

In Vivo Extrapolation of Precipitation with Complex Dissolution Experiments

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



SimulationsPlus

Session Description and Objectives

- What is DDDPlus™
 - How can it be utilized in drug development?
 - What can DDDPlus predict?
 - How do we use DDDPlus for complex precipitation assays?
 - 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 dipyridamole, ketoconazole, and itraconazole precipitation
- Why is precipitation important?
- What *in vitro* experiments can quantify precipitation rates?
- How can *in vitro* dissolution and precipitation can be modeled using DDDPlus?
- How can *in vitro* dissolution parameters translate into PBPK simulations and what are the pitfalls?

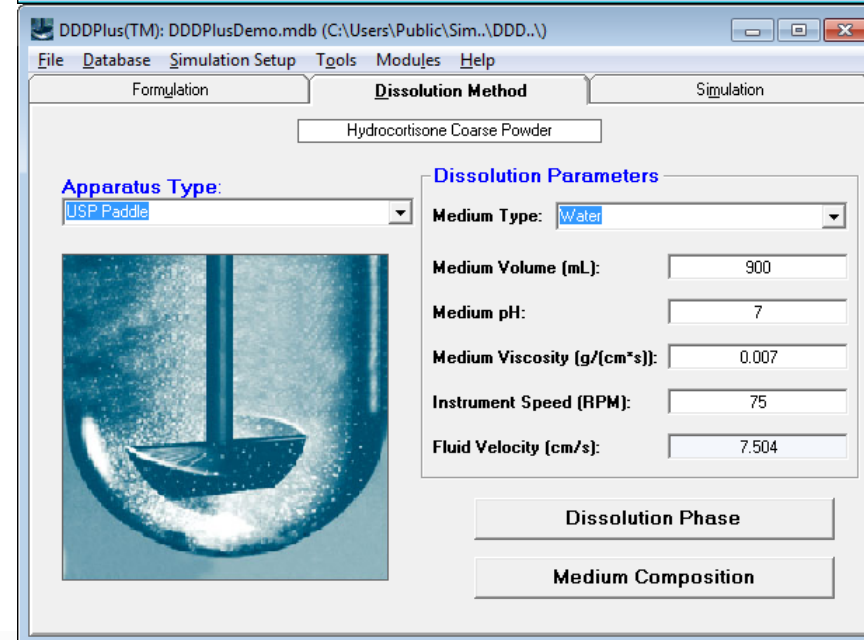
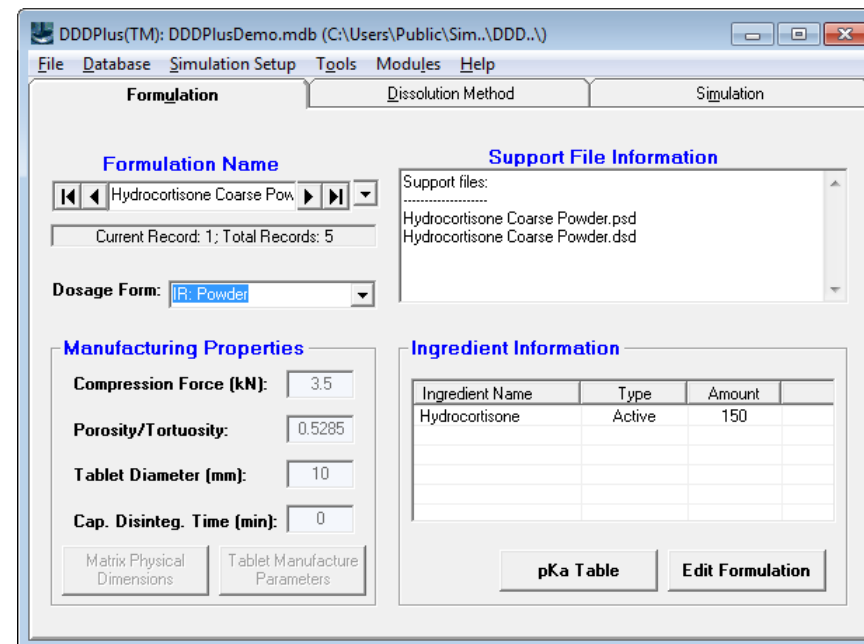


Biography and Contact Information

- James Mullin
 - Sr. Principal Scientist at Simulations Plus
 - <https://www.simulations-plus.com/>
 - jim@simulations-plus.com
 - Graduate degree in chemical engineering
 - 17+ years experience computational modeling
 - PBPK, CFD, and chemical process modeling.
 - Product manager of DDDPlus and MembranePlus™
 - Contributes to development of GastroPlus software
 - Provides consulting services for PBPK modeling

What is DDDPlus?

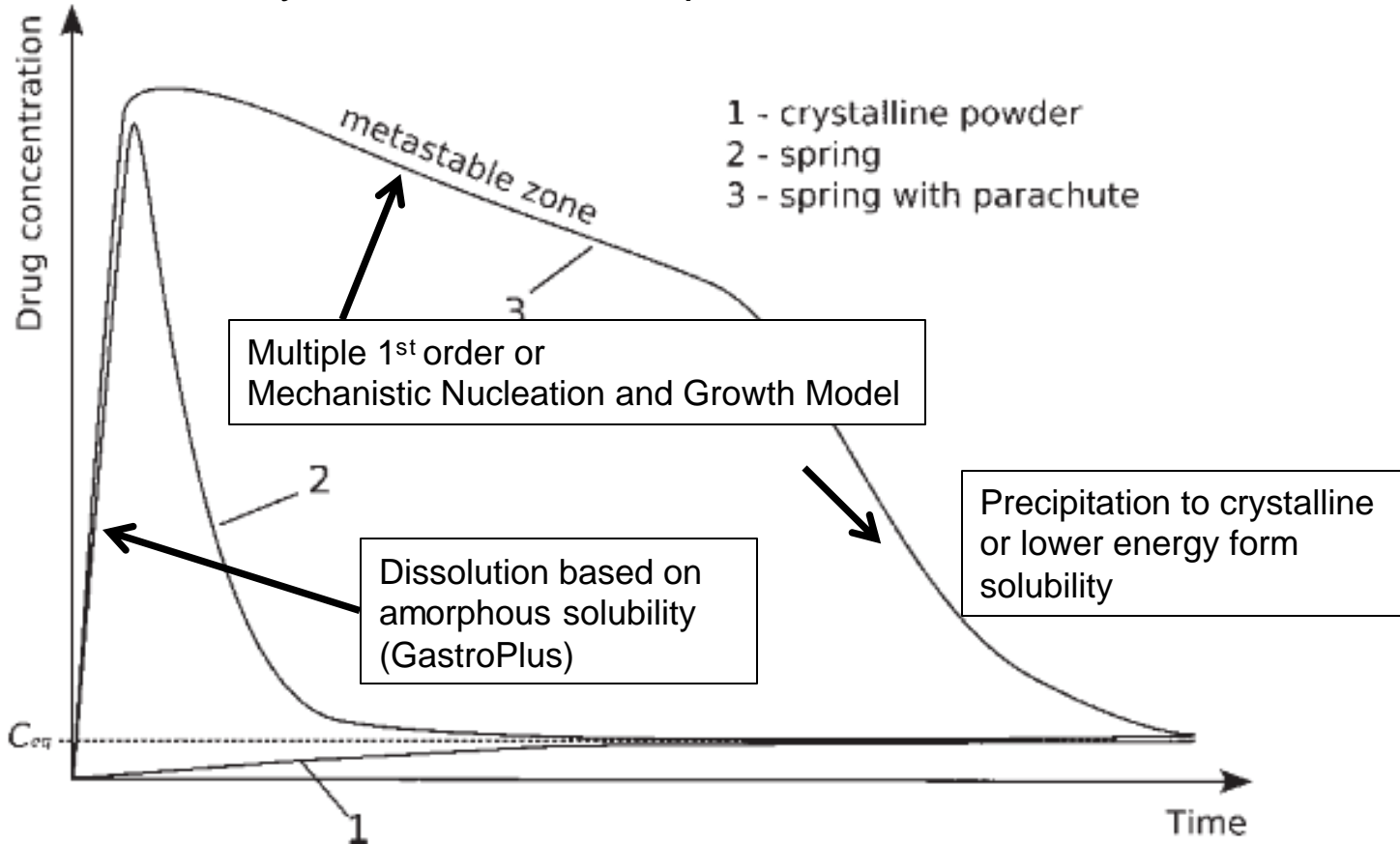
- Reimagining how companies design and analyze *in vitro* dissolution & precipitation studies
- Provides models for most dosage forms and experimental conditions
 - Immediate/delayed/controlled release oral products plus long-acting injectable formulations
 - USP, ASD, biphasic, membrane dissolution apparatus
- Significant momentum behind the DDDPlus/GastroPlus marriage to capture IVIVE of precipitation kinetics and establish product specs



Precipitation and Supersaturating Drug Delivery Systems

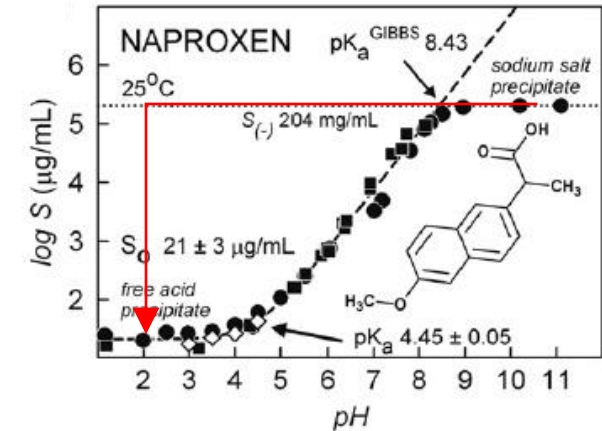
Schematic diagram of “Spring and Parachute”

Key Variable C/S – Supersaturation Ratio

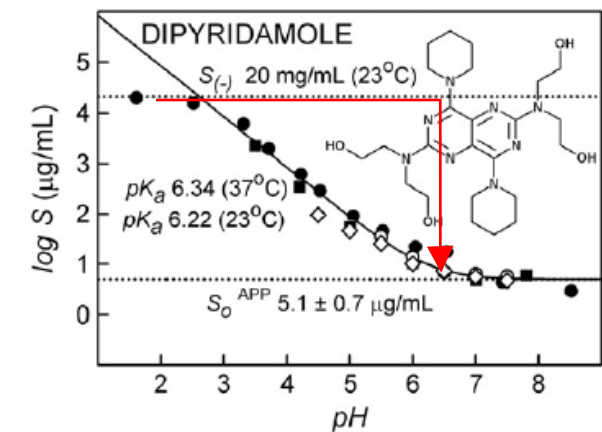


Brouwers J, J. Pharm. Sci. 98(8):2549 (2009)

Salt Forms of Acidic Drugs



Basic compounds with high gastric vs. intestinal solubility

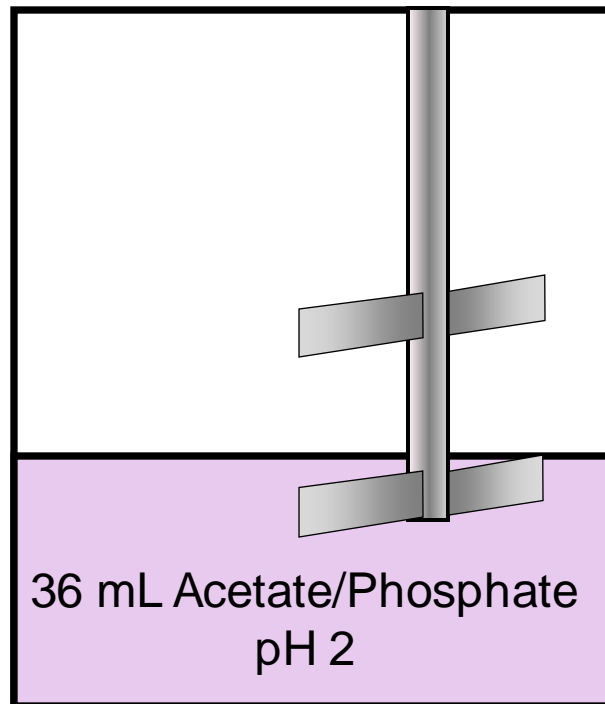


Biphasic Dissolution Model

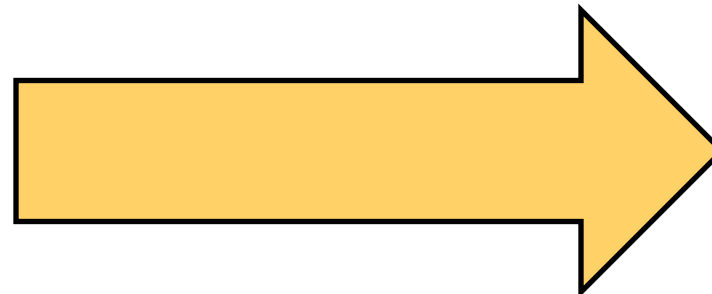
Compounds Dosed:

- Dipyridamole
- Ketoconazole
- Itraconazole (capsule/solution)

Gastric Stage

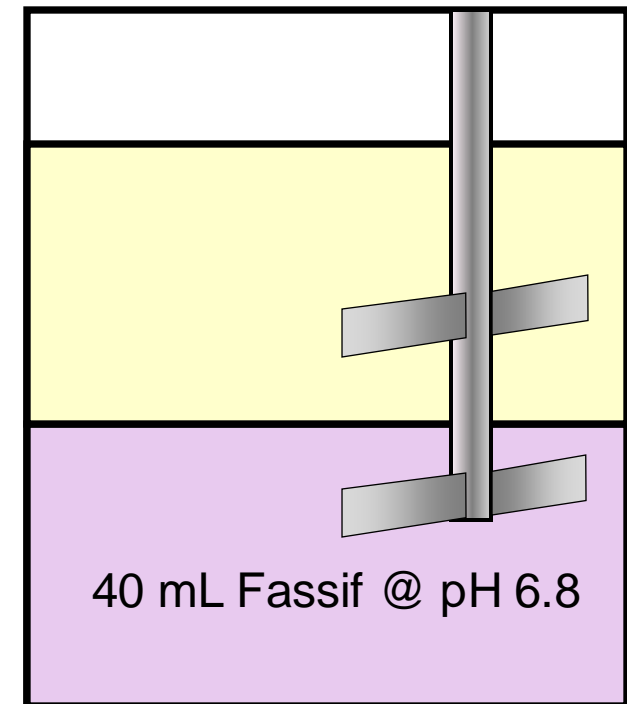


40 mL Decanol
Area = 19.63 cm²



4 mL 10X Fassif V2 + NaOH
pH 6.8

Intestinal Buffer Stage

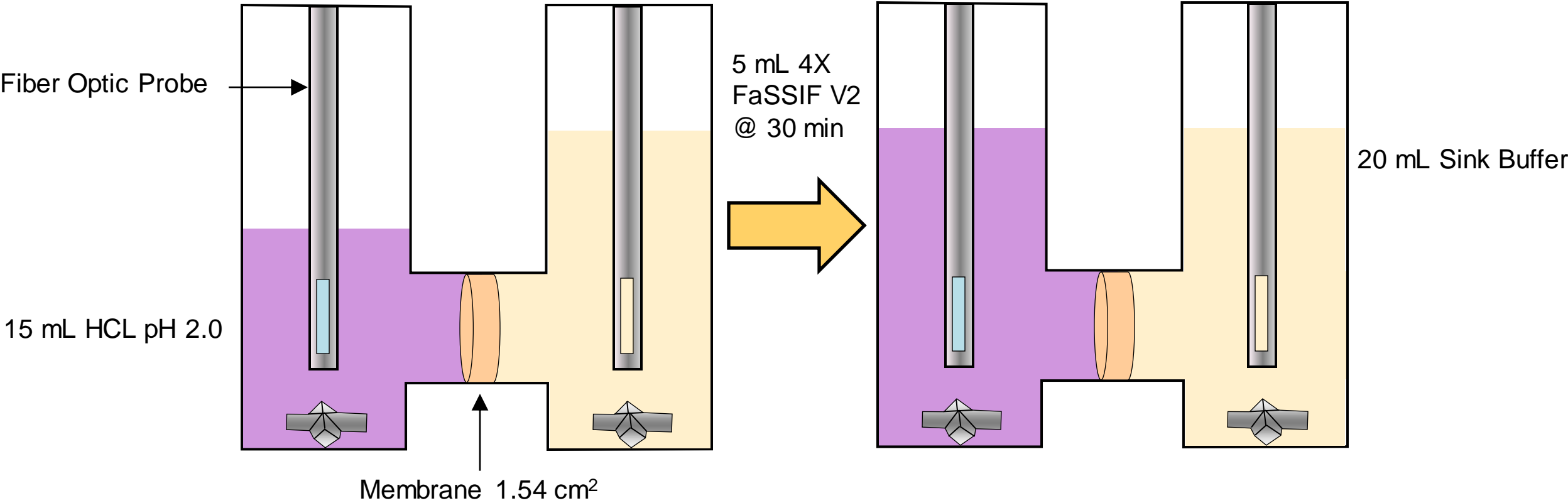


Reproduced from: O'Dwyer, Pharmaceutics 2020, 12, 272

Membrane Dissolution Model

Gastric Stage

Intestinal Buffer Stage

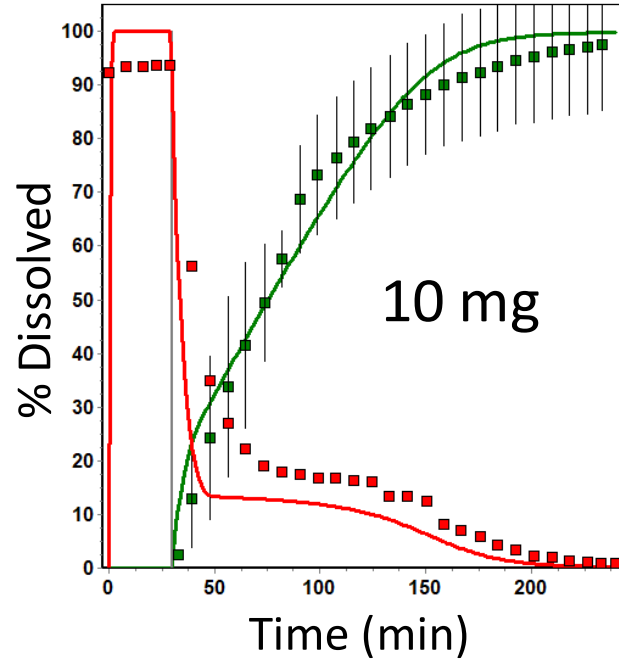


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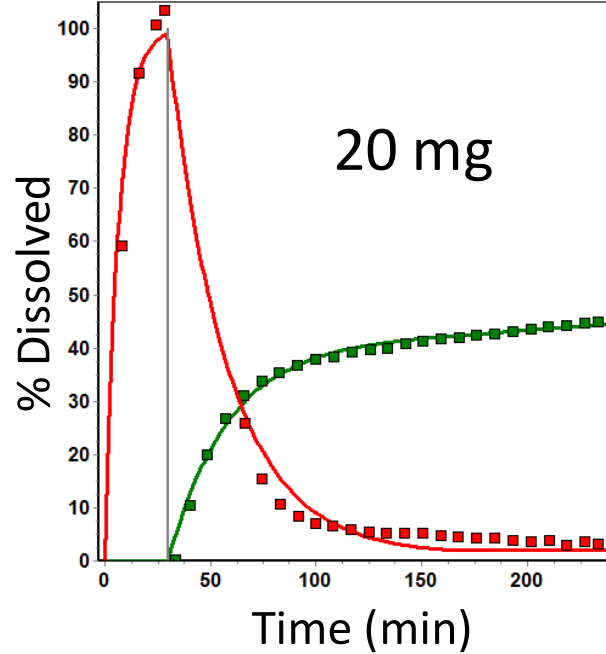


Biphasic First Order Precipitation Results

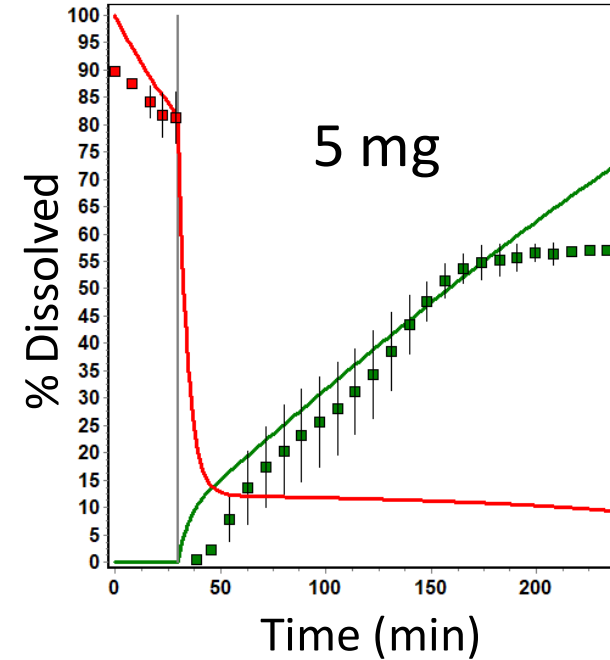
Dipyridamole



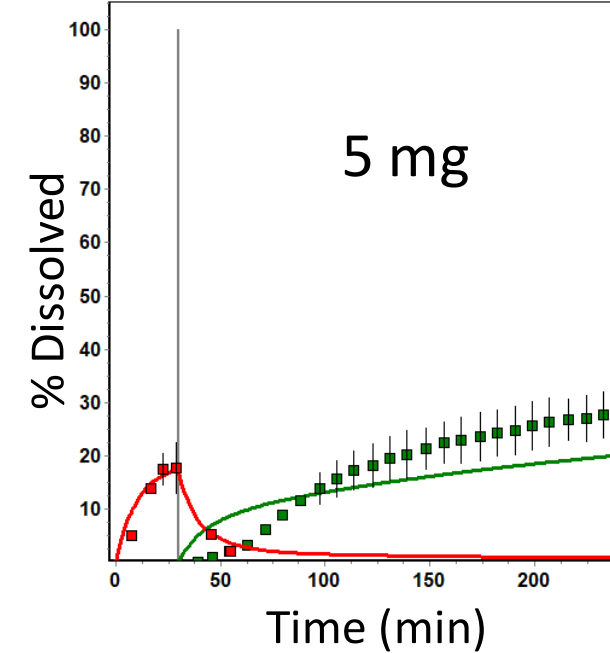
Ketoconazole



Itraconazole Solution



Itraconazole Capsule



PPT Time = 396 sec
PPT Size = 4.27 μm

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

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

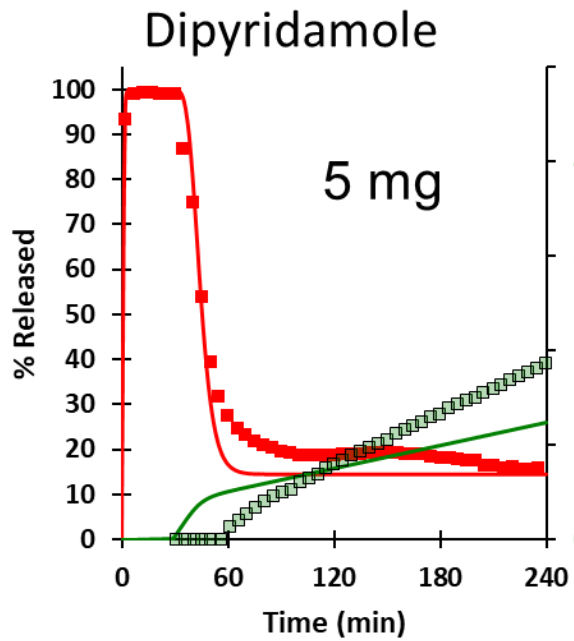
Particle Size = 13 μm
PPT Time = 900 sec
PPT Size = 1 μm

—■— Aqueous
—■— Organic

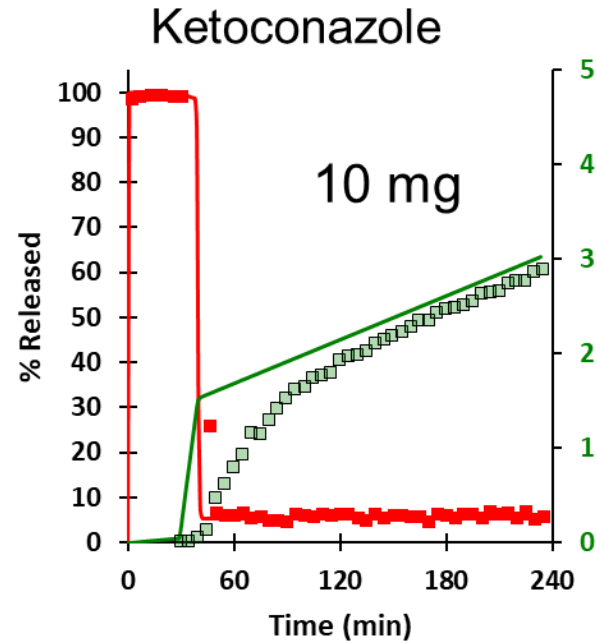
PPT Size = 1 μm



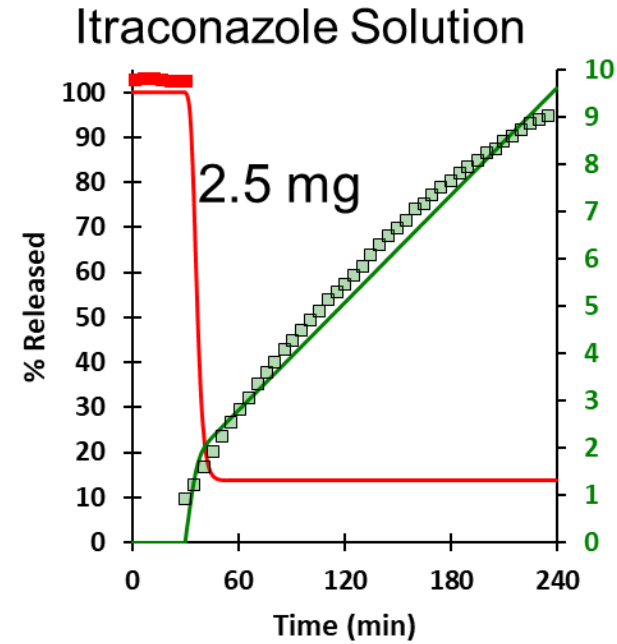
Membrane Mechanistic Precipitation Results



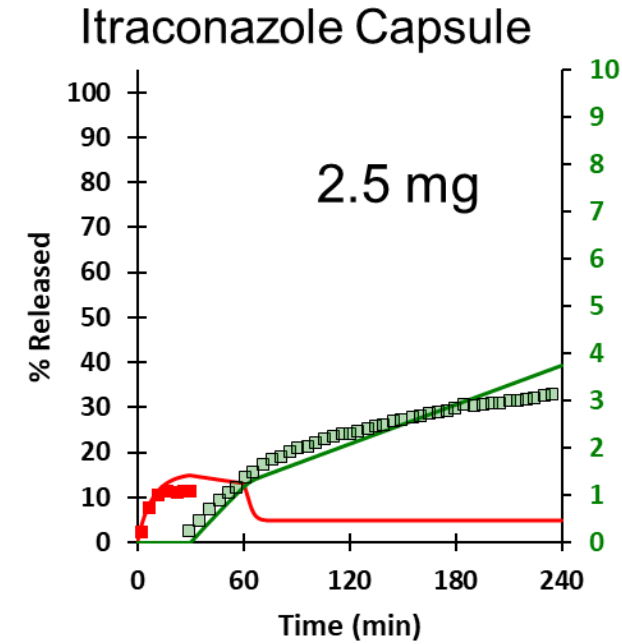
Surface Integration = $0.0639 \mu\text{m}$
Exponential Correction = 0.0639



Surface Integration = $0.095 \mu\text{m}$
Exponential Correction = 0.095



Surface Integration = $0.011 \mu\text{m}$
Exponential Correction = 0.011



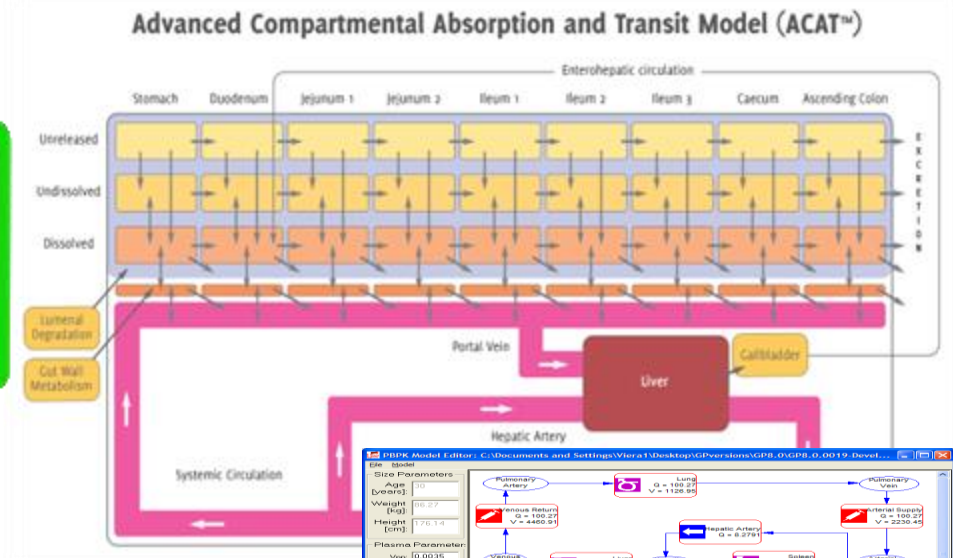
Surface Integration = $5.60\text{e-}4 \mu\text{m}$
Exponential Correction = $5.60\text{e-}4$

- Aqueous
- Receiver

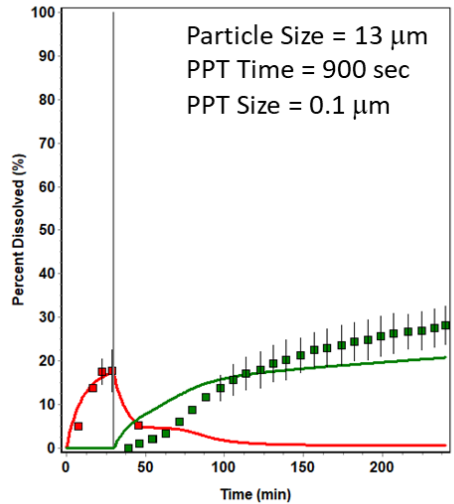
Slope of drug appearing in receiver is based on the solubility difference between amorphous drug and cyclodextrin solution.



In Vitro Dissolution Supporting GastroPlus Models

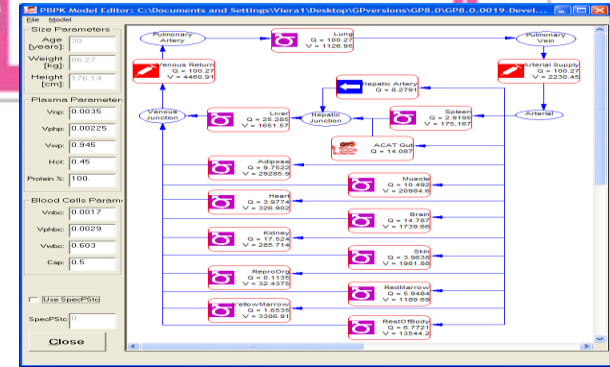
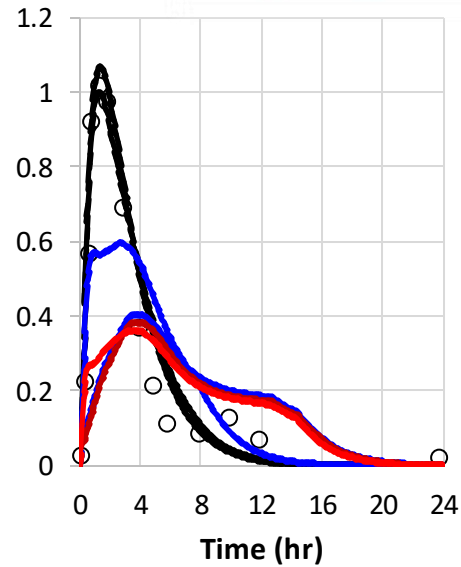


First Order Precipitation



Precipitation Parameters

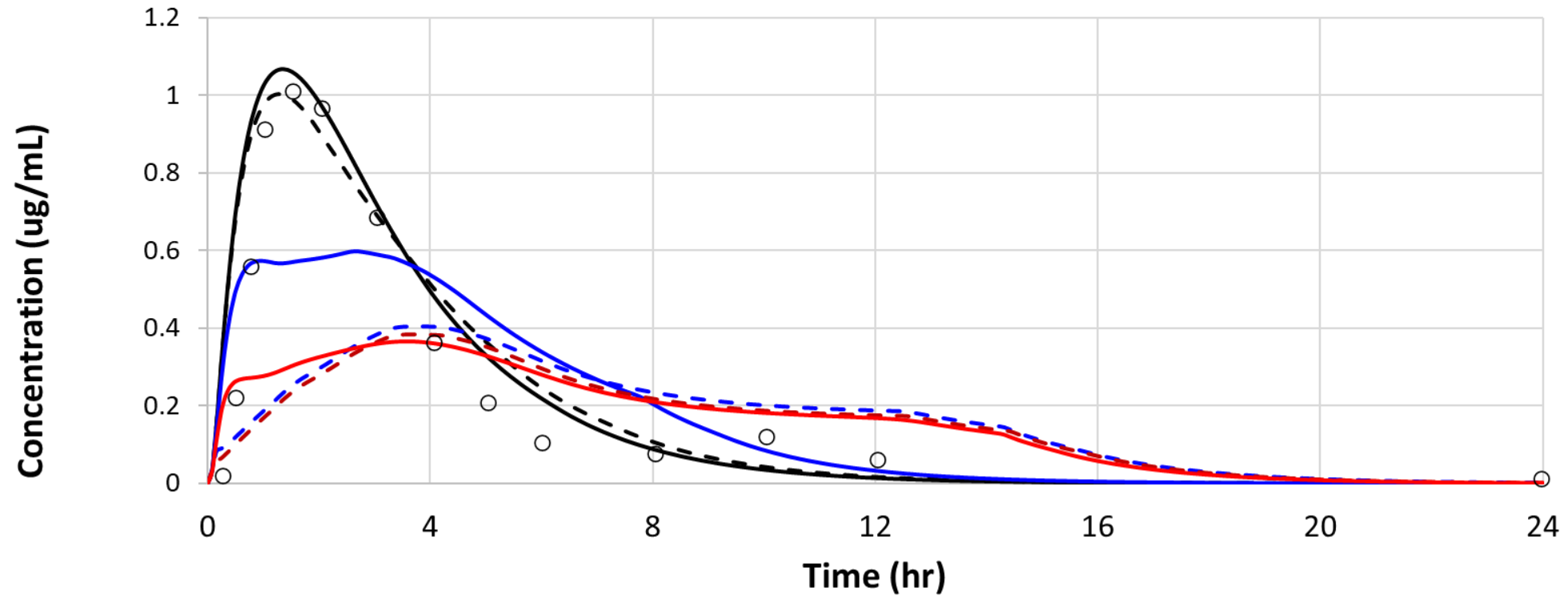
Concentration (ug/mL)



Physiologically based Pharmacokinetics (PBPK)



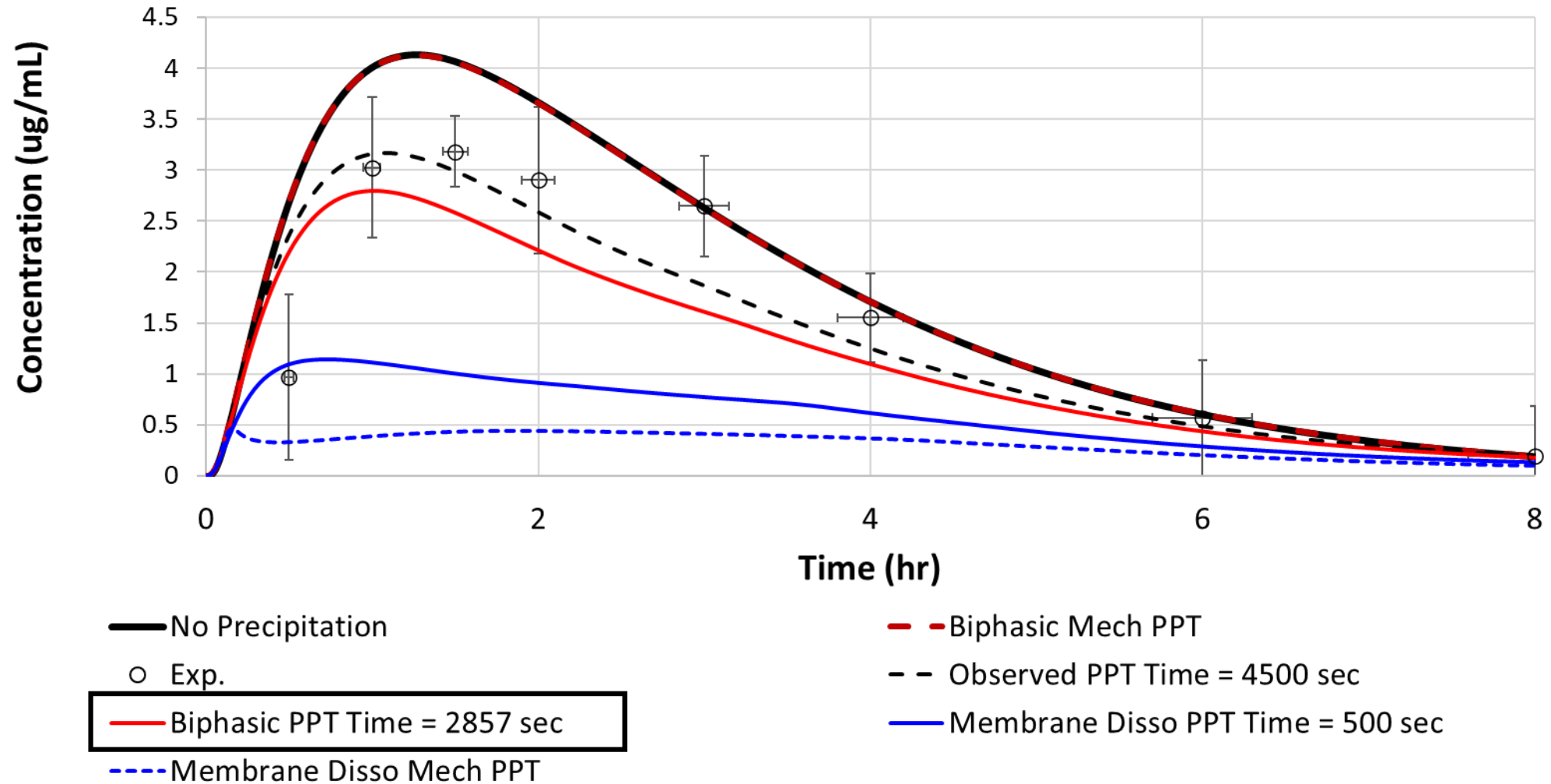
Dipyridamole GastroPlus PBPK IVIVE Precipitation Model 75 mg Tablet



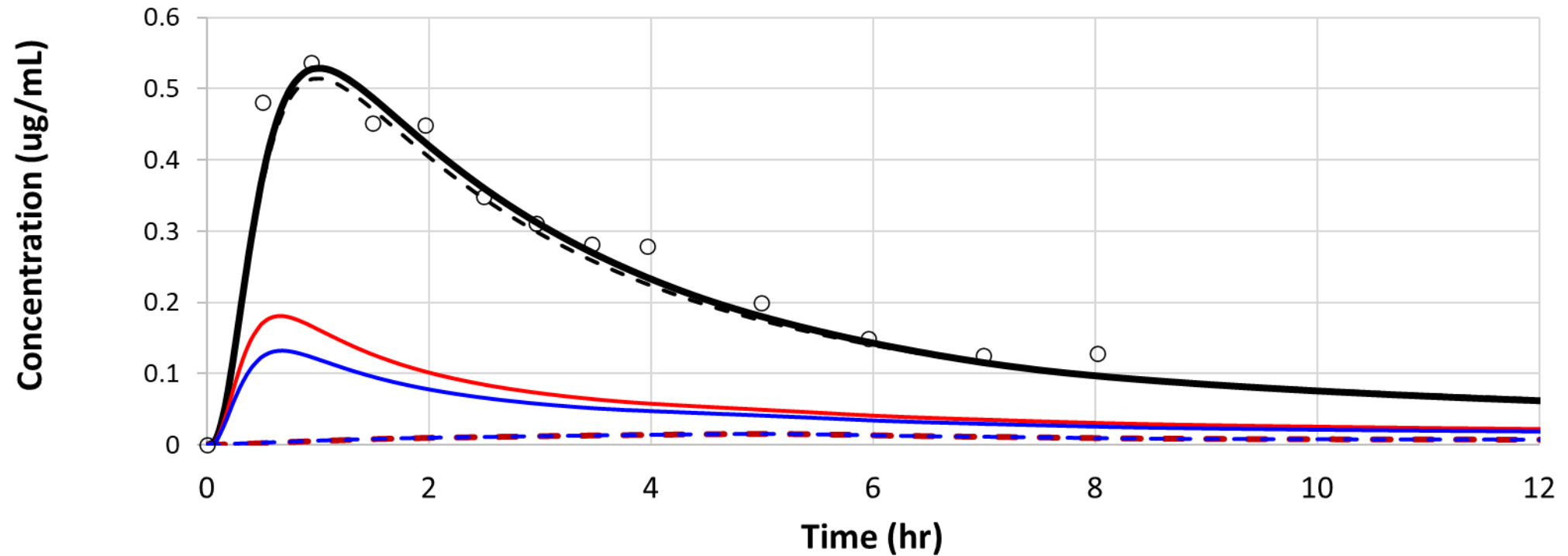
- No Precipitation
- - Observed PPT Time = 22000 sec
- - Membrane Disso Mech PPT
- Biphasic PPT Time = 396 sec
- Exp.
- Membrane Disso PPT Time = 1429 sec
- - Biphasic Mech PPT

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

Ketoconazole GastroPlus PBPK IVIVE Precipitation Model 200 mg IR Tablet



Itraconazole GastroPlus PBPK IVIVE Precipitation Model 200 mg IR Solution



— No Precipitation

○ Exp.

— Biphasic PPT Time = 350 sec

- - Membrane Disso Mech PPT

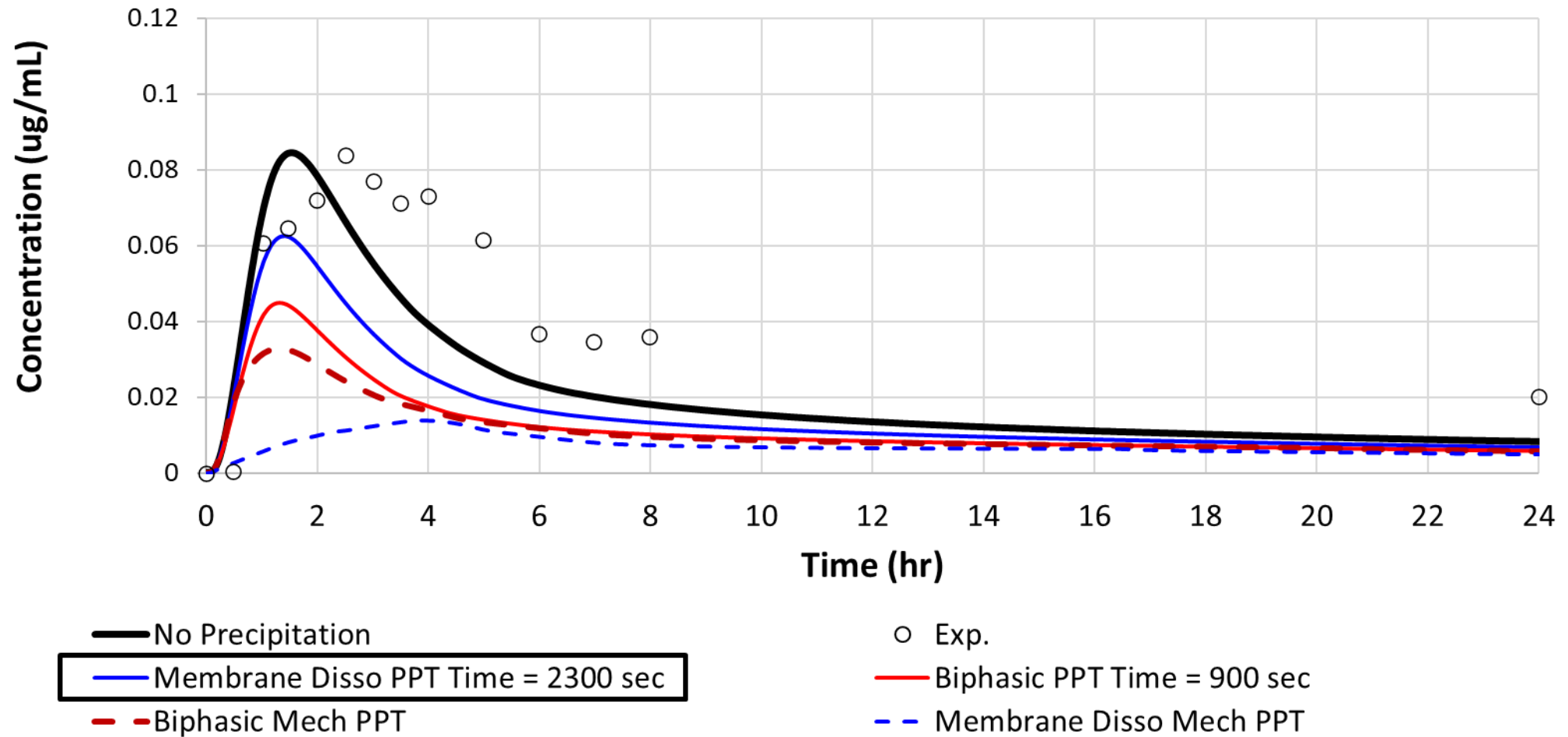
- - Biphasic Mech PPT

- - Observed PPT Time = 4500 sec

— Membrane Disso PPT Time = 450 sec

Itraconazole IVIVE Precipitation

200 mg IR Capsule



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

Questions

- Contact Info:

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- <https://www.linkedin.com/company/simulations-plus>

