Integrating Biopharmaceutic Data and Gastrointestinal Physiology Using Mechanistic Modeling

Rodrigo Cristofoletti

October 1st 2021

UF College of Pharmacy
UNIVERSITY of FLORIDA

PBPK-IVIVE linked models

- Estimate fundamental parameters (deconvolution)

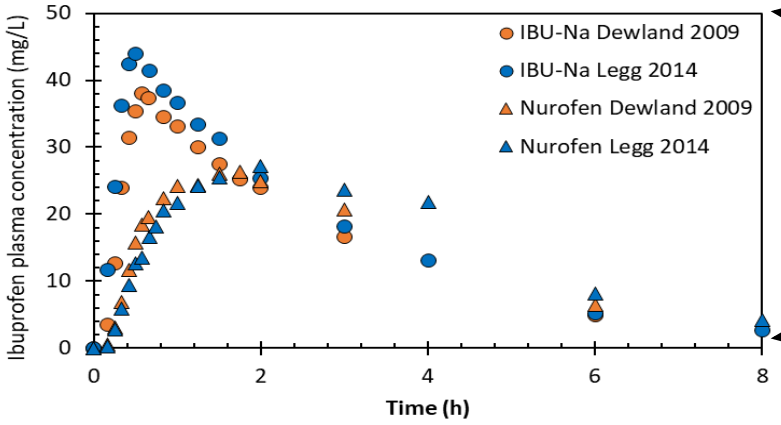
Process	*In vitro* system	Models	Fundamental parameters
Metabolism	Hepatocytes, human liver microsomes or recombinant enzymes	Michaelis-Menten model	K_m and V_{max}
Uptake Transport	Overexpressing cell lines suspended or plated	Mechanistic compartmental uptake models	CL_{diff}, $f_{u,cell}$, K_m and V_{max}
Dissolution / Precipitation	One- or multi-stage dissolution apparatuses	Diffusion layer models, Z-factor, Mooney model, biphasic dissolution model, transfer model, transmembrane flux model, etc.	Dependent on apparatus and model choice

- Reassemble the process using PBPK modeling (convolution)
  - *Integrate drug- and formulation-specific parameters with physiology*

Oral PBPK modeling for poorly soluble weak acids

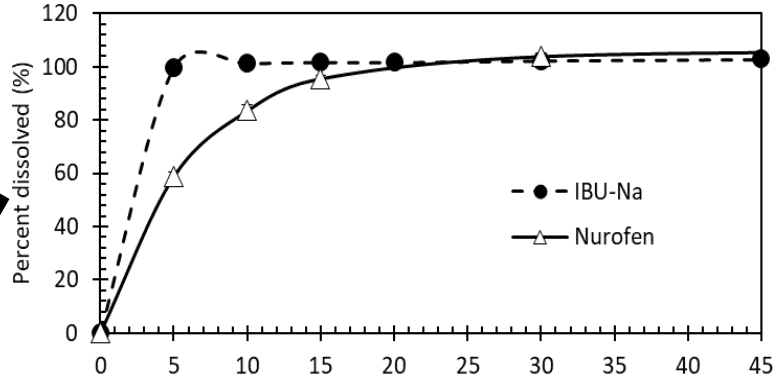
- Reverse translation: identifying a biopredictive dissolution method
  - Ibuprofen (BCS II weak acid): free acid *vs* sodium salt

Oral PK (200 mg)

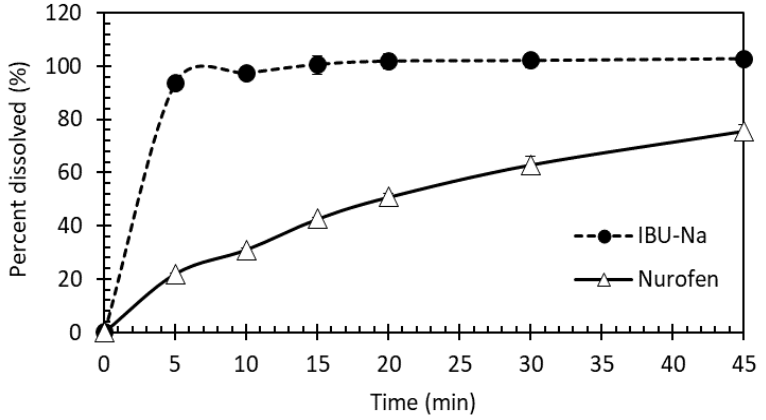


90% CI for C_{max}: 1.21 - 1.41

90% CI for AUC: 0.98 – 1.04



Phosphate buffer, pH = 6.8
50 mM
75 rpm



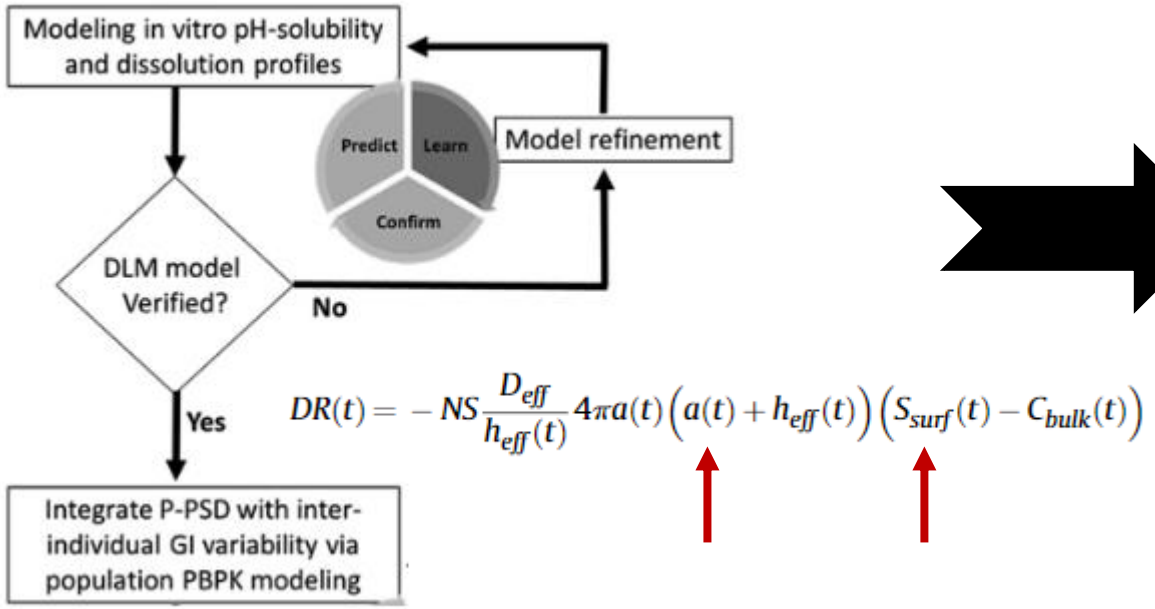
Phosphate buffer, pH = 6.8
5 mM
Titration with NaOH to keep bulk pH constant
75 rpm

Modified from Legg et al, 2014. *Drugs RD* 14(4):283-290; Dewland et al, 2009. *BMC Clin Pharmacol* 9:19;
Modified from Cristofoletti et al, 2017. *J Pharm Sci* 106(1):92-99.

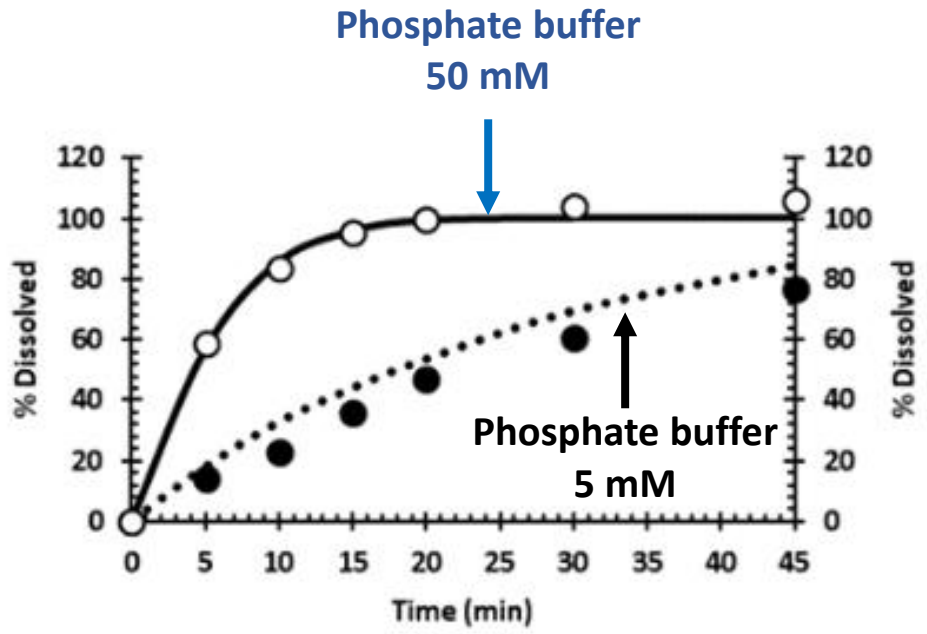
UF College of Pharmacy UNIVERSITY of FLORIDA

Oral PBPK modeling for poorly soluble weak acids

- Model-based analysis of *in vitro* dissolution data (deconvolution)
  - Simultaneous fitting of a DLM to multiple *in vitro* dissolution profiles
  - Deriving a product-specific particle size distribution (P-PSD)



$$DR(t) = -NS\frac{D_{eff}}{h_{eff}(t)}4\pi a(t)\left(a(t)+h_{eff}(t)\right)\left(S_{surf}(t)-C_{bulk}(t)\right)$$



Symbols: *in vitro* data for ibuprofen
Lines: predicted *in vitro* dissolution of ibuprofen

Modified from Cristofoletti et al, 2019. *J Pharm Sci* 108:3842-3847.

UF College of Pharmacy UNIVERSITY of FLORIDA

Oral PBPK modeling for poorly soluble weak acids

- Integration drug and formulation parameters with physiology (convolution)
  - Simulating *in vivo* dissolution profiles

Drug and formulation parameters

- pH-solubility profile
- P-PSD
- P_{app}

Gastrointestinal physiology

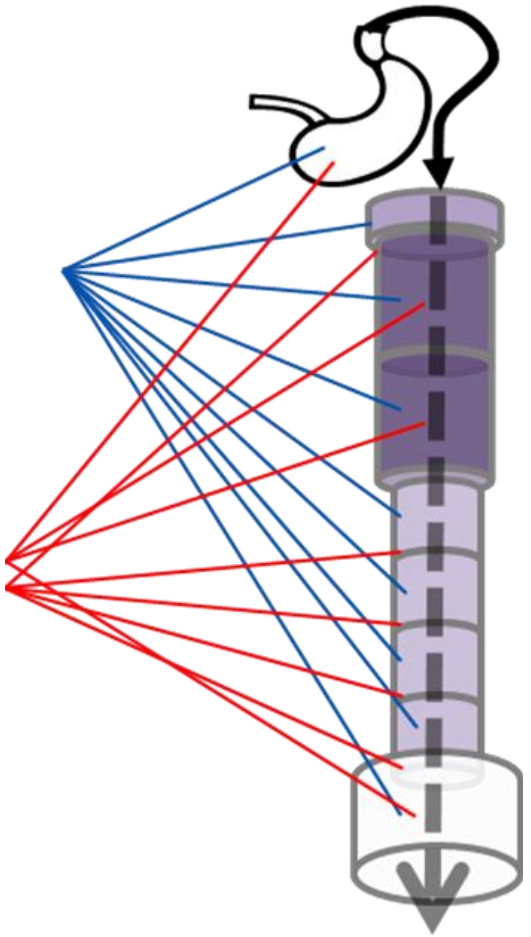
- Intraluminal pH
- Buffer capacity
- Intestinal fluid volume

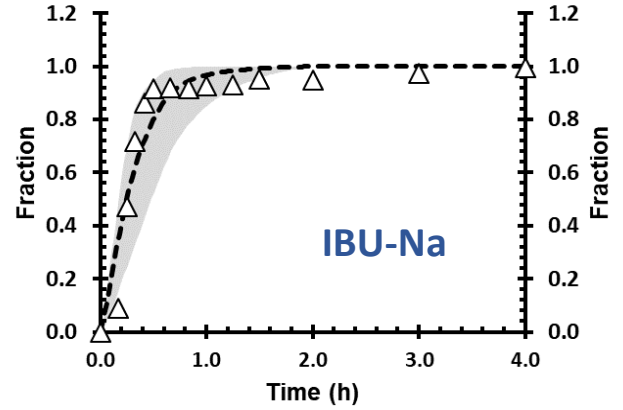
Subject 1
Intraluminal
Dissolution

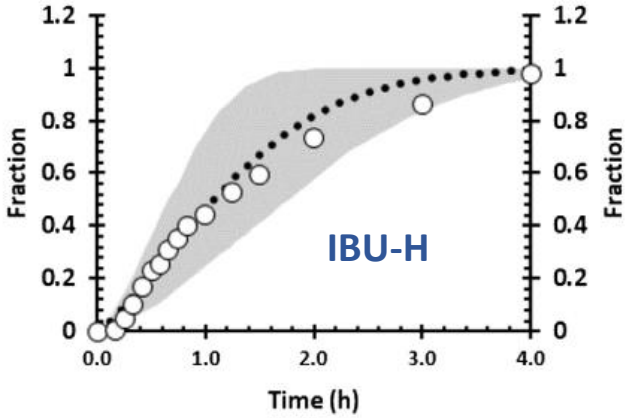
Subject 2
Intraluminal
Dissolution

.
.
.

Subject n







Symbols: deconvoluted *in vivo* dissolution
Lines: simulated *in vivo* dissolution

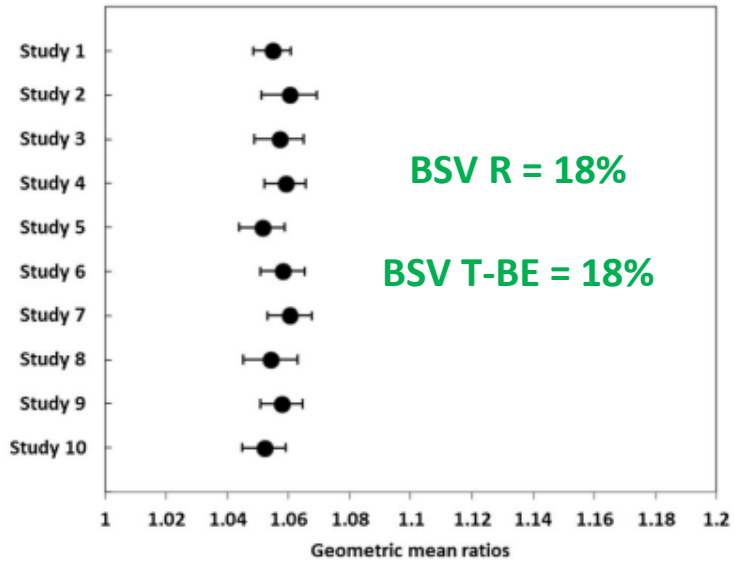
Cristofoletti et al, 2019. *J Pharm Sci* 108:3842-3847.

UF College of Pharmacy
UNIVERSITY of FLORIDA

Oral PBPK modeling for poorly soluble weak acids

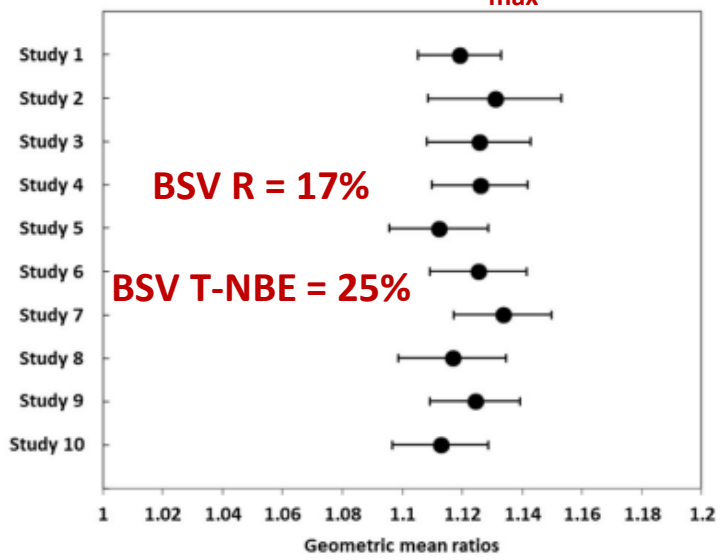
- Virtual BE trials
  - Reference, test BE and test non-BE formulations containing ibuprofen free acid
  - *Post-hoc* assignment of WSV to BE metrics ("Fixed subjects")

T-BE/R
90% CIs of C_{max}



OBS 90% CI of C_{max} : 1.06 – 1.21
***Post-hoc* 90% CI of C_{max}: 0.97 – 1.13**

T-NBE/R
90% CIs of C_{max}



OBS 90% CI of C_{max} : 1.18 – 1.35
***Post-hoc* 90% CI of C_{max}: 1.04 – 1.26**

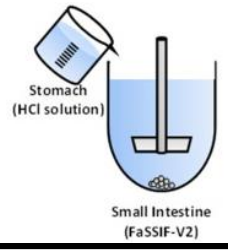
Konstantinidis et al, 2020. *AAPS J Pharm* 22:113.

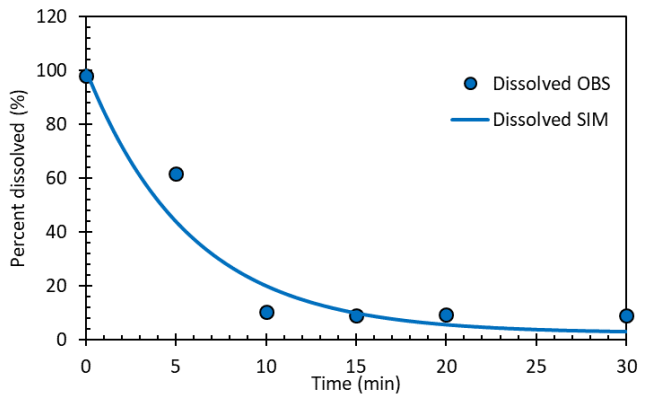
UF College of Pharmacy UNIVERSITY of FLORIDA

Oral PBPK modeling for poorly soluble weak bases

- Model-based analysis of *in vitro* precipitation data from different systems
  - Ketoconazole (BCS II weak base)

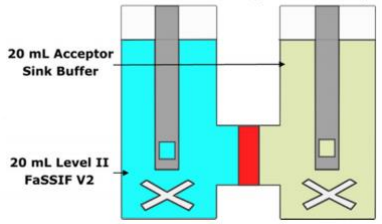
Dumping test

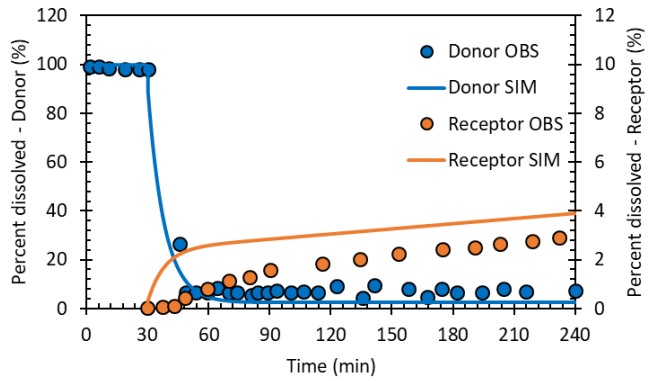




Mean precipitation time = 350 s

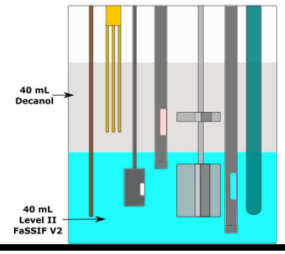
Transmembrane flux

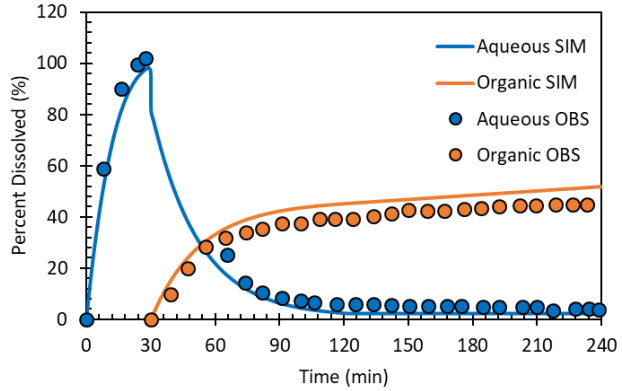




Mean precipitation time = 500 s
Surface area = 1.54 cm²

Biphasic dissolution





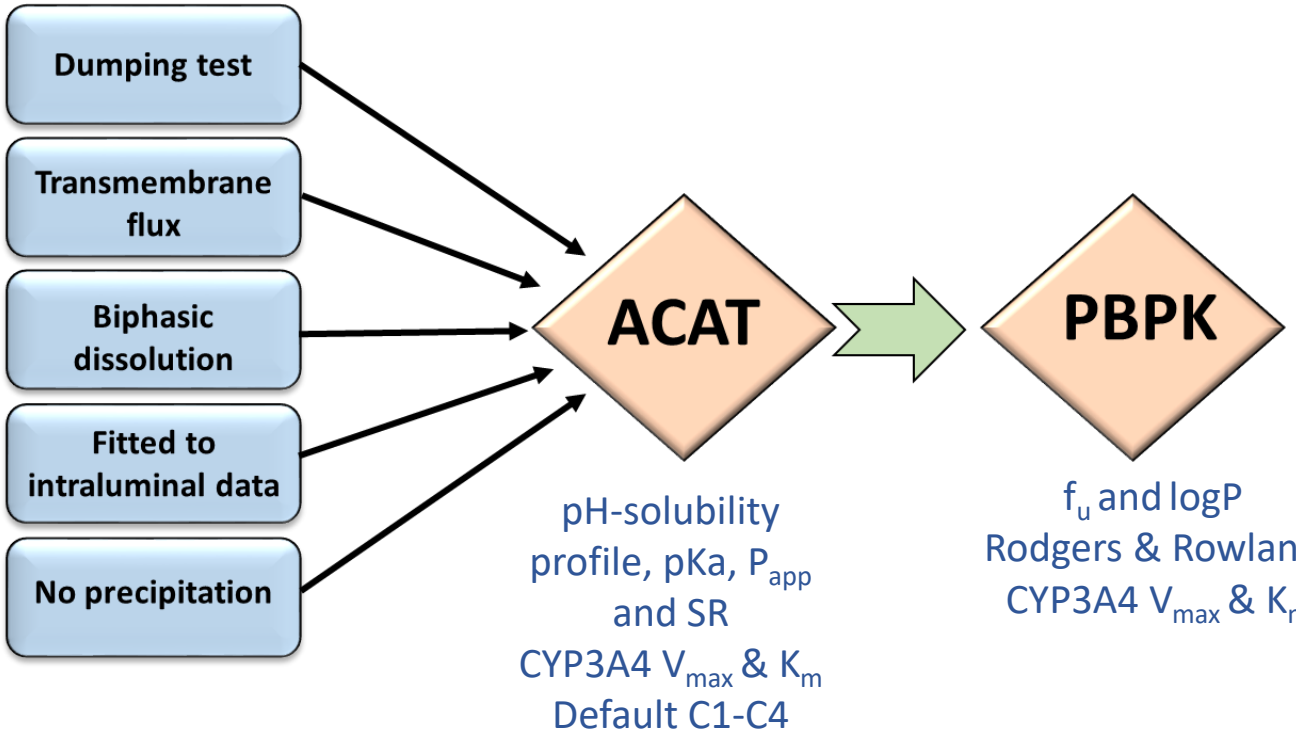
Mean precipitation time = 2850 s
Surface area = 19.63 cm²

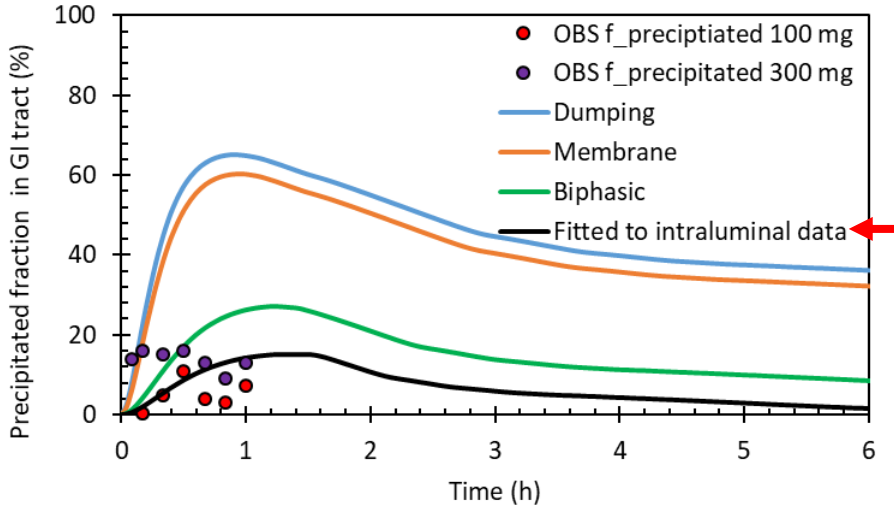
Kambayashi et al, 2016. *Eur J Pharm Biopharm* 103:95-103; O'Dwyer et al, 2020. *Pharmaceutics* 12:272.

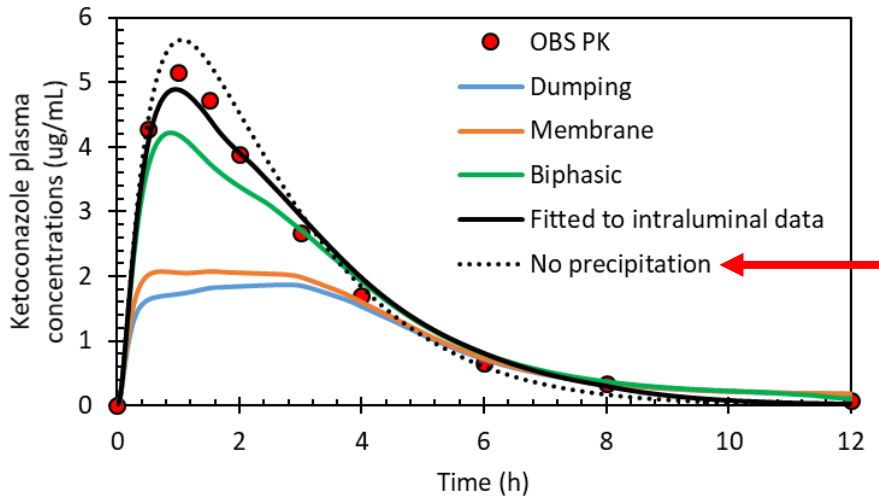
UF College of Pharmacy UNIVERSITY of FLORIDA

Oral PBPK modeling for poorly soluble weak bases

- IVIVE-PBPK modeling
  - Ketoconazole solution 200 mg – fasted
    - Different *in vitro* systems, different results





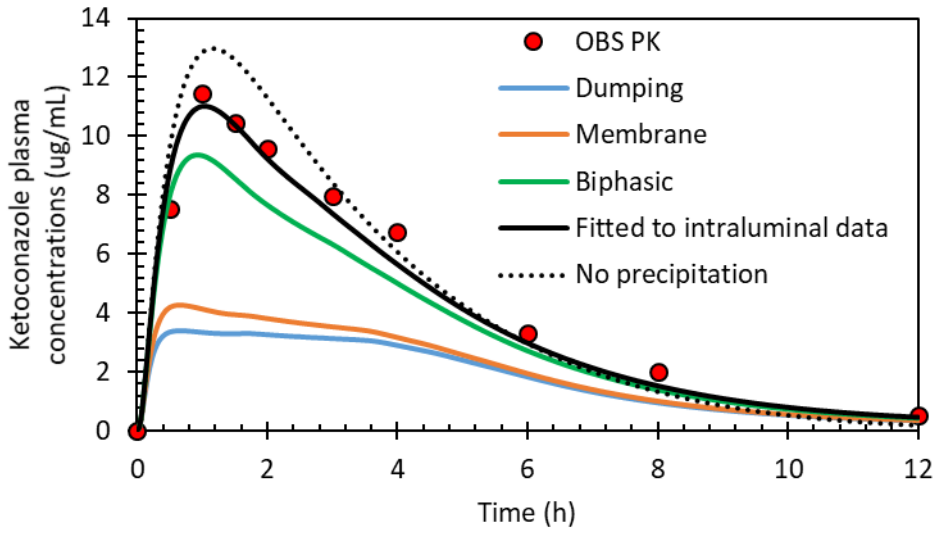


Psachoulias et al, 2011. *Pharm Res* 28:3145-3158; Huang et al, 1986. *Antimicrob Agents Chemother* 30(2):206-210; Pathak et al, 2017. *Mol Pharm* 14(12):4305-4320; Cristofoletti et al. 2017 *J Pharm Sci* 106(2):560-569.

UF College of Pharmacy UNIVERSITY of FLORIDA

Oral PBPK modeling for poorly soluble weak bases

- IVIVE-PBPK modeling
  - Ketoconazole solution 400 and 800 mg – fasted
    - Dose-dependent first-order precipitation rate

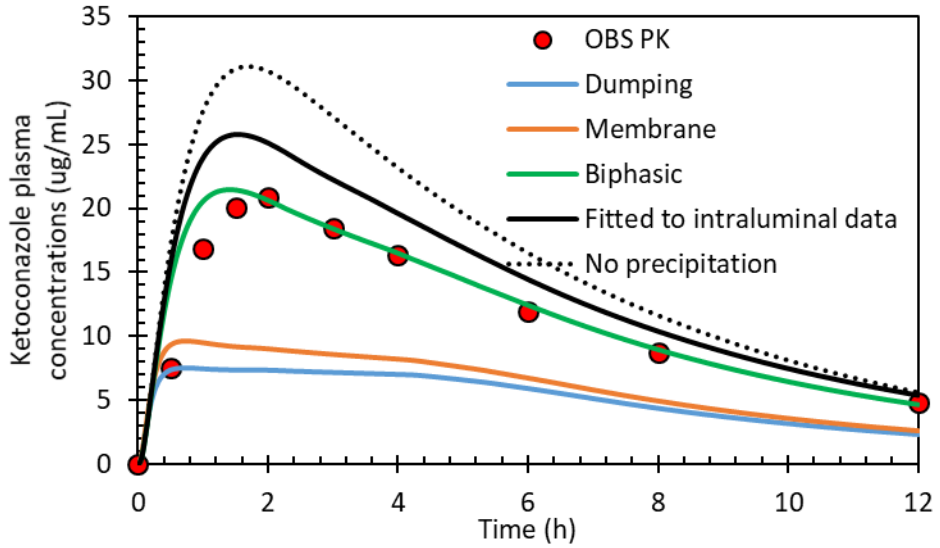


400 mg

OBS $AUC_{0\text{-inf}}$ = 55 ug.h/mL

SIM $AUC_{0\text{-inf}}$ = 50 ug.h/mL

CL/F = 7.3 L/h



800 mg

OBS $AUC_{0\text{-inf}}$ = 170 ug.h/mL

SIM $AUC_{0\text{-inf}}$ = 176 ug.h/mL

CL/F = 4.5 L/h

Huang et al, 1986. *Antimicrob Agents Chemother* 30(2):206-210.

UF College of Pharmacy UNIVERSITY of FLORIDA

Summary

- Model-based analysis of *in vitro* data is helpful to derive fundamental input parameters for PBPK models, however navigating between different *in vitro* models might be challenging;

- Generalization of first-order precipitation rate across different doses is not straightforward;

- Further research is needed to optimize propagation of WSV through simulations.

Thank you!

rcristofoletti@cop.ufl.edu

UF College of Pharmacy
UNIVERSITY of FLORIDA