Best Practices for Membrane & Biphasic *In Vitro* Dissolution with DDDPlus™ & GastroPlus®

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What is DDDPlus™?

Reimagining how companies design and analyze *in vitro* dissolution studies

- Now utilized by >50 companies globally plus the US and China FDAs

Provides models for most dosage forms and experimental conditions

- Immediate/delayed/controlled release oral products plus long-acting injectable formulations
- USP, ASD, biphasic, membrane dissolution apparatus

Significant momentum behind the DDDPlus/GastroPlus marriage to capture IVIVE of precipitation kinetics and establish product specs

Introduction

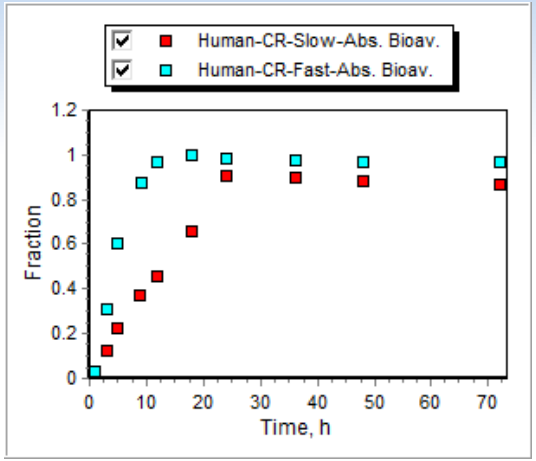
- What is DDDPlus
  - How can it be utilized in drug development?
  - What can DDDPlus predict?
  - What inputs are necessary?
  - What results can be obtained?

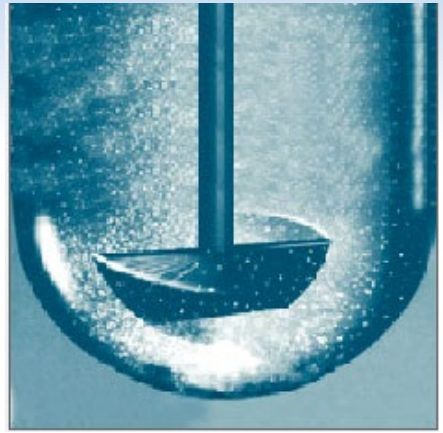
- Case Study – synergy of DDDPlus and GastroPlus
  - Biphasic and membrane dissolution experiments for determination of precipitation kinetics.
  - *In Vitro to In Vivo* (IVIVE) extrapolation of precipitation

How Can Simulation Software be Used?

Dissolution Method Development

- How can I design my *in vitro* experiment to correlate with the *in vivo* release?





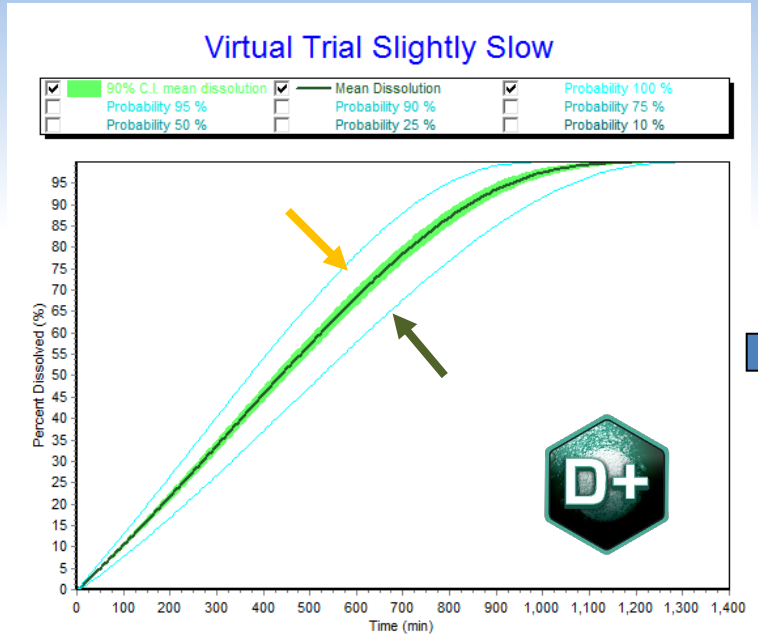
Formulation Design

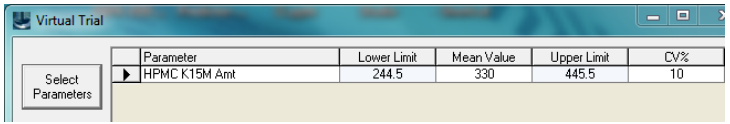
- How do I modify my formulation to produce an *in vitro* dissolution rate that meets my target?

Establish design or safe spaces

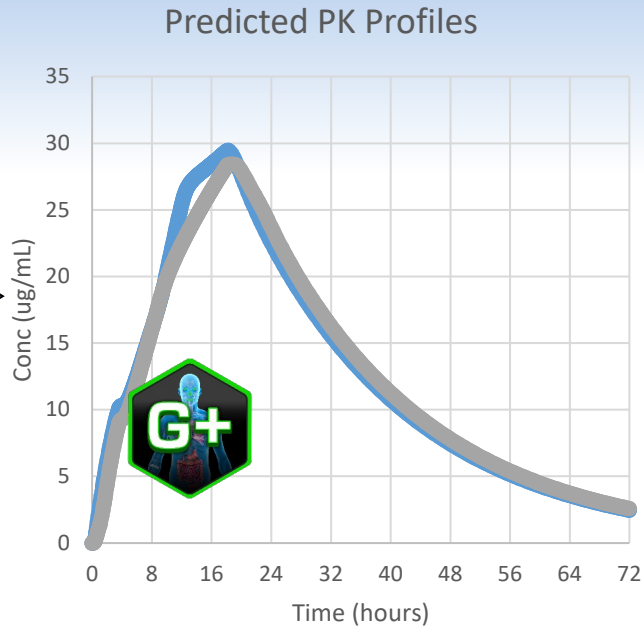
10% variability around HPMC content

25 virtual lots simulated in DDDPlus





100th percentile ('extreme') dissolution profiles loaded into GastroPlus to predict PK



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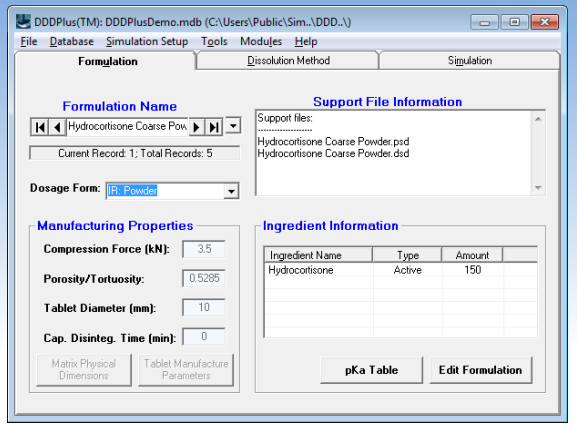
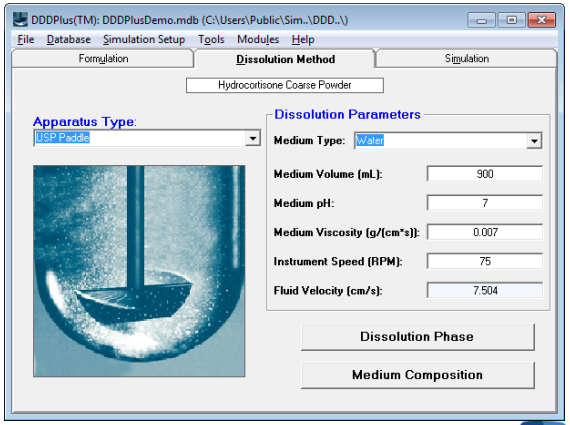
What does DDDPlus consider?

DDDPlus is a state-of-the-art formulation simulation computer program that contains equations to account for the following:

- Dissolution rate for active pharmaceutical ingredient (API) and excipients
- Multiple particle size distribution for API and excipients
- Variety of dosage form models
- Solubility-dynamic microclimate pH calculation for API and excipients
- pH of buffers from composition of acids, bases, and salt equivalents.
- Selection of USP and biorelevant experimental apparatus and conditions





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DDDPlus User Inputs

Formulation:

Compression force	Porosity
Tablet diameter	Matrix dimensions (for controlled-release)
Disintegration time	

Ingredient(s):

Name	Type (API, wetting agent, disintegrant, other)
Salt type (if any)	Mol. Weight
Diffusion coefficient	pKa(s)
Solubility factor	Solubility @ **reference pH**
Particle size distribution	(type, mean, standard deviation, # bins)

Dissolution Method:

Vessel Type	Speed
Medium Volume	Initial pH
Buffer	Surfactants
Different experimental phases	

IMPORTANT: applying measured *in vitro* dissolution data to optimize model parameters is a key step in developing a validated model!

Formulation Models

Immediate Release *(IR)*

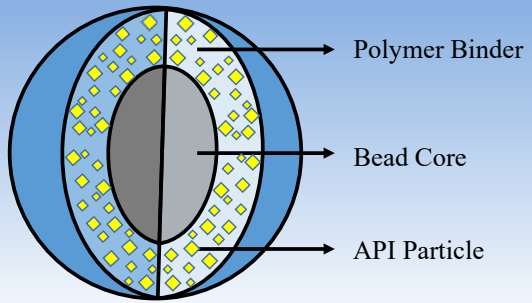
- Powder
- Solution (for precipitation studies)
- Tablet
- Capsule
- Bead Coating

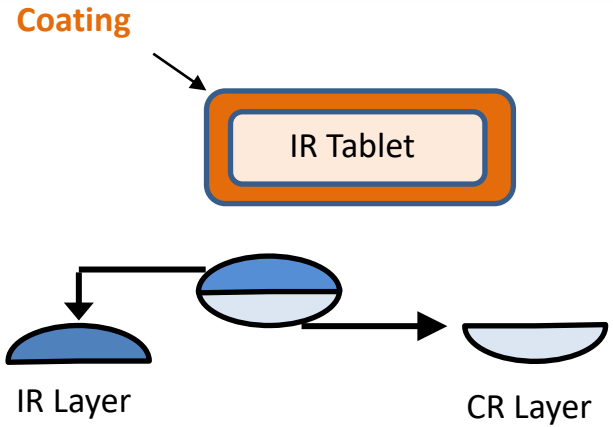
Delayed Release *(DR)*

- Coated Tablet

Controlled Release *(CR)*

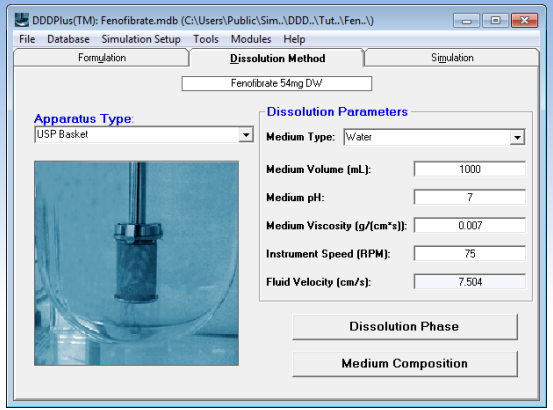
- Polymer Matrix (Swellable)
- Polymer Matrix (Non-Swellable)
- Bilayer Tablet
- Bead Coating
- Long-Acting Injectable (LAI) Microsphere

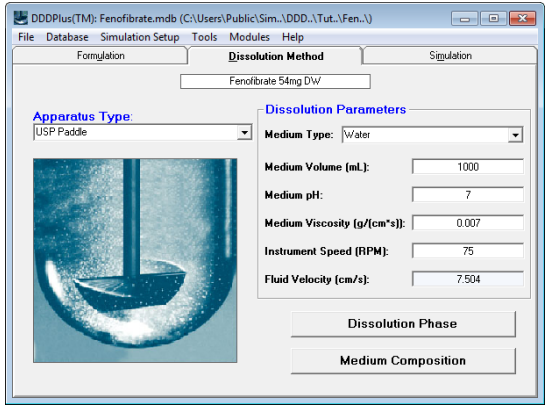


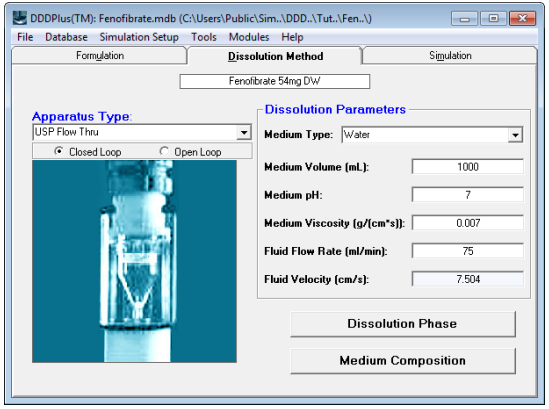


Experimental Apparatus Options

- USP 1 Basket
- USP 2 Paddle
- USP 4 Flow-through
  - ✓ Open or closed loop
- Pion µDiss Profiler™
- Artificial Stomach Duodenum (ASD)
- Membrane Dissolution
- Biphasic Dissolution

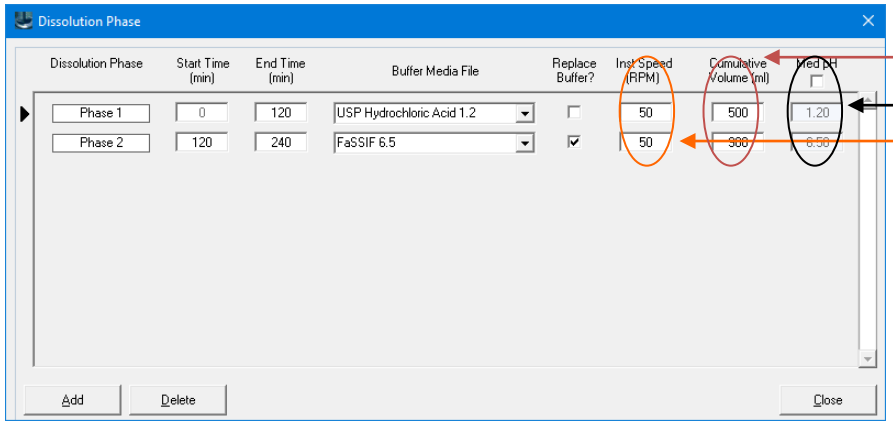






Improved Multi-stage Dissolution Experiments

- Redesigning *in vitro* experiments can help when an *in vitro-in vivo* correlation cannot be achieved
  - *in vivo* environment sometimes cannot be accurately reproduced using standard *in vitro* conditions
- DDDPlus lets you optimize *in vitro* experimental conditions to produce a desired dissolution profile by incorporating multiple "phases"
  - Instrument speed, medium volume, and pH can vary for each "phase" you define, as well as the start and end times for each phase
  - New! Fully mechanistic pH buffer and microclimate pH calculations based on buffer compositions and if replacement or mixing of buffers is occurring



By adjusting:

- Medium volume
- pH
- Instrument Speed

Full pH calculations of all the buffer mixtures are accounted for or you can replace the media with fresh buffer.

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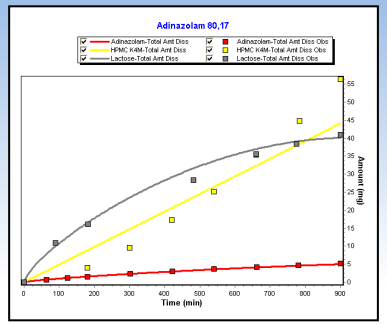
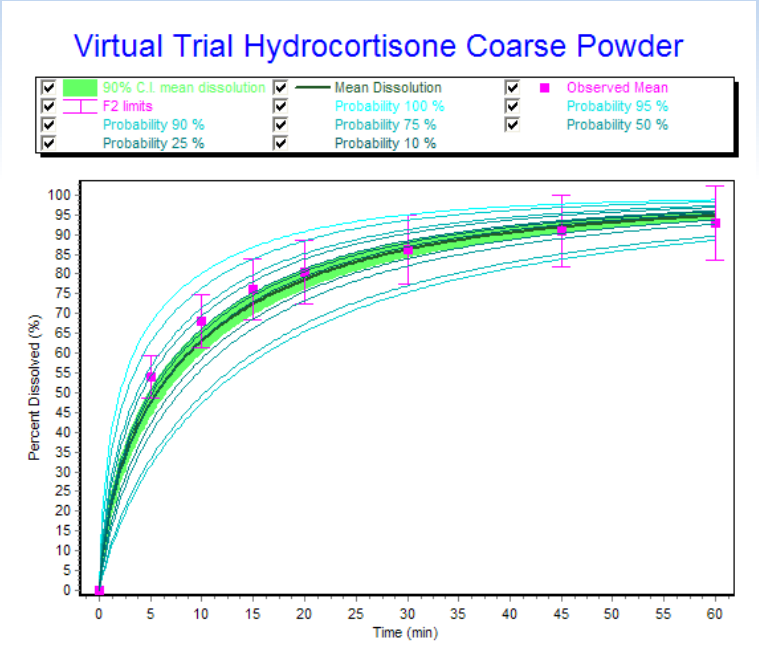
DDDPlus™ Outputs

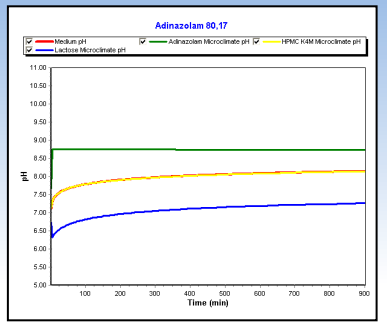
Dissolution profiles for all formulation ingredients



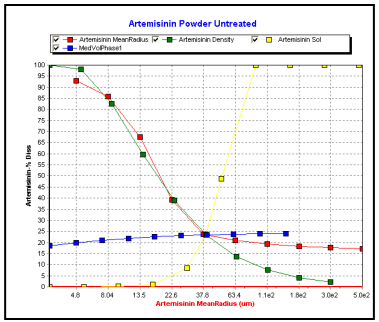
Virtual Trials



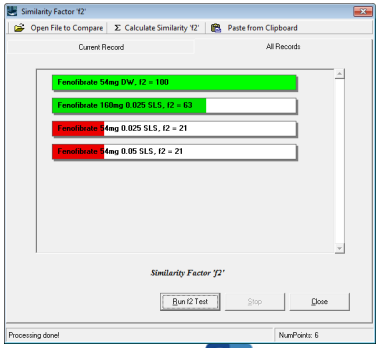
Medium/microclimate pH changes



Parameter Sensitivity Analysis “Spider” Plots



f1 (difference) & f2 (similarity) calculations



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Case Study – Synergy of DDDPlus and GastroPlus

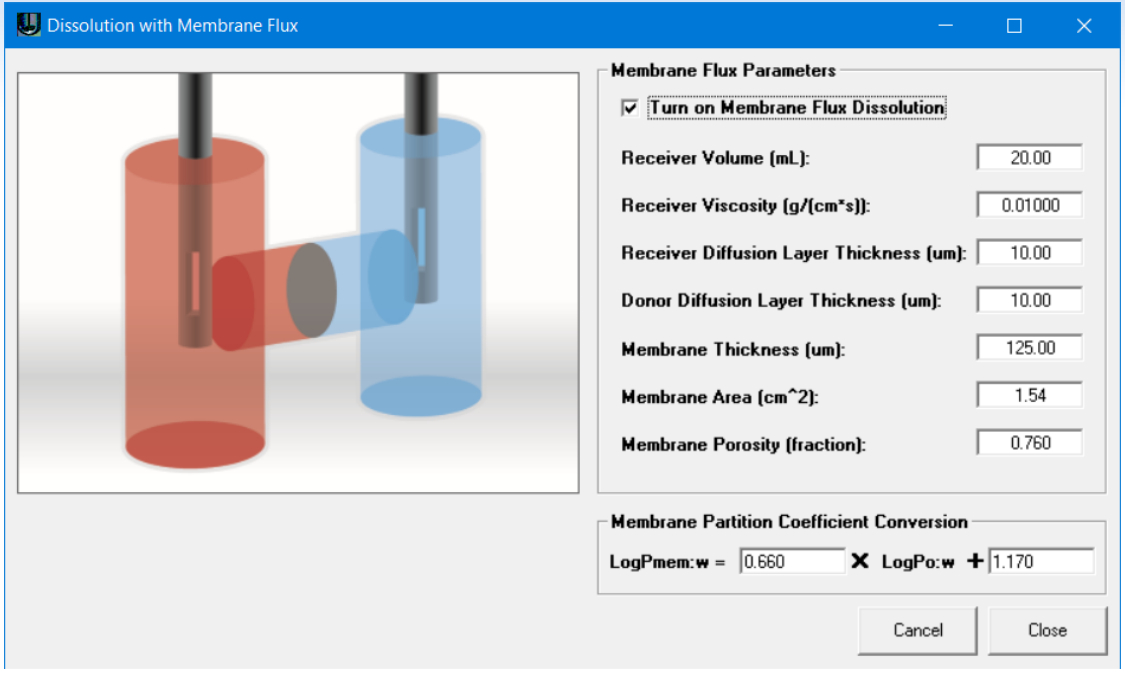
- Leverage DDDPlus to determine dissolution, precipitation kinetics, and formulation solubility for:
  - Compounds:
    - Dipyridamole
    - Ketoconazole
    - Itraconazole
  - Theory of membrane dissolution, biphasic dissolution, and precipitation models
  - DDDPlus precipitation model results for biphasic and membrane dissolution

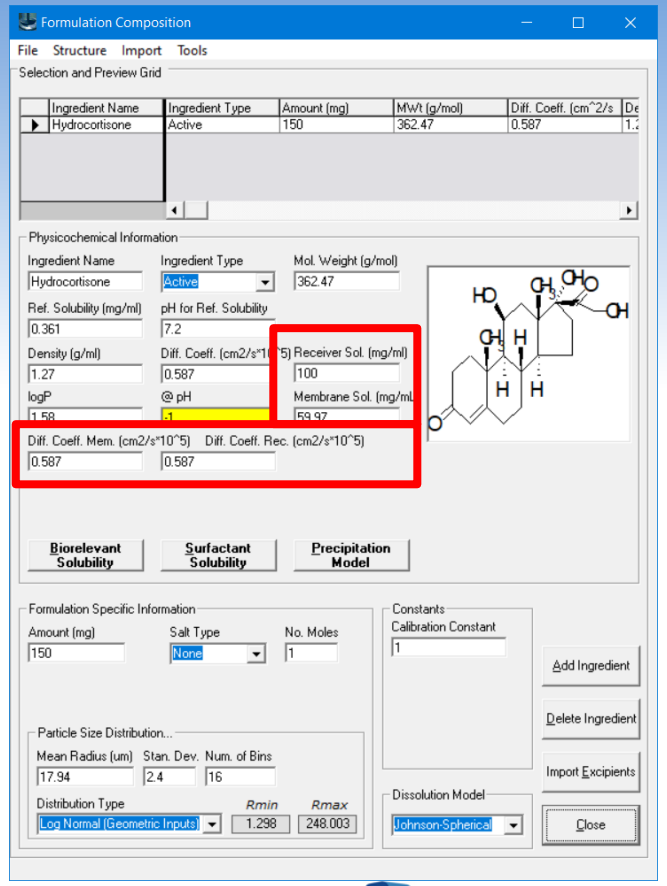
- Utilize GastroPlus to predict *In Vivo* PK with DDDPlus precipitation kinetics from DDDPlus

Membrane Dissolution Experiment

- Membrane dissolution is a useful tool for:
  - Assessing formulation solubility for amorphous or enabled formulations vs. crystalline drug
  - Fitting precipitation kinetics for weakly basic compounds with simultaneous absorption.
- Input Parameters:
  - Donor and receiver diffusion layer thickness
  - Partition coefficient into membrane lipid phase
  - Solubility in receiver solution (assumes sink – proprietary buffer).
  - System parameters – membrane area, thickness, and porosity.
- Output Results:
  - Formulation solubility determined from drug absorption rate
  - Precipitation kinetics

DDDPlus Membrane Dissolution Options





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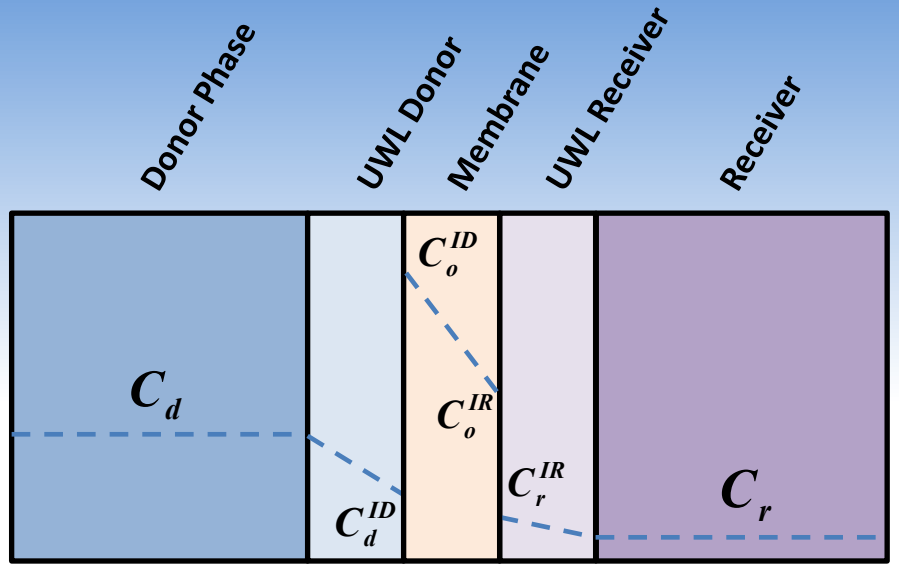
Transmembrane Flux for Membrane Assays



$$j_{overall} = \frac{D_A D_o D_R K_{od}}{D_A D_R h_o + D_o\left(D_R h_d K_{od} + D_A h_r K_{or}\right)}\left(C_d - K_r C_r\right)$$

Where: $K_r = \frac{K_{or}}{K_{od}}$

Steady-State Flux Equations:

$$j_{d,uwl} = \frac{D_A}{h_d}\left(C_d - C_d^{ID}\right) \qquad j_o = \frac{D_o}{h_o}\left(C_o^{ID} - C_o^{IR}\right)$$

$$j_{r,uwl} = \frac{D_R}{h_r}\left(C_r^{IR} - C_r\right) \qquad j_{r,uwl} = j_o = j_{d,uwl}$$

Where: $C_d^{ID} K_{od} = C_o^{ID}$ *and* $C_r^{IR} K_{or} = C_o^{IR}$

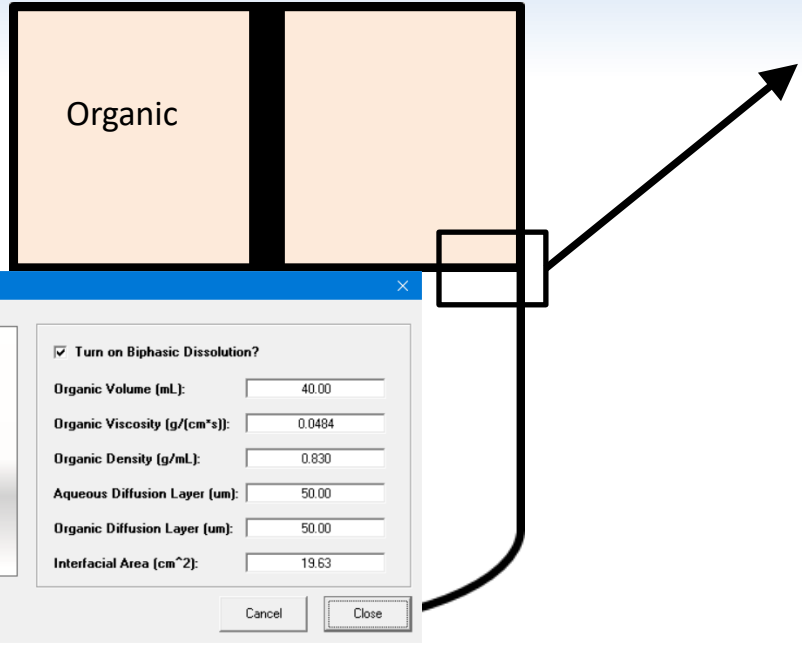
C_d	Concentration in donor compartment
C_d^{ID}	Concentration at donor/membrane interface
C_o^{ID}	Concentration in organic/donor interface
C_o^{IR}	Concentration in organic/receiver interface
C_r^{IR}	Concentration at receiver/membrane interface
C_r	Concentration in receiver compartment
D_o, D_A	Diffusion coefficient
h_d, h_o, h_r	Diffusion layer thickness in donor/organic/receiver
$K_{od} = \frac{C_o^{eq}}{C_d^{eq}}$	Organic to donor partition coefficient
$K_{or} = \frac{C_o^{eq}}{C_r^{eq}}$	Organic to receiver partition coefficient

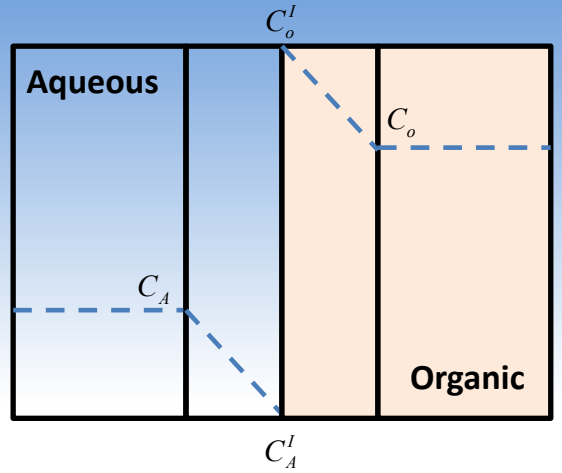
Biphasic Dissolution Experiment

- Biphasic dissolution is a useful tool for:
  - Assessing formulation solubility for amorphous or enabled formulations vs. crystalline drug
  - Fitting precipitation kinetics for weakly basic compounds with simultaneous absorptive phase
- Input Parameters:
  - Aqueous and organic diffusion layer thickness
  - Partition coefficient into organic phase (LogP surrogate for decanol)
  - System parameters – aqueous to organic contact area
- Output Results:
  - Formulation solubility determined from drug absorption rate
  - Precipitation kinetics

Biphasic Dissolution Model

- Allows simultaneous prediction of precipitation in aqueous phase while drug can be extracted into organic
- This will hopefully lead to better *in vitro* to *in vivo* extrapolation for precipitation
- IR formulations only



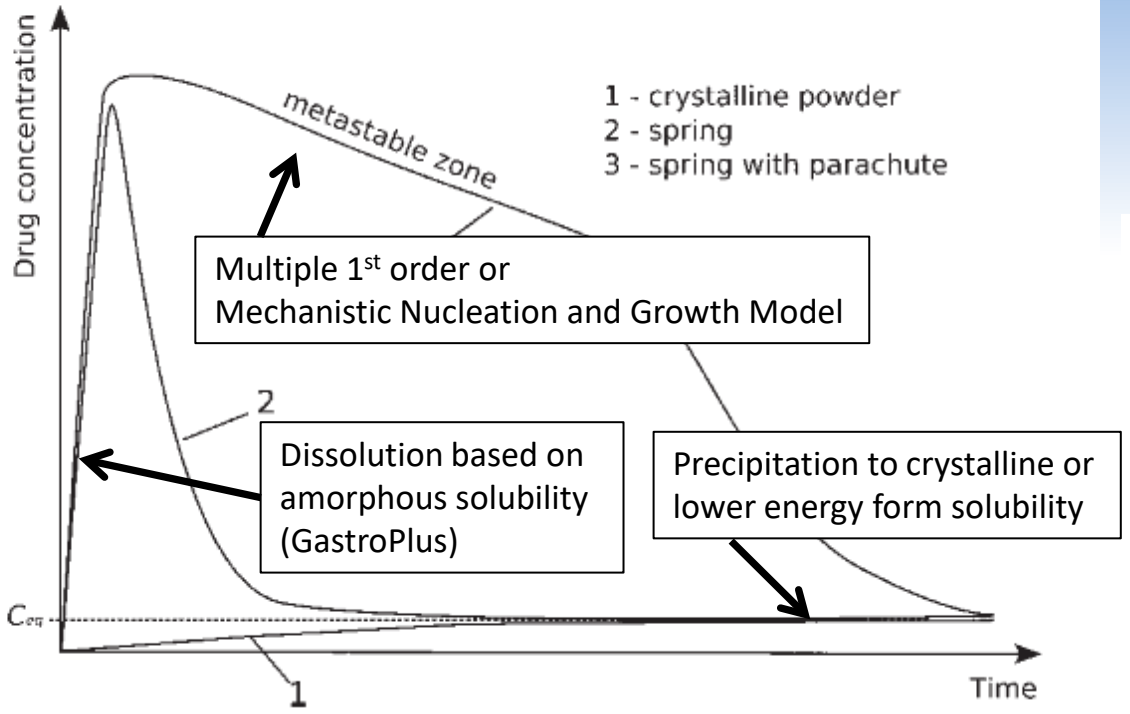


$$\frac{dm_o}{dt} = \frac{k_A k_o K_{o:w}}{k_A + k_o K_{o:w}} A_I \left(C_A - \frac{C_o}{K_{o:w}} \right)$$

m_o	Mass in organic
C_o	Concentration in Organic
C_A	Concentration in Aqueous
$k_A k_o$	Mass Transfer Coefficient in Aqueous and Organic
$K_{o:w}$	Organic/Water Partition Coefficient
A_I	Interfacial Area

Precipitation and Supersaturating Drug Delivery Systems

Schematic diagram of "Spring and Parachute"



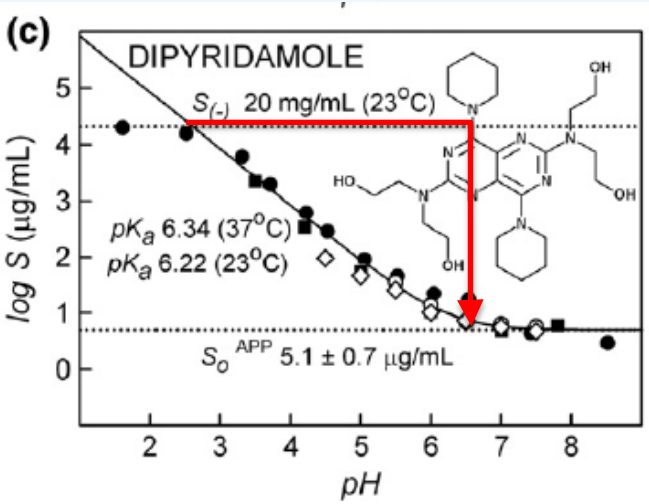
Brouwers J, J. Pharm. Sci. 98(8):2549 (2009)

Key Variables:

- C/S – Supersaturation Ratio

Basic compounds with high gastric vs. intestinal solubility

Salt Forms of Acidic Drugs



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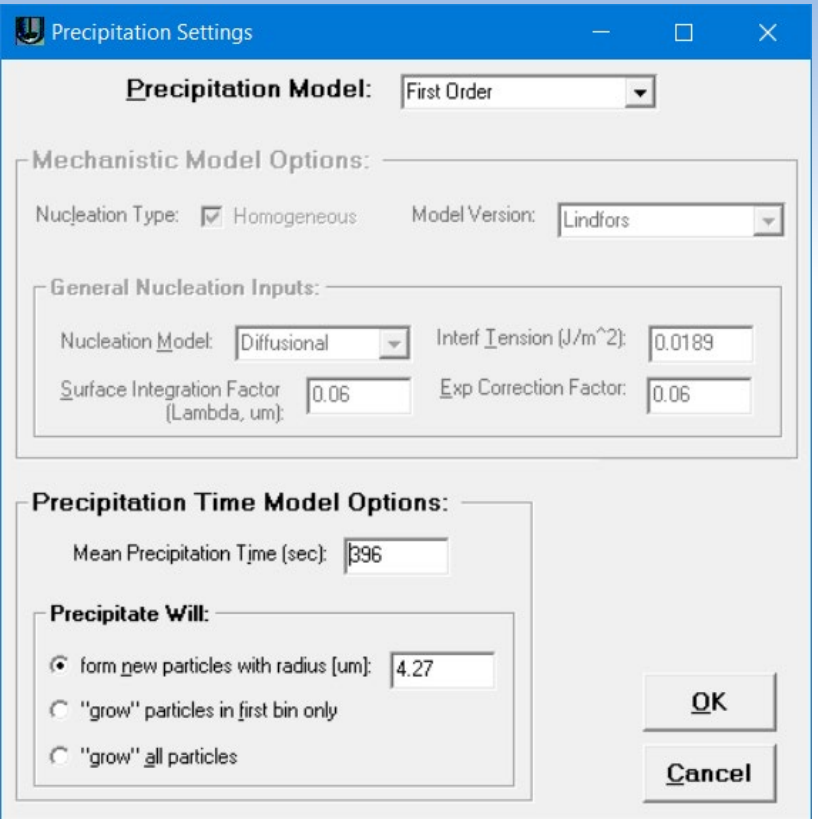
Precipitation Model Options in DDDPlus/GastroPlus

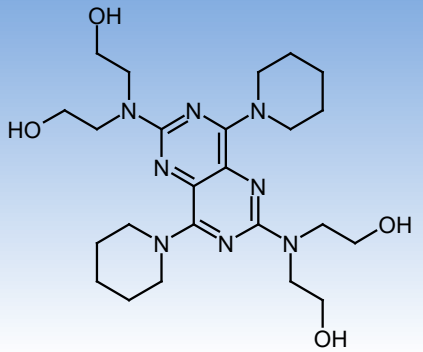


First order precipitation:

- Precipitate will form new particles with user-defined radius.
- Precipitate will "grow" in smallest particle size distribution bin only.
- Precipitate will "grow" all particles.
- Default precipitation time (900 s) determined from exponential fit to transfer assay data for dipyridamole from Kostewicz, 2004.
- Precipitation time as function of lumenal pH.

Mechanistic Nucleation and Growth (MNG) precipitation model

Dipyridamole Transfer Assay
First Order Precipitation



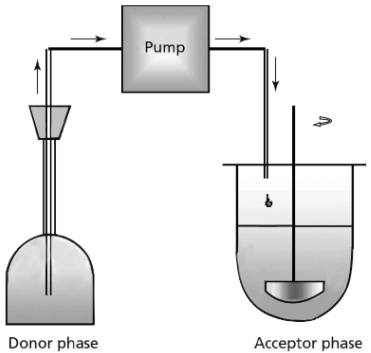
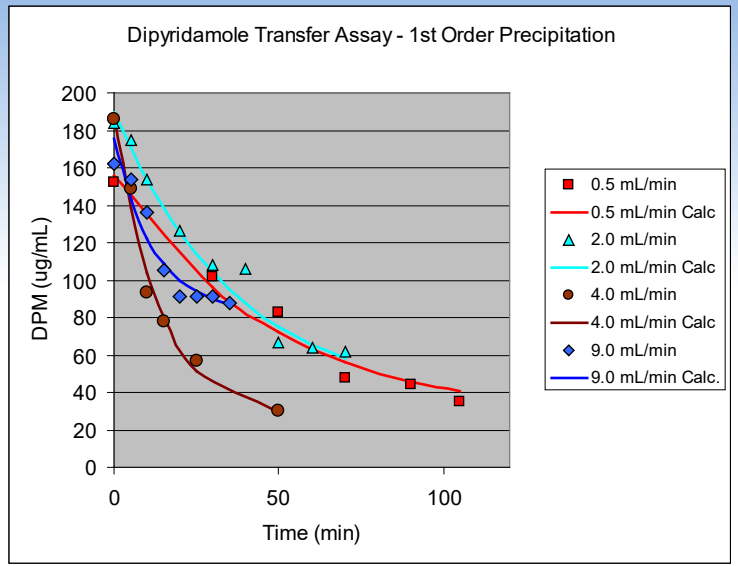
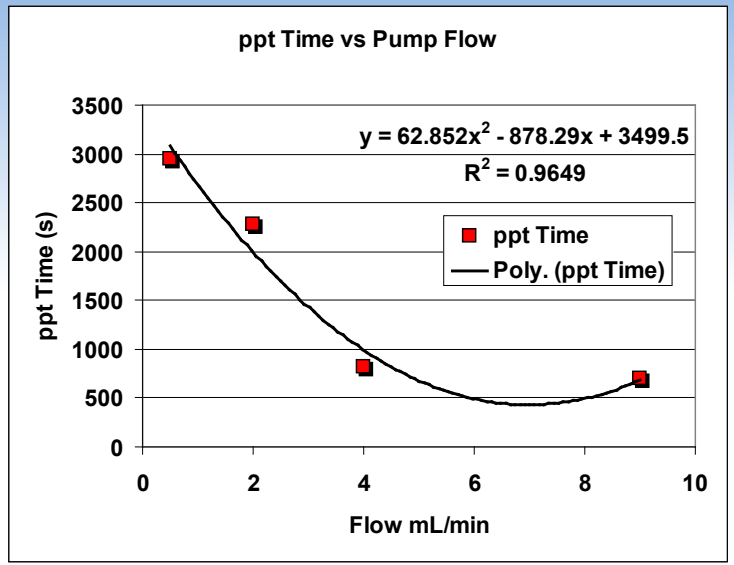


Figure 2 Experimental set-up to examine precipitation.





@ 4.25 mL/min the ppt. Time = 900 s

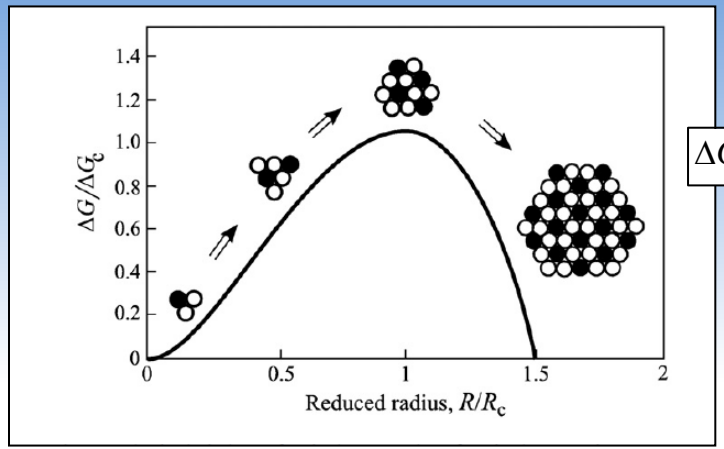
GastroPlus First Order Precipitation:

$$\frac{dM_i}{dt} = \left(\frac{V_i}{T_{precip}}\right)(C_i - S_i)$$

M_i – Mass in compartment i
V_i – Volume of compartment i
T_p – Precipitation Time
C_i – Concentration in compartment i
S_i – Solubility in compartment i

Kostewicz E, et al., J. Pharm. Pharmacol. 56:43 (2004)

Classical Nucleation and Growth



$$\Delta G_{system} = \Delta G_{cluster} + \Delta G_{bulk}$$

Rodriguez-Hornedo N, J. Pharm. Sci. 88(7):651 (1999)
De Yoreo JJ, Rev. Mineralogy Geochem. 54:57 (2003)
Lindfors L, J. Colloid Interfac. Sci. 325 (2):404 (2008)
Sugano K., Int. J. Pharmaceut. 378:142 (2009))

The nucleation rate J (the net production of critical clusters per unit time and unit bulk volume) is a function of the steady state concentration of the critical clusters and the transport of monomers to the critical clusters.

J=Pre-exponential Term * e$^{\text{Exponential Term}}$

Pre-exponential Term:

$$D_{mono} N_{Av} c^2 \left(\frac{k_B T}{\gamma}\right)^{1/2} \ln\left(\frac{c}{S}\right) \frac{R^*}{R^* + \lambda}$$

Exponential Term:

$$-ExpCorr \frac{16\pi}{3} \left(\frac{\gamma}{k_B T}\right)^3 \frac{v_m^2}{\ln\left(\frac{c}{S}\right)^2}$$

- D_{mono} = diffusion coefficient of the monomer (3.42E-4 cm^2/min)
- N_A = Avogadro's number (6.02E+23 molecs/mole)
- c = Conc. of free monomer (moles/cm^3)
- S = Solubility at the current pH
- k_b = Boltzman's constant (1.38E-21 cJoules/Deg. K)
  (Note: Joule = Newton-meter)
- T = 310^o K
- γ = Interfacial tension (Newtons/cm)
- ν_m = Molecular volume = (V_m/N_A = XX cm^3/molec / 6.02E+23 molec/mole)
- R^* = Critical radius (cm)
- λ = Effective radius from Lindfors (cm)
- *ExpCorr* = exponential correction factor

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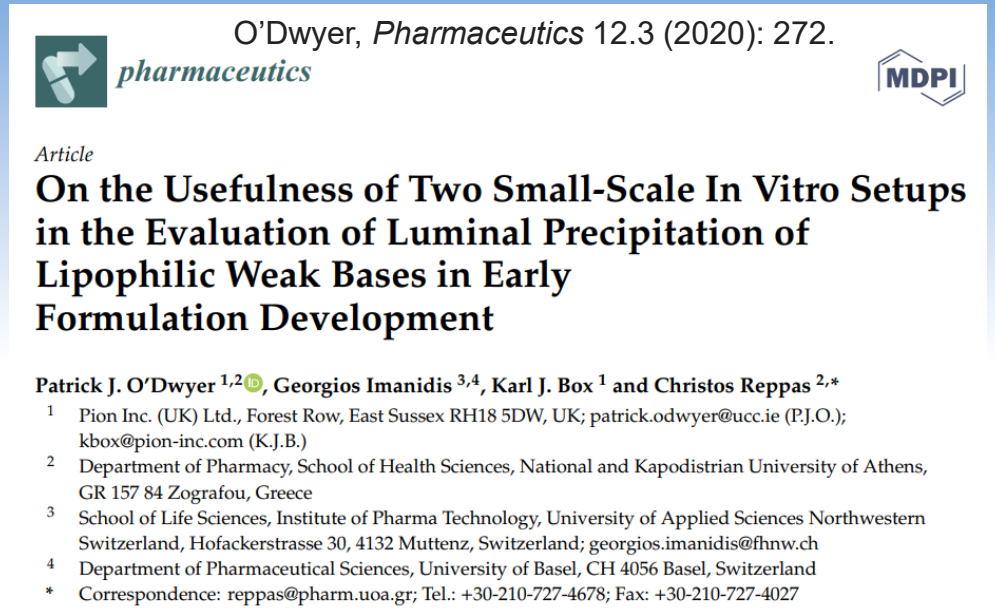
Case Study - Data



O'Dwyer, *Pharmaceutics* 12.3 (2020): 272.

pharmaceutics

MDPI

Article

On the Usefulness of Two Small-Scale In Vitro Setups in the Evaluation of Luminal Precipitation of Lipophilic Weak Bases in Early Formulation Development

Patrick J. O'Dwyer [1,2], Georgios Imanidis [3,4], Karl J. Box [1] and Christos Reppas [2,*]

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2 Department of Pharmacy, School of Health Sciences, National and Kapodistrian University of Athens, GR 157 84 Zografou, Greece
3 School of Life Sciences, Institute of Pharma Technology, University of Applied Sciences Northwestern Switzerland, Hofackerstrasse 30, 4132 Muttenz, Switzerland; georgios.imanidis@fhnw.ch
4 Department of Pharmaceutical Sciences, University of Basel, CH 4056 Basel, Switzerland
* Correspondence: reppas@pharm.uoa.gr; Tel.: +30-210-727-4678; Fax: +30-210-727-4027

- Comprehensive dataset for biphasic and membrane dissolution with corresponding *iv vivo* predictions
- Precipitation parameters were estimated based on aqueous concentration or organic concentrations for itraconazole. A full mechanistic interpretation was not performed.

Dose and Formulation Models

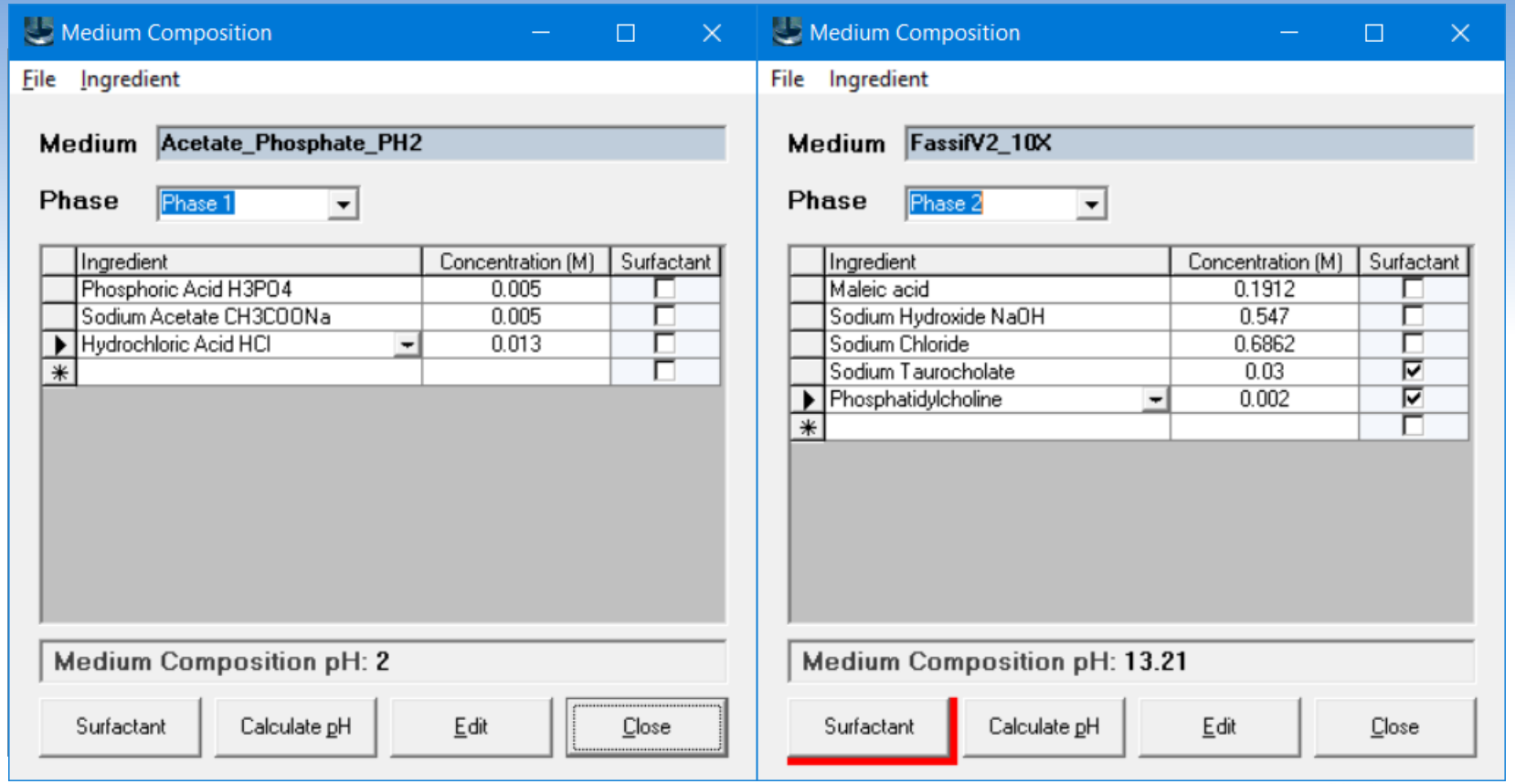
Dosing Biphasic Experiment:

- Dipyridamole
  - 10 mg crystalline suspension
  - 0.25 mg/mL dose (40 mL media)
- Ketoconazole
  - 20 mg crystalline suspension
  - 0.5 mg/mL dose (40 mL media)
- Itraconazole
  - 5 mg dose sporanox solution
  - 5 mg dose sporanox capsule
  - 0.125 mg/mL dose (40 mL media)

Dosing Membrane Experiment:

- Dipyridamole
  - 5 mg crystalline suspension
  - 0.25 mg/mL dose (20 mL media)
- Ketoconazole
  - 10 mg crystalline suspension
  - 0.5 mg/mL dose (20 mL media)
- Itraconazole
  - 2.5 mg dose sporanox solution
  - 2.5 mg dose sporanox capsule
  - 0.125 mg/mL dose (20 mL media)

Biphasic Dissolution Model Settings



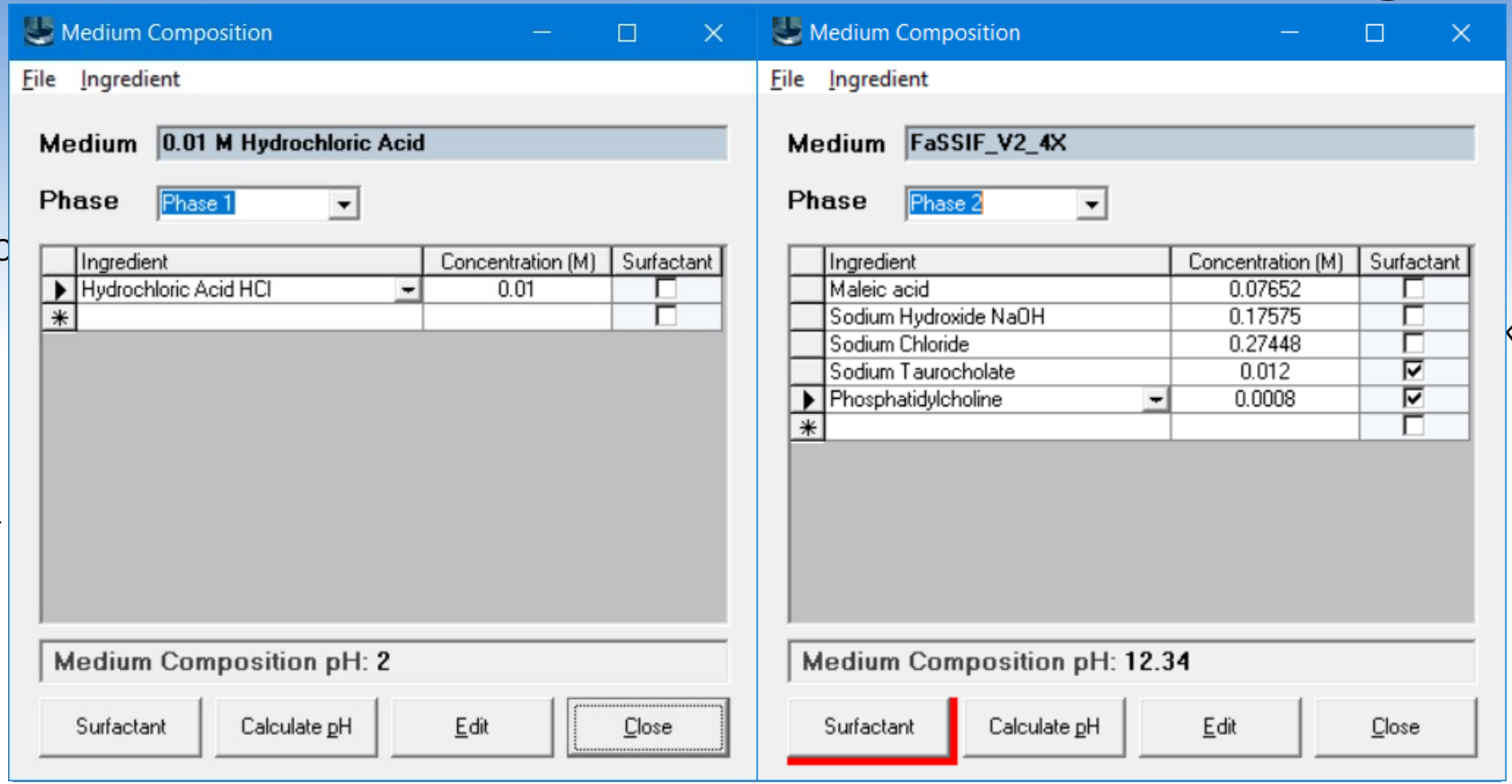
Reproduced from: O'Dwyer, Pharmaceutics 2020, 12, 272

Membrane Dissolution Model Settings

Fiber C

15 mL

k Buffer



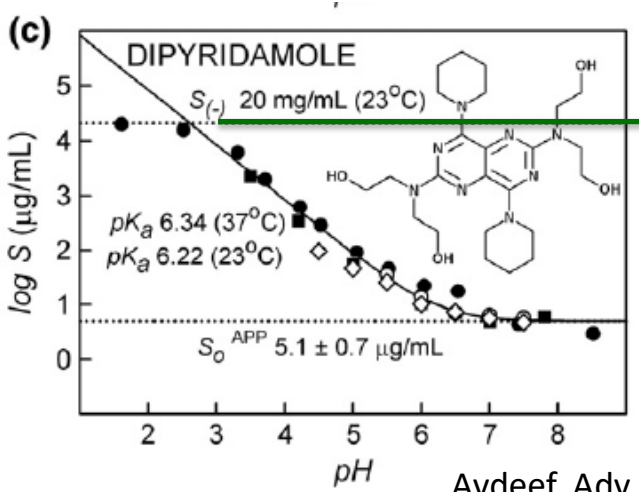
Reproduced from: O'Dwyer, Pharmaceutics 2020, 12, 272

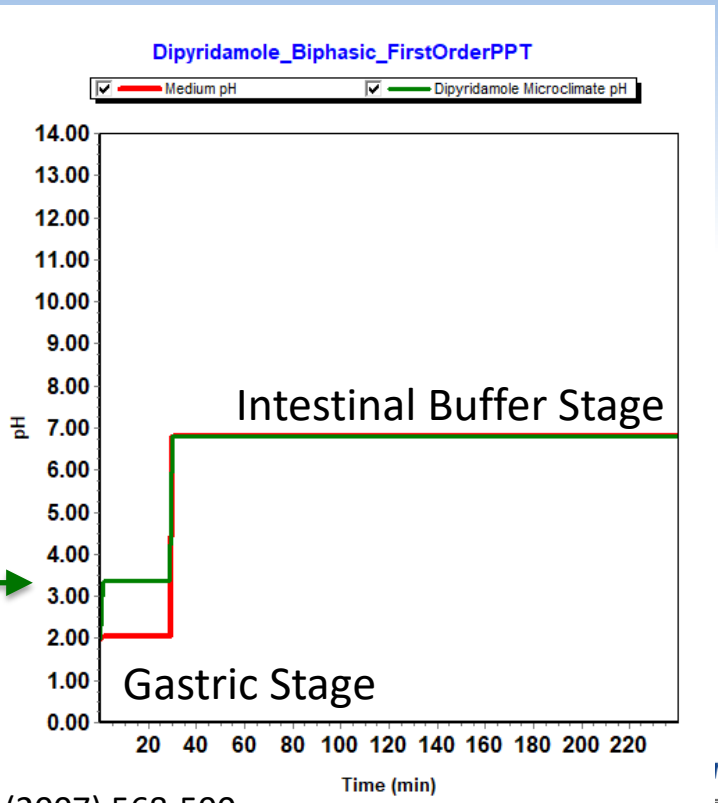
Dipyridamole pH Prediction
Multi-stage Biphasic Dissolution

Free base dissolving will change the local microclimate and solubility

Microclimate pH

Media pH

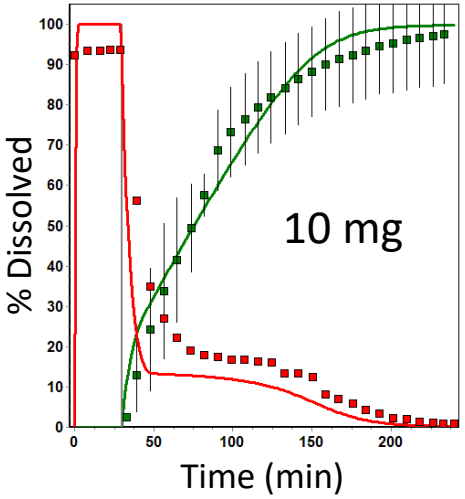




Avdeef, Adv. Drug Del. Rev. 59 (2007) 568-590

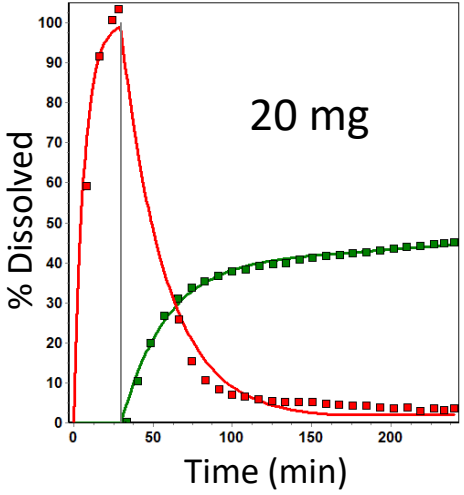
Biphasic First Order Precipitation Results

Dipyridamole



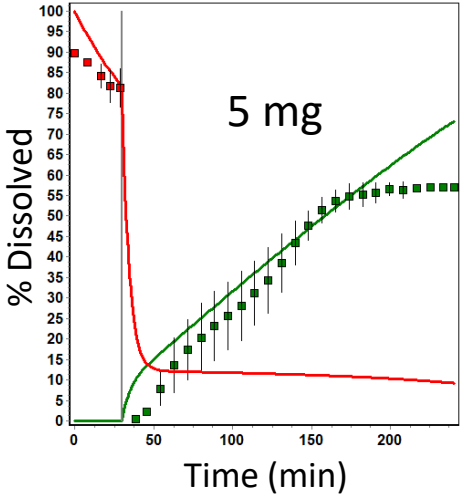
PPT Time = 396 sec
PPT Size = 4.27 µm

Ketoconazole



Particle Size = 10 µm
PPT Time = 2857 sec
PPT Size = 1 µm

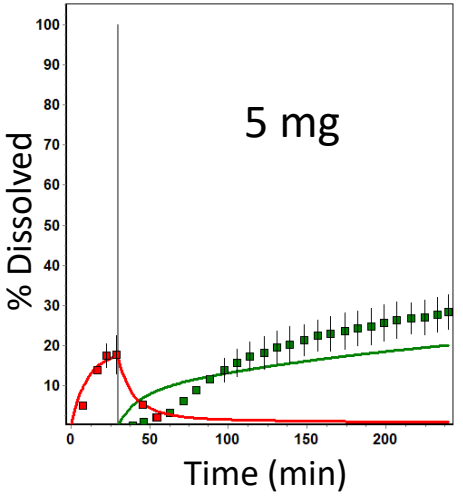
Itraconazole Solution



Ingredient	Itraconazole
Time, min	Prec. Time (s)
0	3800
30	350

PPT Size =1 µm

Itraconazole Capsule



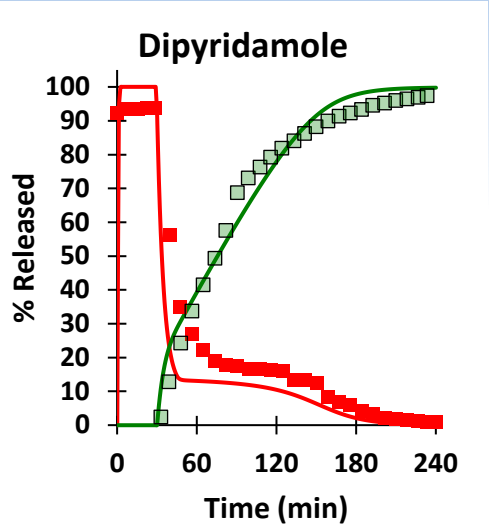
Particle Size = 13 µm
PPT Time = 900 sec
PPT Size =1 µm

Aqueous
Organic

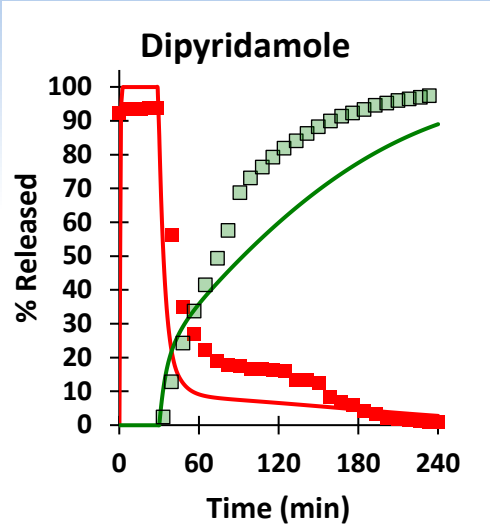
SimulationsPlus
SCIENCE + SOFTWARE = SUCCESS

Parameter Sensitivity Analysis - Precipitate Size

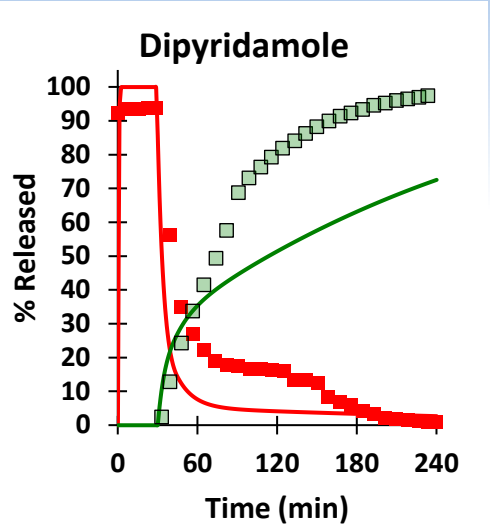
PPT Size = 4.27 μm



PPT Size = 15 μm



PPT Size = 30 μm



Redissolution of precipitate can be an important aspect that allows for appearance of drug in organic to be predicted correctly.

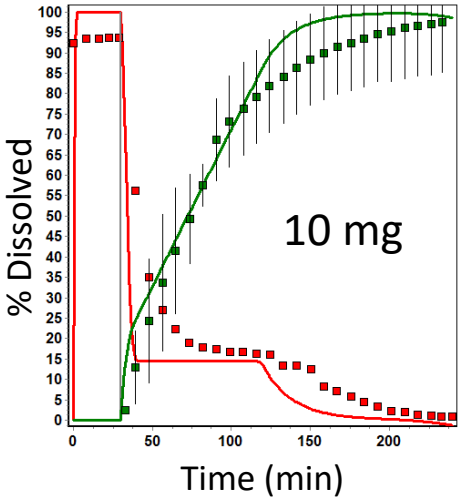
Aqueous

Organic

SimulationsPlus
SCIENCE + SOFTWARE = SUCCESS

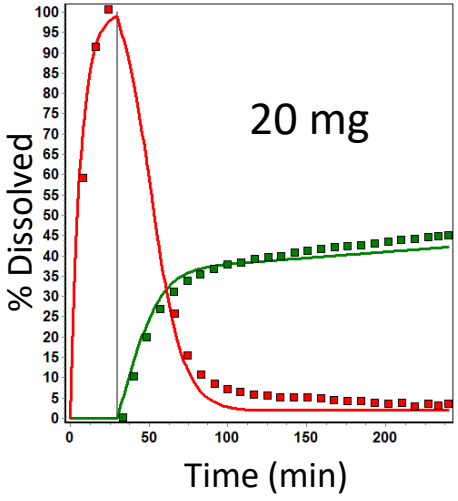
Biphasic Mechanistic Precipitation Results

Dipyridamole



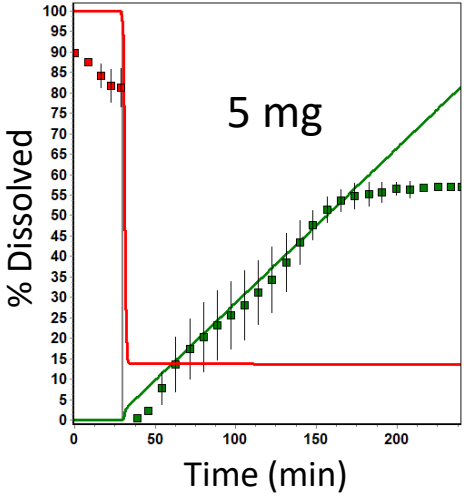
Surface Integration = 0.0371 µm
Exponential Correction = 0.0417

Ketoconazole



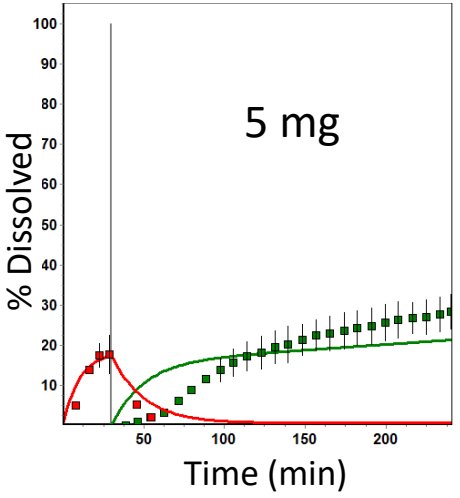
Surface Integration = 0.268 µm
Exponential Correction = 0.3

Itraconazole Solution



Surface Integration = 0.003 µm
Exponential Correction = 0.003

Itraconazole Capsule



Surface Integration = 0.05 µm
Exponential Correction = 0.05

Aqueous
Organic

SimulationsPlus
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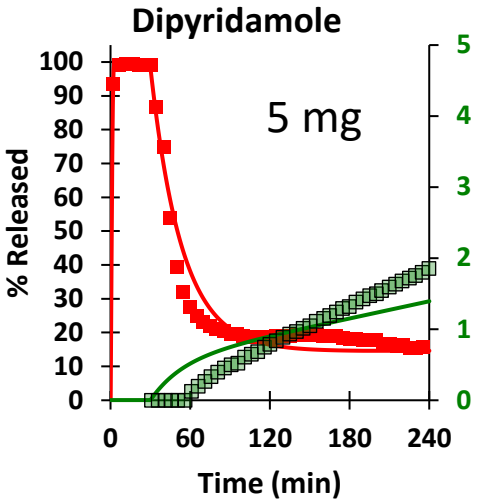
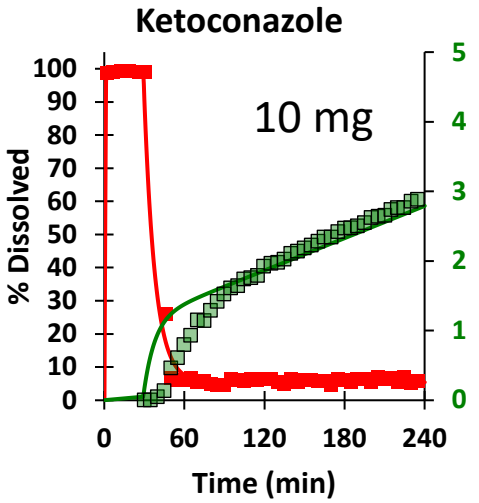
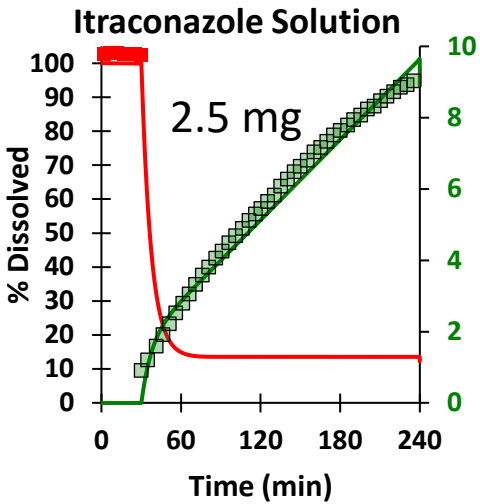
Membrane First Order Precipitation Results



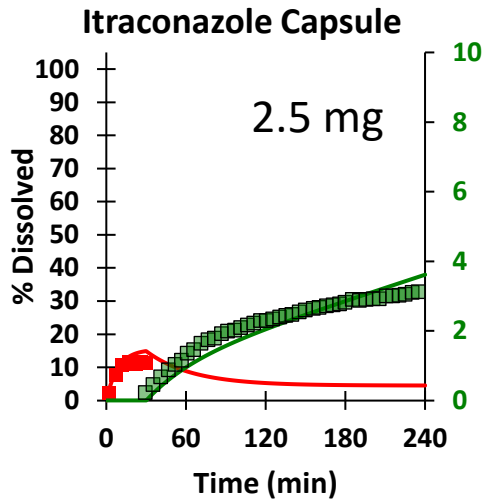
PPT Time = 1429 sec
PPT Size = 0.32 μm



PPT Time = 500 sec
PPT Size = 1 μm



PPT Time = 450 sec
PPT Size = 1 μm



Particle Size = 13 μm
PPT Time = 2300 sec
PPT Size =1 μm

Aqueous
Receiver

Amount of drug appearing in receiver is based on the solubility difference between amorphous drug and cyclodextrin solution.

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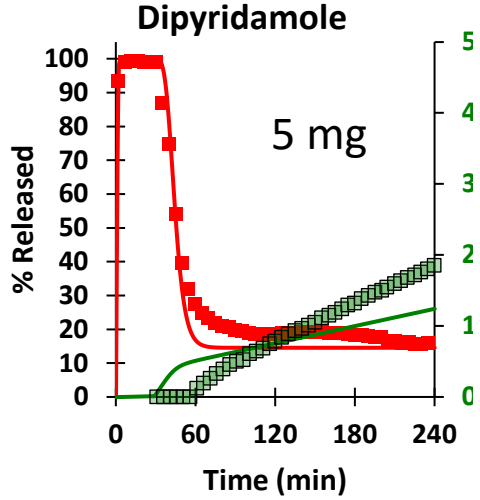
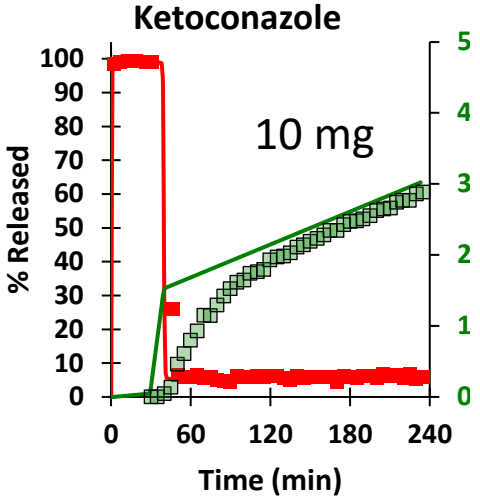
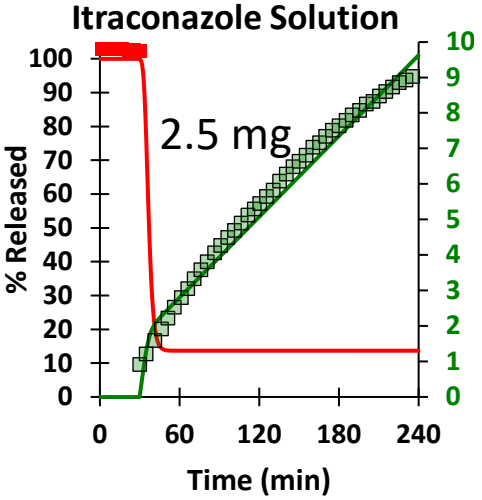
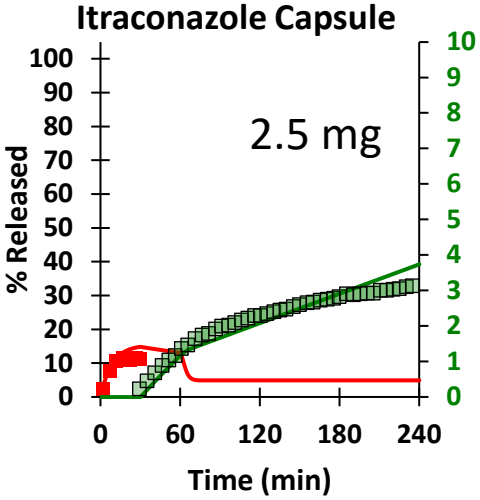
SCIENCE + SOFTWARE = SUCCESS

Membrane Mechanistic Precipitation Results









Surface Integration = 0.0639 μm
Exponential Correction = 0.0639

Surface Integration = 0.095 μm
Exponential Correction = 0.095

Surface Integration = 0.011 μm
Exponential Correction = 0.011

Surface Integration = 5.60e-4 μm
Exponential Correction = 5.60e-4

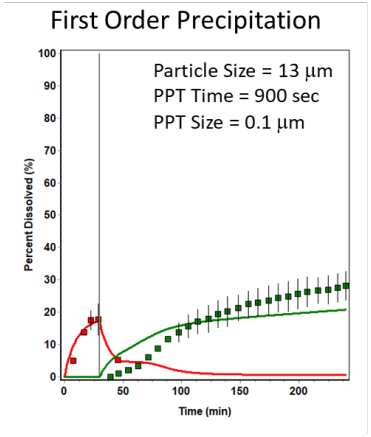
Slope of drug appearing in receiver is based on the solubility difference between amorphous drug and cyclodextrin solution.

Aqueous

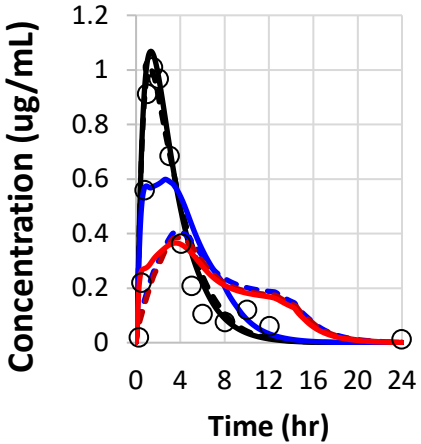
Receiver

SimulationsPlus
SCIENCE + SOFTWARE = SUCCESS

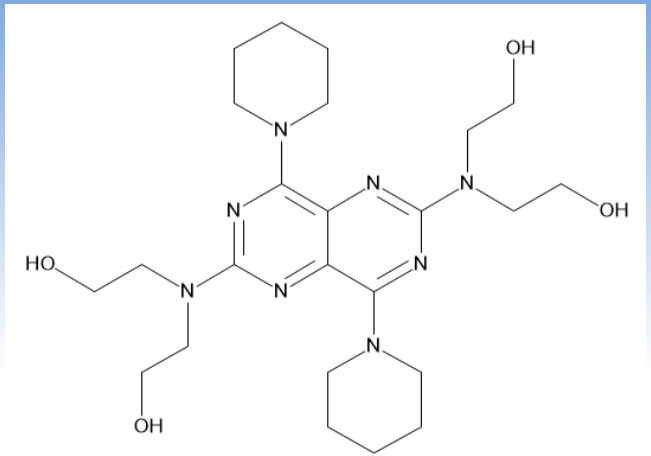
In Vitro Dissolution in GastroPlus Models



Precipitation Parameters



Dipyridamole GastroPlus Model



Molecular Weight: 504.64 g/mol

AP 10 = ADMET Predictor v.10
S+ stands for properties predicted with Simulations Plus models
S+Sw = solubility in pure water
S+SF = solubility factor
S+Peff = human jejunal permeability
S+PrUnbnd = percent unbound in human plasma
S+Rbp = human blood/plasma concentration ratio

S+logP = 3.04 (AP 10.0)
Exp LogP = 3.71 @ pH 7 (FDA Label)

S+pKa = 5.83, 3.56, 1.83, 1.63, 1.43, 1.13, 0.71, 0.29 (AP 10.0)
Exp pKa = 6.307 (Fit to multiple expérimental sources)
S+Sw = 2.34 mg/mL @ pH = 8.75(AP 10.0)
Exp Sw = 0.005 mg/mL @ pH = 11 (Fit to *in* vitro data)

S+Peff = Human: 0.45 x10^{-4} cm/s (AP 10.0)
EXP Caco = 1.124 x10^{5} cm/s
Human Peff = 1.81 × 10^{-4} cm/s (Converted from Exp)

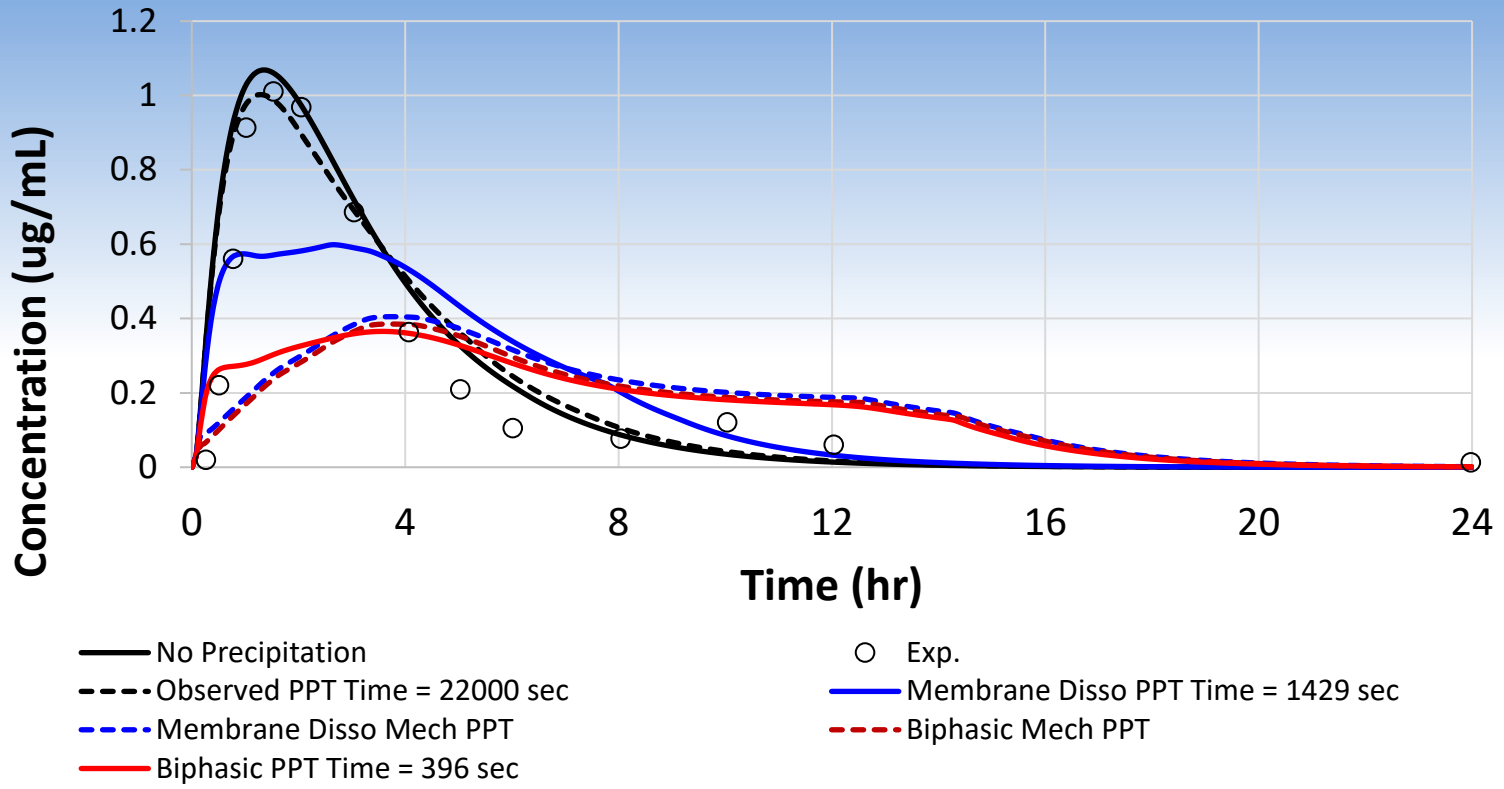
S+PrUnbnd (human) = 8.99 % (AP 10.0)
Exp PrUnbnd (%) = 0.20% (FDA Label)

S+Rbp (human) = 0.67 (AP 10.0)
Exp Rbp = 0.647 (Serebrauny 2009, calc)

Clearance (L/hr/kg) = 0.195 (Nielson-Kudsk 1979)
Clearance (L/hr) = 12 (Australian Label)
Clearance average (L/hr) = 13.59

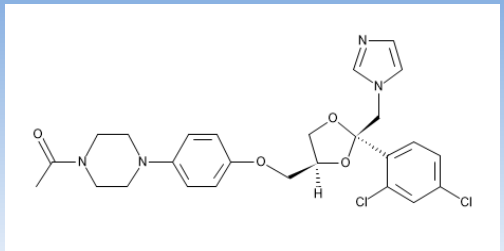
PBPK model adjusted to experimental Vdss by adjusting LogP to 3.184 to calculate Kp

Dipyridamole 75 mg Tablet Precipitation *IVIVE*

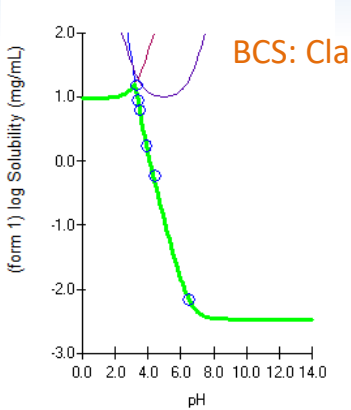


Ricevuti, *Eur. J. Drug Metab. Pharmacokinet.* **1991**, *16*, 197–201

Ketoconazole GastroPlus Model



Molecular Weight: 531.44 g/mol



AP9.5= ADMET Predictor v. 9.5
S+ stands for properties predicted with Simulations Plus models
S+Sw = solubility in pure water
S+Peff = human jejunal permeability
S+PrUnbnd = percent unbound in human plasma
S+Rbp = human blood/plasma concentration ratio

S+logP = 3.74 (AP 9.5)
Exp LogP = 3.73 (Walter-JPharmPharmacol-40-689-1988)

S+pKa = 6.15 (base 1), 4.22 (base 2) (AP 9.5)
Exp pKa = 6.51 (base 1), 3.4 (base 2) (Walter-JPharmPharmacol-40-689-1988)
S+Sw = 0.11 mg/mL @ pH = 8.23 (AP 9.5)
Exp Sw = 0.0069 @ pH = 6.5 (Poelma-JPharmPharmacol-43-5-317)

S+Peff = Human: 3.38 x10^{-4} cm/s (AP 9.5)
Exp Caco = 1.35 x10^{5} cm/s (Ingels-International Journal of Pharmaceutics-274-221–2004)

Human Peff = 3.22 × 10^{-4} cm/s (Converted from caco2 permeability value from Ingles data (Ingels-International Journal of Pharmaceutics-274-221–2004)

S+PrUnbnd (human) = 4.38 % (AP 9.5)
Exp PrUnbnd (%) = 1 % (Daneshmend-ClinPharmacokinet-14-13-1988)

S+Rbp (human) = 0.69 (AP 9.5)
Exp Rbp = 0.6 (Matthew-PharmRes-10-3-418-1993)

Changed log D (7.0) = 2.6 to calculate Kps and then changed back to 3.73 to run simulation

Metabolism CYP3A4: Km = 15 nM with Vmax = 0.048 nmol/min/mg Prot.

Transporters Pgp: Gut Km = 4.57 mg/L, Vmax = 0.006 mg/s
PBPK Km = 4.57 mg/L, Vmax = 0.001 m/s/mg trans

SimulationsPlus
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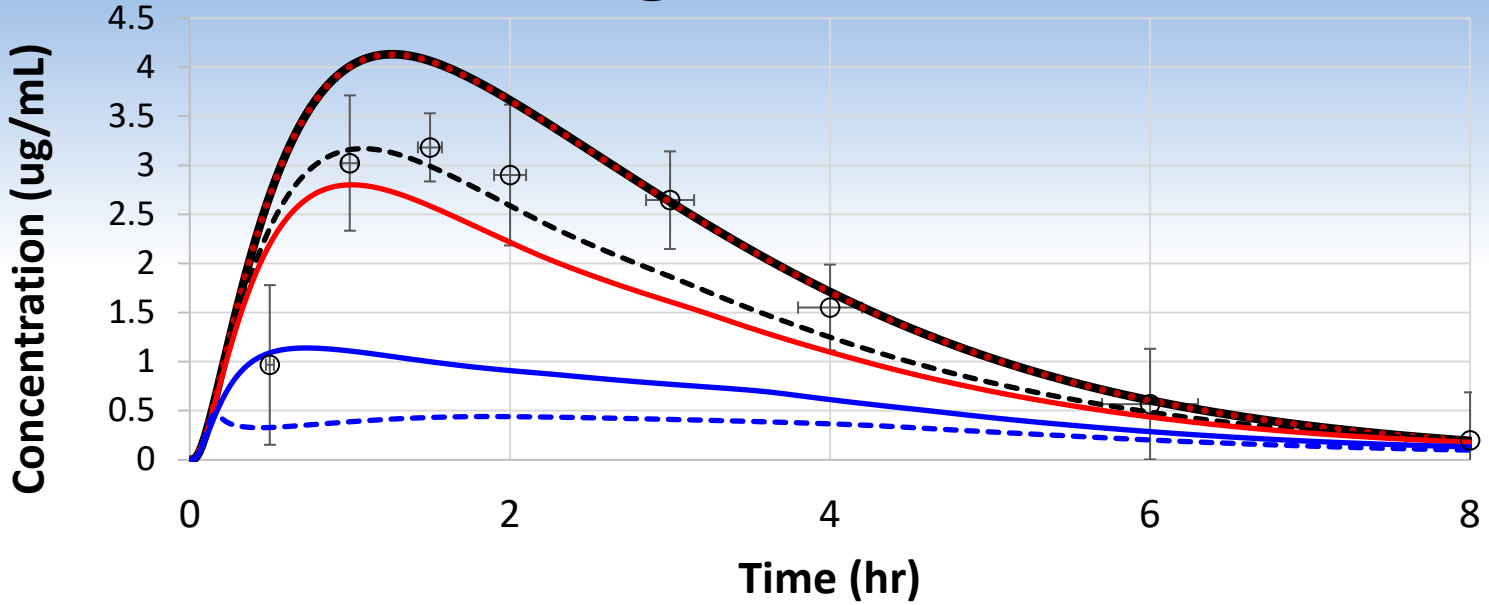
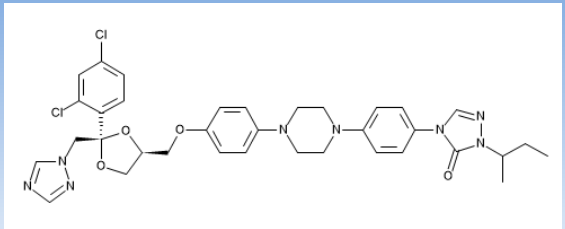
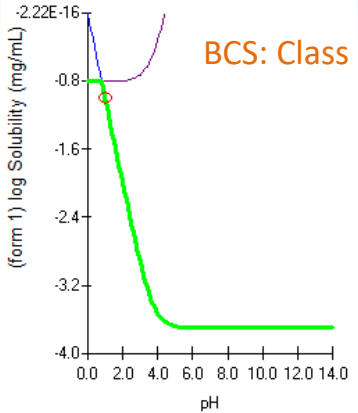
Ketoconazole IVIVE Precipitation 200 mg IR Tablet



Itraconazole GastroPlus Model



Molecular Weight: 705.65 g/mol



AP9.5= ADMET Predictor v. 9.5
S+ stands for properties predicted with Simulations Plus models
S+Sw = solubility in pure water
S+Peff = human jejunal permeability
S+PrUnbnd = percent unbound in human plasma
S+Rbp = human blood/plasma concentration ratio

S+logP = 4.89 (AP 9.5)
Exp LogP = 5.66 (FDA SPORANOX® (itraconazole) Capsule Label Information)

S+pKa = 4.57, 3.69, 2.93, 1.28 (AP 9.5)
Exp pKa = 3.7 (FDA SPORANOX® (itraconazole) Oral Solution Information" 2002)
S+Sw = 0.00733 mg/mL @ pH = 7.07 (AP 9.5)
Exp Sw = 0.1 mg/mL @ pH = 1.2 @ 60 min (Yin-DrugDesDevelTher-9-2801-2015)
GSE Sw = 0.000189 mg/mL (Yalkowski Equation)

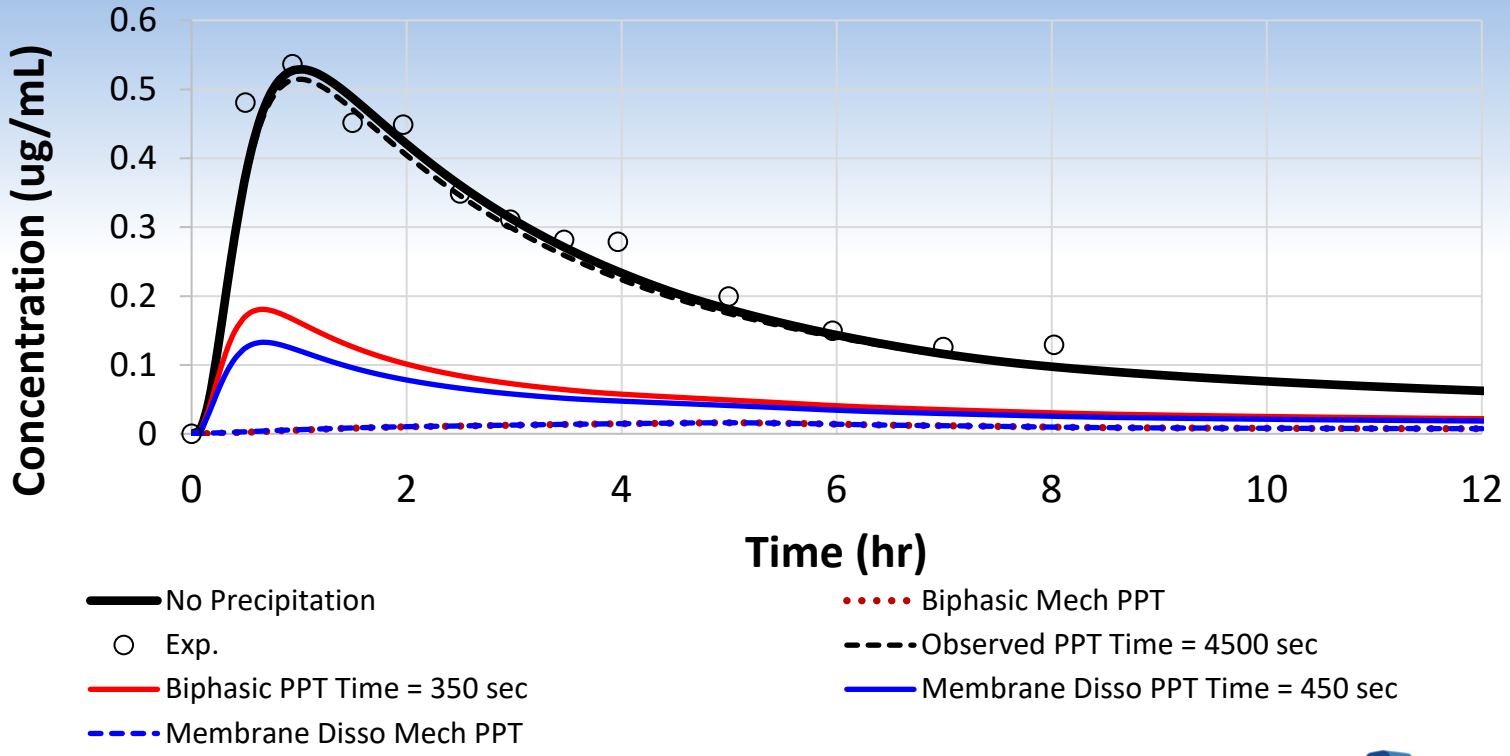
S+Peff = Human: 1.85 x10^{-4} cm/s (AP 9.5)
Mem+ Caco = 2.66 x10^{5} cm/s
Human Peff = 3.85 × 10^{-4} cm/s (Converted from MembranePlus Peff)

S+PrUnbnd (human) = 2.75 % (AP 9.5)
Exp PrUnbnd (%) = 0.20% (FDA Label)

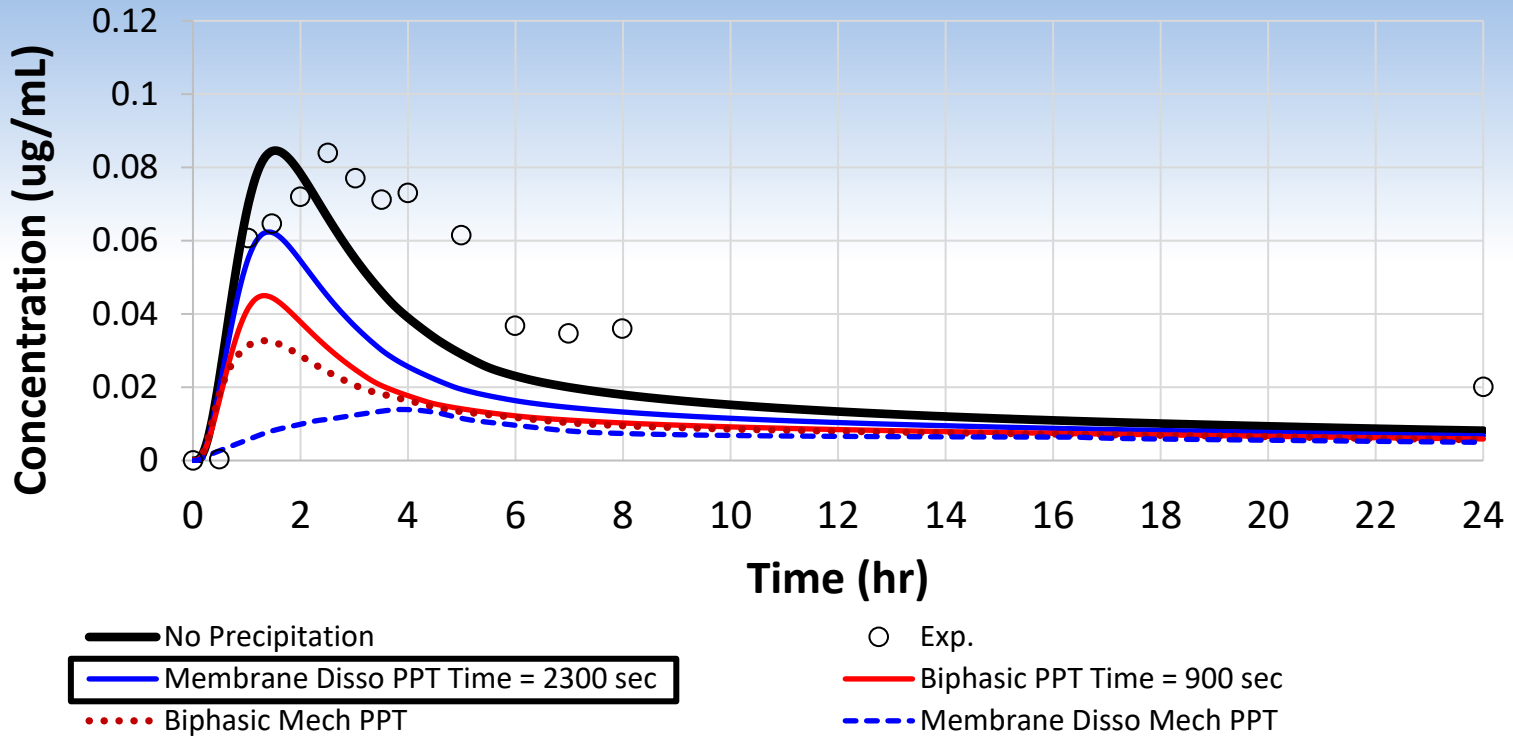
S+Rbp (human) = 0.67 (AP 9.5)
Exp Rbp = 0.58 (Kato-PharmRes-25-8-1891-2008)

Metabolism CYP3A4: Km = 0.00275 mg/L, Vmax (gut) = 0.0764 nmol/min/mg Prot.
Vmax (pbpk) = 0.00022

Itraconazole IVIVE Precipitation
200 mg IR Solution



Itraconazole IVIVE Precipitation
200 mg IR Capsule



SimulationsPlus
SCIENCE + SOFTWARE = SUCCESS

Conclusion

- DDDPlus provides complex models to handle:
  - Membrane dissolution
  - Biphasic dissolution
  - Artificial Stomach Duodenum test

- IVIVE is challenging for all complex *in vitro* tests
  - Precipitation is best optimized to experimental PK data in our current understanding
  - However, in vitro tests provide valuable information on propensity to crystallize and formulation solubility