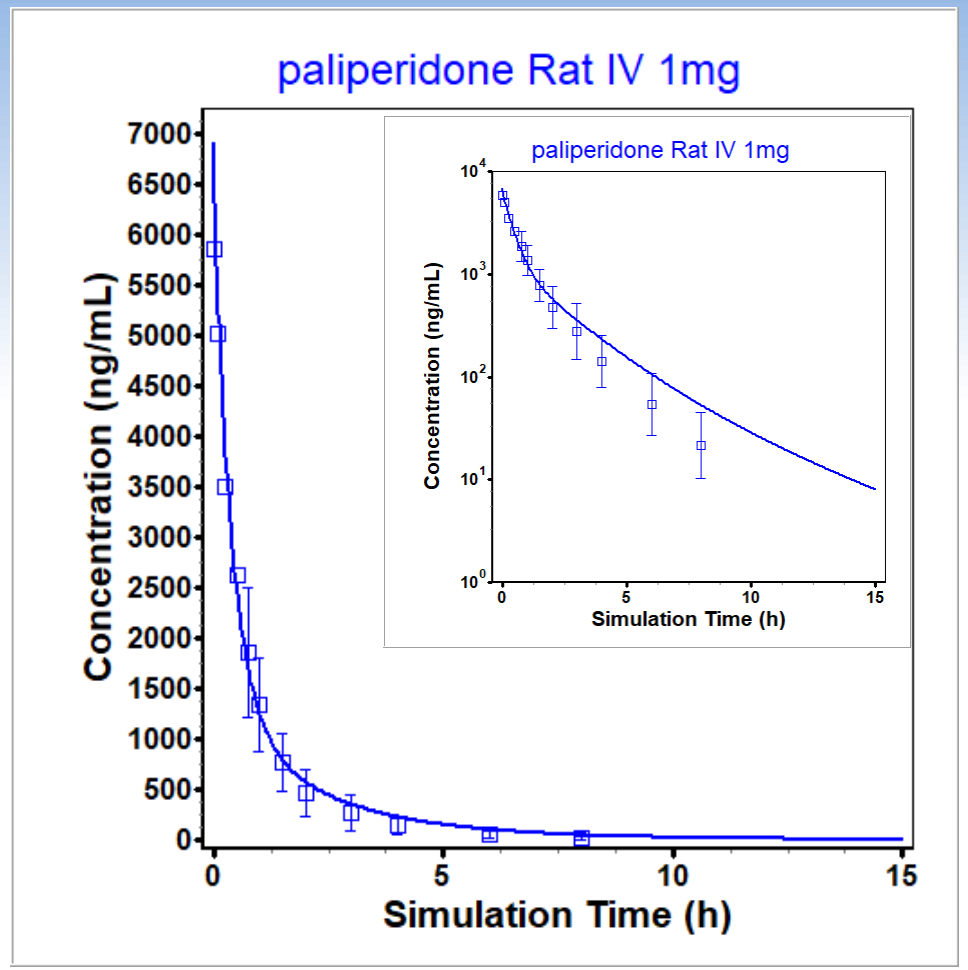
Darville – J Cont Rel – 2016, 230:95

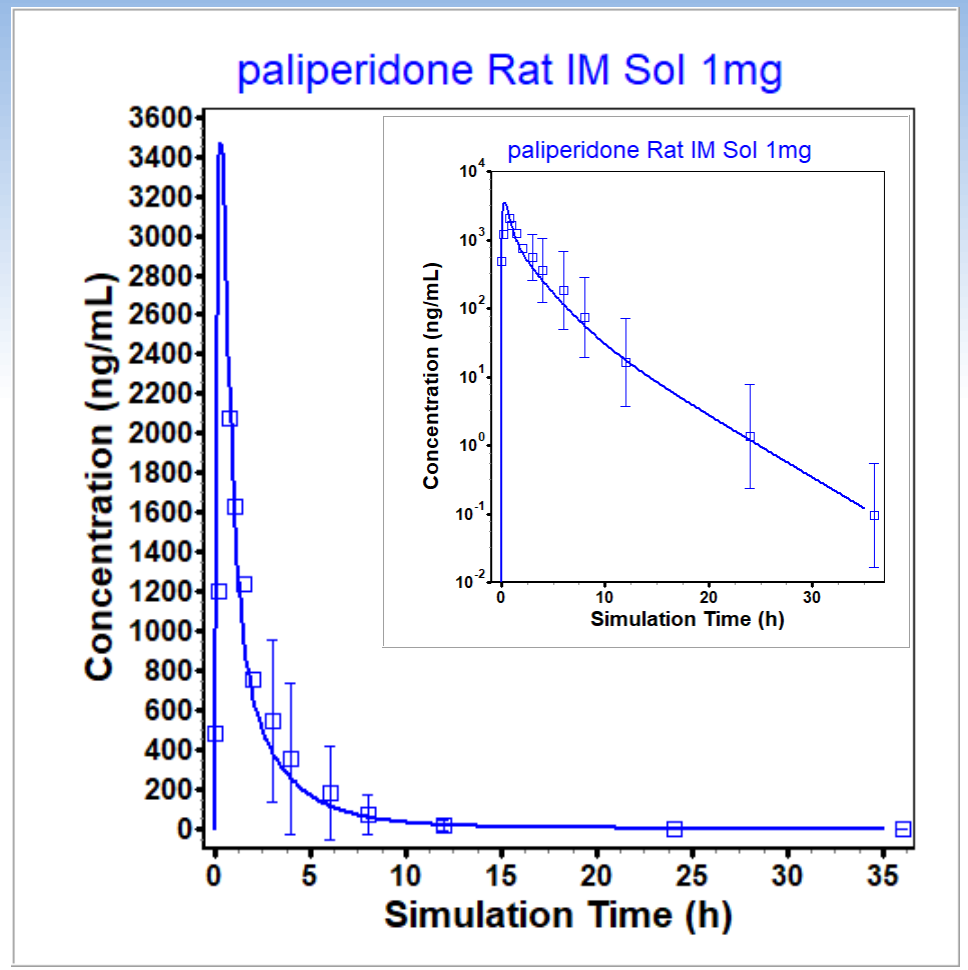
Paliperidone Properties

Paliperidone		
Variable	Value	Source
MW (g/mol)	426.2	
Exp. LogP	2.39	NDA 21-999 Approval Letter
Measured pKa	8.27/2.06	Schönher 2015
Exp Sol. @ pH 12.9 (mg/ml) Exp Sol. @ pH 1 (mg/ml) Exp Sol. Factor	0.01 23 2120	
Caco Papp A-B (10^5 cm/s) Caco Papp B-A (10^5 cm/s) Caco Ave. (10^5 cm/s)	1.89 3.47 2.68	NDA 21-999 Approval Letter
Exp. Fup (%)	26.8	NDA 21-999 ClinPharmReview_Part1
Exp. Rbp	0.805	Vermeir_DMD_2008_36(4)_769-779

Paliperidone Baseline PK Model: IV and IM Solution

Compartmental PK model fitted to *in vivo* data; default settings for IM solution administration





Observed data from:
Darville – J Cont Rel 2016, 30:95.

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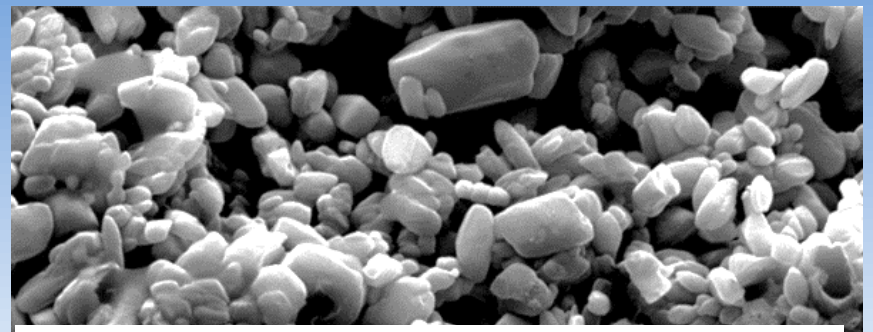
Paliperidone Palmitate (PP) IM Suspension



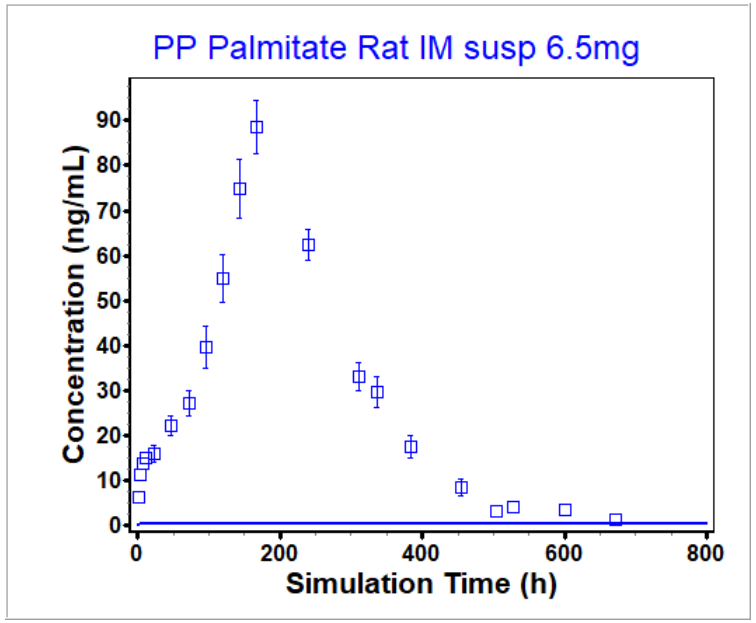
Characterization of the Microsuspensions

The median particle size and particle size distribution of the PPP-LAI suspension were measured by LD analysis with a Mastersizer® MicroPlus instrument (Malvern Instruments Ltd., Worcestershire, UK) at ambient temperature. The suspension was dispersed in purified water to achieve a degree of obscuration between 12% and 15%. Real and imaginary refractive index values for PPP were 1.56 and 0.01, respectively, and the dispersant refractive index was 1.33. Particle sizes were calculated using the Mie theory and are reported as volume-based median equivalent sphere diameters ($D_{v,50}$) plus or minus the standard deviations ($n = 3$). Because of the exceptional monodispersity of the PS particles reported by the manufacturer (1.063 ± 0.01 μm), additional particle size measurements

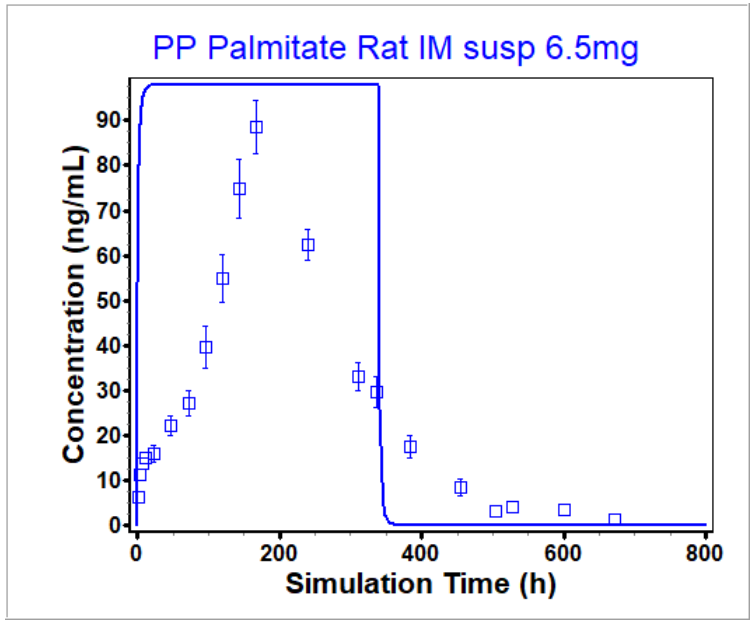
Darville – J Pharm Scie 2014, 103:2072

- Simulation assumes that PP properties drive initial dissolution but once dissolved, it breaks down quickly to paliperidone
- Assuming that similar suspension was used in the study
- Solubility for Paliperidone Palmitate not available – estimates from logP using Yalkowsky equation range from 0.165 to 2.225 ng/mL (depending on the source of logP prediction)

Solubility 1ng/mL



Solubility 500ng/mL



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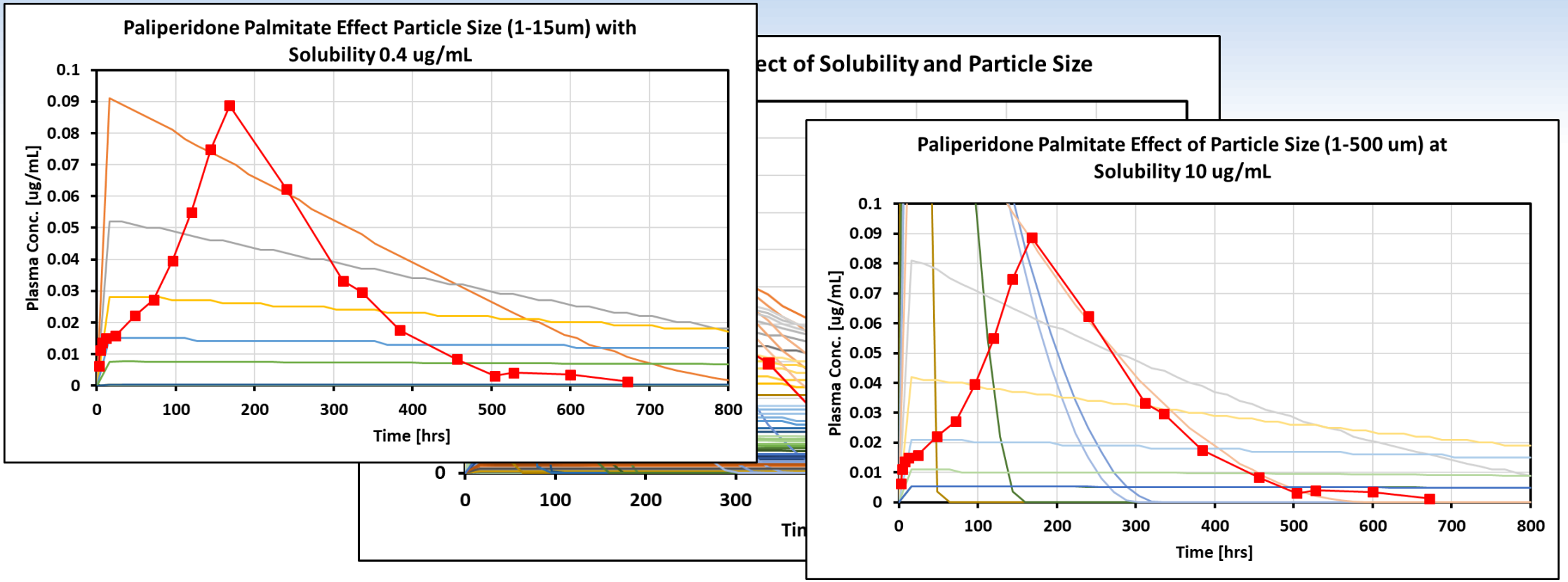
Paliperidone Palmitate: Solubility and Particle Size

Parameter sensitivity analysis was performed to evaluate the effect of solubility and particle radius on PK after IM suspension administration:

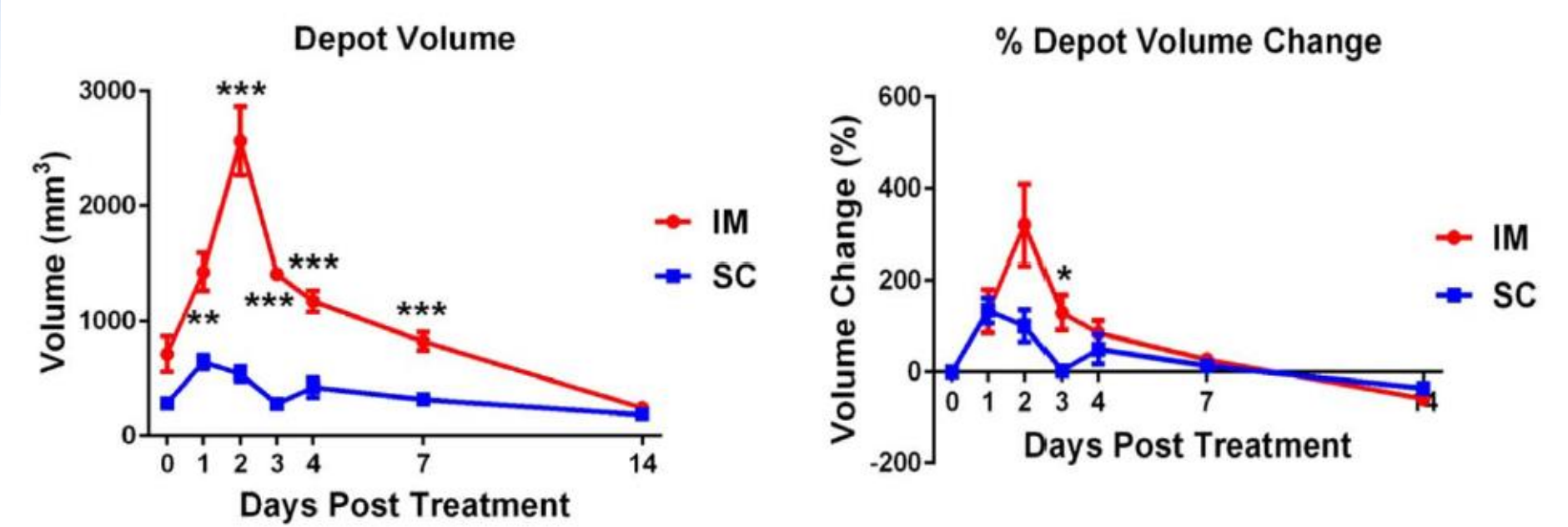
- Combinations of solubilities in range 10 ng/mL – 10 ug/mL and particle radii in range 1-500 um were investigated
- Analysis did not reveal any combination of particle sizes and solubilities that would match shape of PK profile



Inflammation

Jucker investigated the changes in IM and SC drug depot morphology after injection of cabotegravir suspension:

- The depot volume increased rapidly by day 2 about 3-7 fold after IM and 1 fold after SC injection of cabotegravir
- Injection of vehicle did not affect the depot volume suggesting that API or presence of particles is key driver for depot volume changes (inflammation)

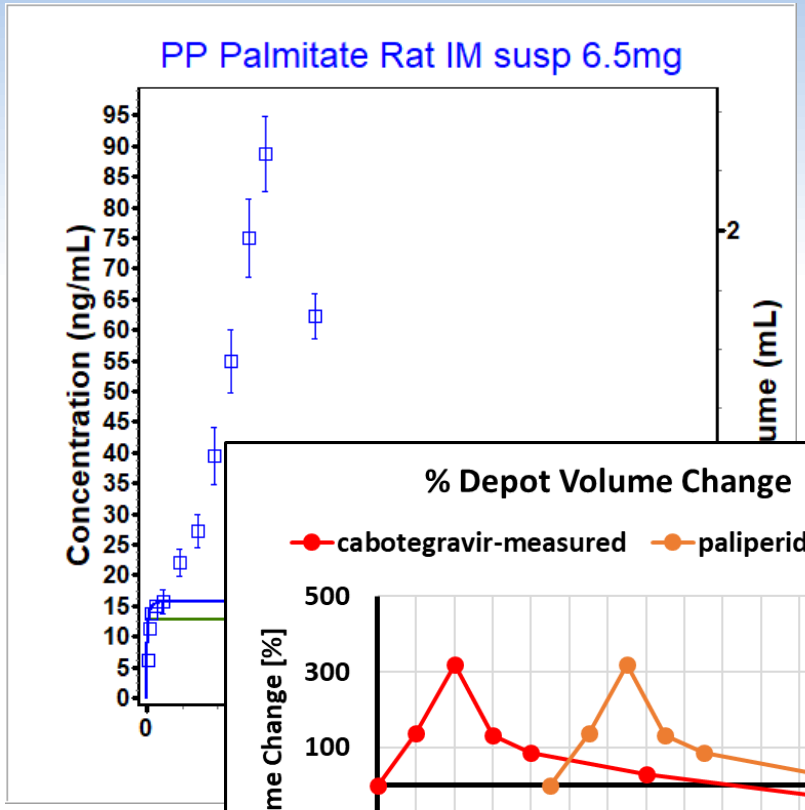


Jucker – J Contr Rel 2017, 268: 102-112

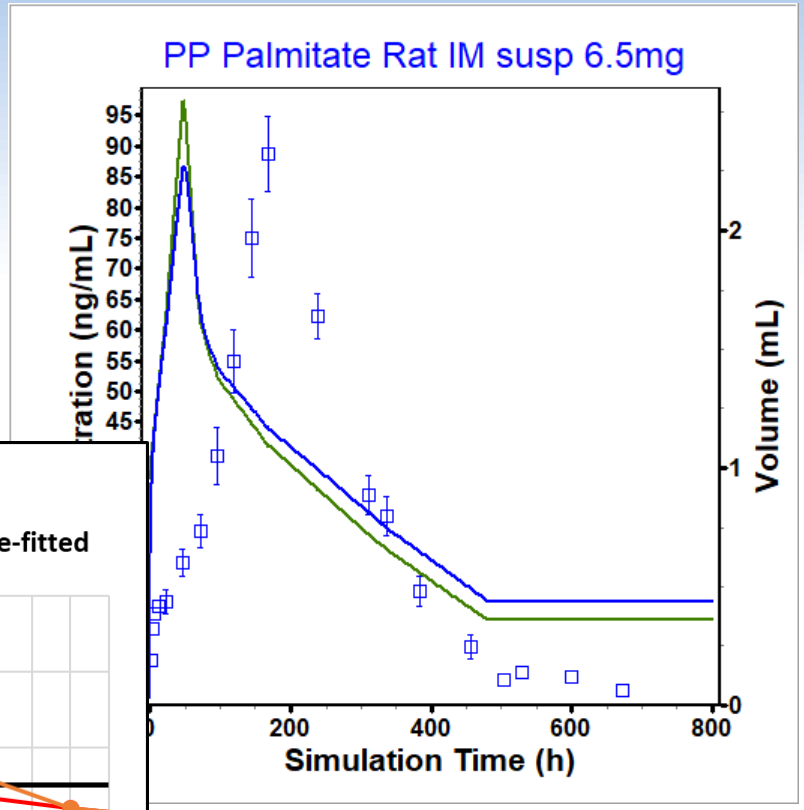
Effect of Inflammation on Paliperidone PK

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

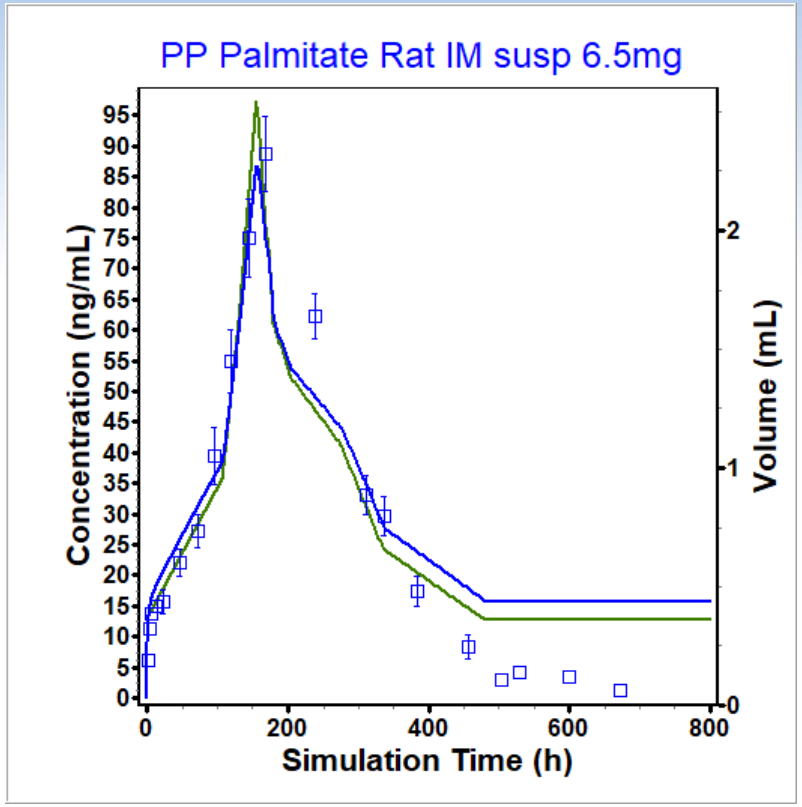
Fixed depot volume = 0.336 mL (volume at the end point)



Depot volume changes as measured for cabotegravir



Depot volume changes measured for cabotegravir shifted by 4.5 days



Green – depot volume

Blue – plasma concentration

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Summary

- 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
- Presented examples explored the effects of different processes separately, but in reality they are likely to occur simultaneously
- Uncertainty in drug properties (i.e. solubility) complicates the analysis – experimental values for properties that can be measured separately would increase confidence in deconvoluted parameters that are difficult to measure directly

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- Discovery Cheminformatics

Questions?