Translating the effect of product manufacturing variants from *in vitro* to the clinic. Current possibilities and gaps for immediate release formulations

FDA PBBM Workshop, Sept 24, 2019

Jim Mullin, Team Leader – Simulation Technologies

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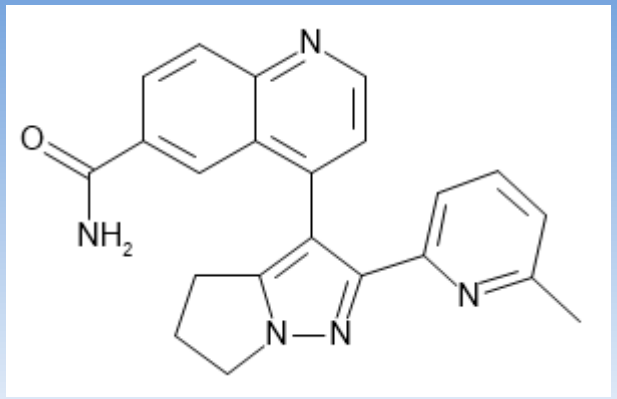
Introduction

- Case Study 1:
  - Utilization of *in vitro* dissolution data and Z-factor model in PBBM modeling
  - Using ASD model to evaluate *in vitro* precipitation data
  - Potential for IVIVC using Z-factor

- Case Study 2:
  - Lysosomal trapping affect on dissolution specifications for lipophilic base dextromethorphan

Galunisertib PBBM Model



- TGF-b inhibitor for liver carcinoma
- PK data in rat and human available in literature
- Partition coefficient calculated with Lukacova method
  - LogP adjusted to 2.15 to calculate Kp for both human and rat

Property	Value	Ref
LogP	1.85	[1]
pKa	-0.68,2.05[1],4.2 (Base) 11.01 (Acid)	AP 9.5 [1] Exp. Fit
Exp Sol. (mg/mL)	0.05 @ pH 7.5	Exp
Solubility Factor	302	Exp. Fit
FaSSIF Sol. (mg/mL) FeSSIF Sol. (mg/mL)	0.05 0.12	Exp. Exp
Human Peff (10^4*cm/s)	4.8	Fit
Blood:plasma concentration ratio (R_{bp})	0.8 (human) 1.21 (rat)	AP AP
Plasma protein binding (Fup)	9.5% (human) 9.22% (rat)	AP AP
Diff Coef.	0.68	AP
Metabolism (3A4) **PBBM Model Built based on Solution Data**		
Vss L	50.2 L	NCA
Km (mg/mL) CL HLM (uL/min/mg prot) Vmax Gut (mg/s) Vmax PBPK (mg/s/mg enzyme)	79.69 51 - 65[2] 4.533 – 5.778 0.011 - 0.014	AP Fit Solution[2]

AP = ADMET Predictor V 9.5

[2] Fitted HLM clearance was used to generate Vmax with predicted Km. The fitted value for solution was adjusted for the non-crossover population tested for solid dosage forms

Galunisertib *In Vitro* Dissolution Data

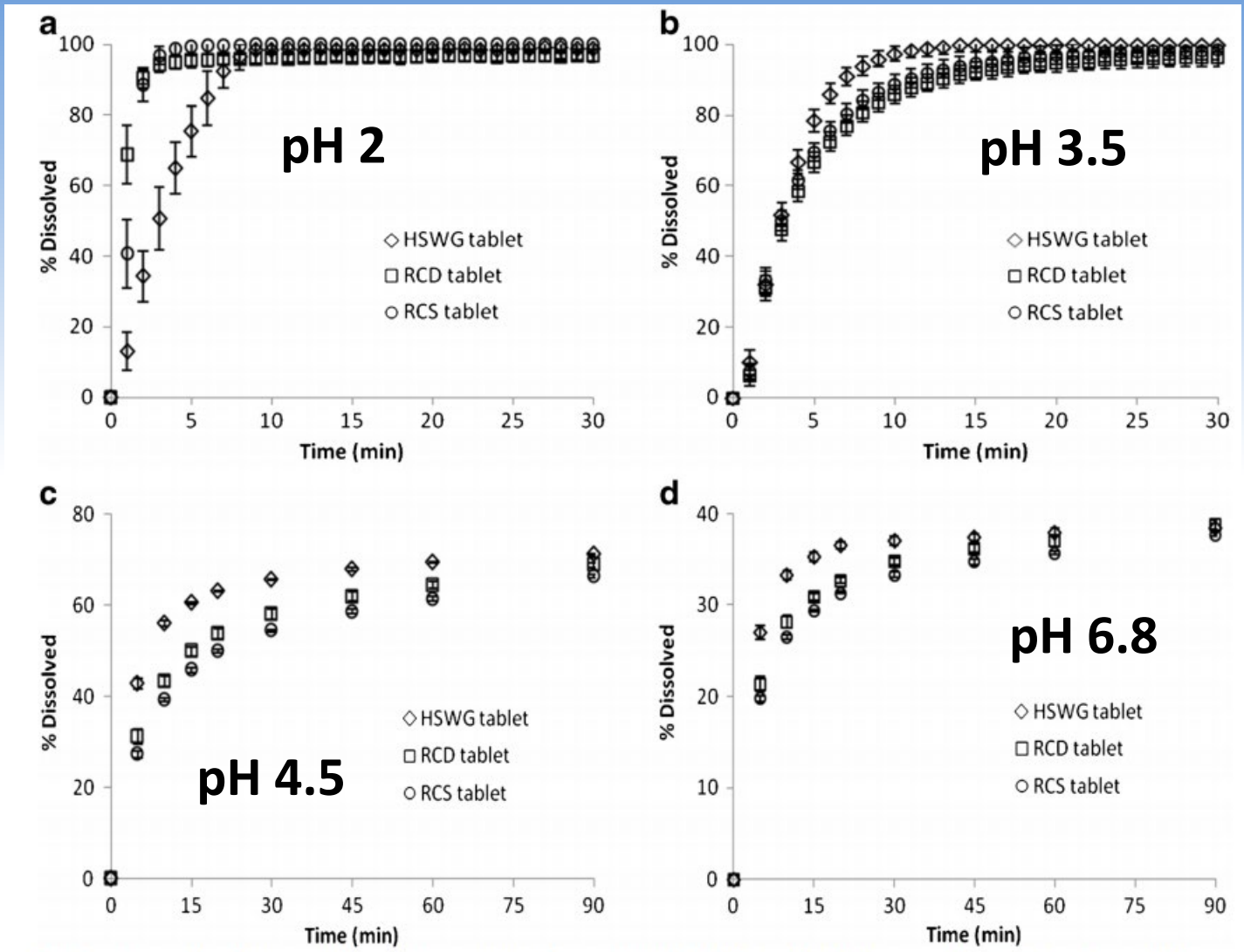


Fig. 3. *In vitro* dissolution profiles of galunisertib tablets. **a** In 0.01 N HCl at pH 2. **b** In citrate phosphate buffer at pH 3.5. **c** In acetate phosphate buffer at pH 4.5. **d** In phosphate buffer at pH 6.8

HSWG – High Shear Wet Granulated
RCD – Roller compacted conventional milling
RCS – Roller compacted slurry milled

Ding, et al, AAPS Journal, 2015, 17(6), pg. 1395-14

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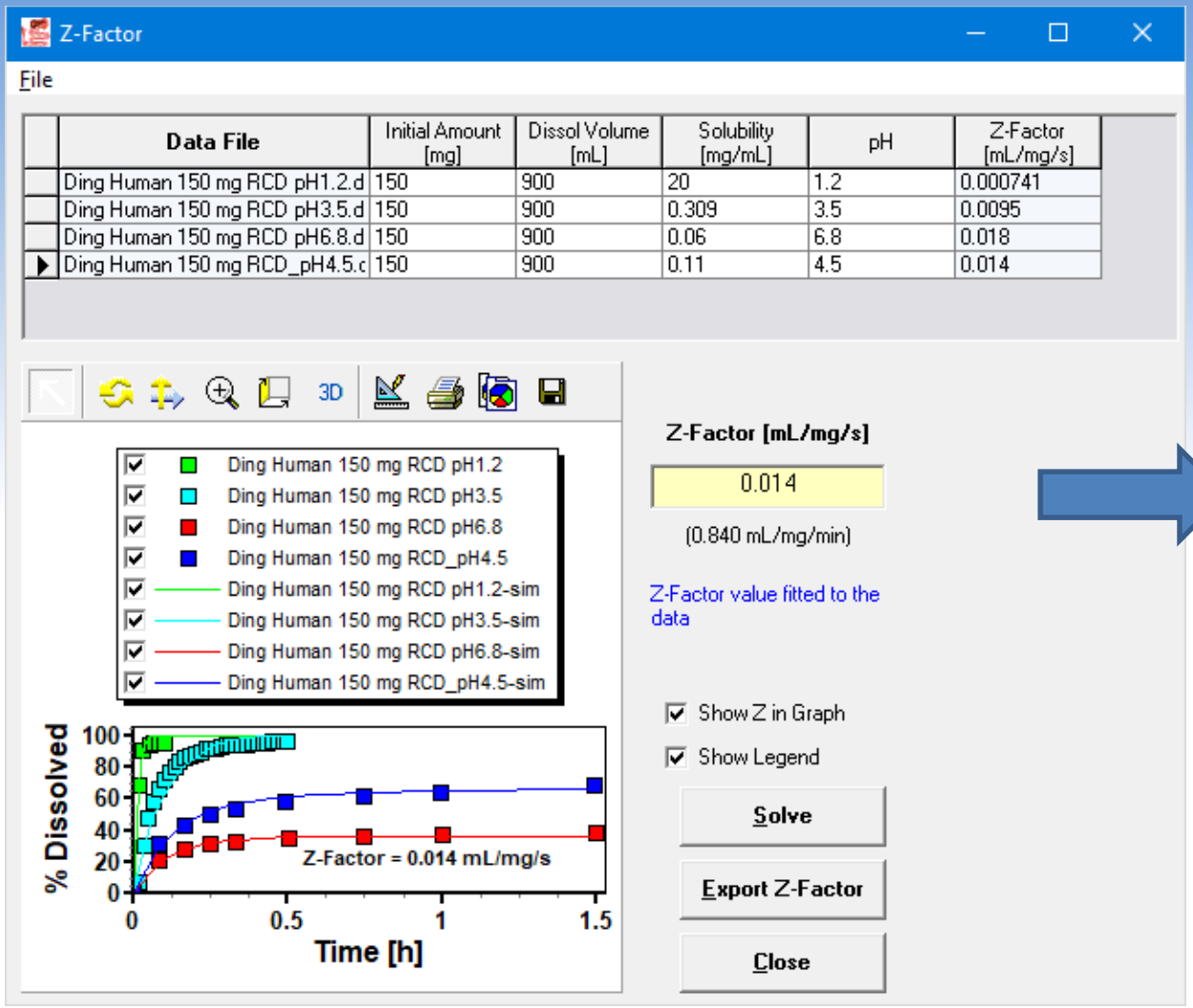
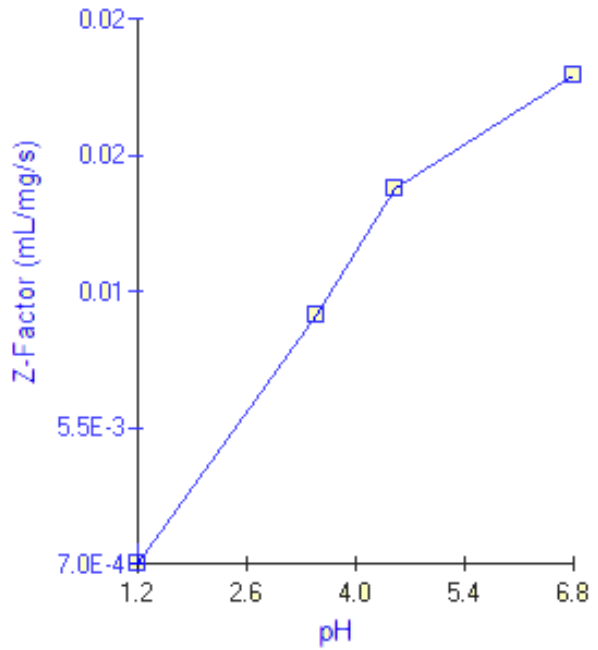
In Vitro Dissolution Z-Factor vs. pH Fit





In Vitro Dissolution Rates

pH	HSWG mL/mg/s	RCD mL/mg/s	RCS mL/mg/s
1.2	0.000165	0.000741	0.000468
3.5	0.012	0.0095	0.01
4.5	0.022	0.018	0.016
6.8	0.029	0.014	0.012

A different z-factor value at low pH may indicate excipient or process related dissolution effect.

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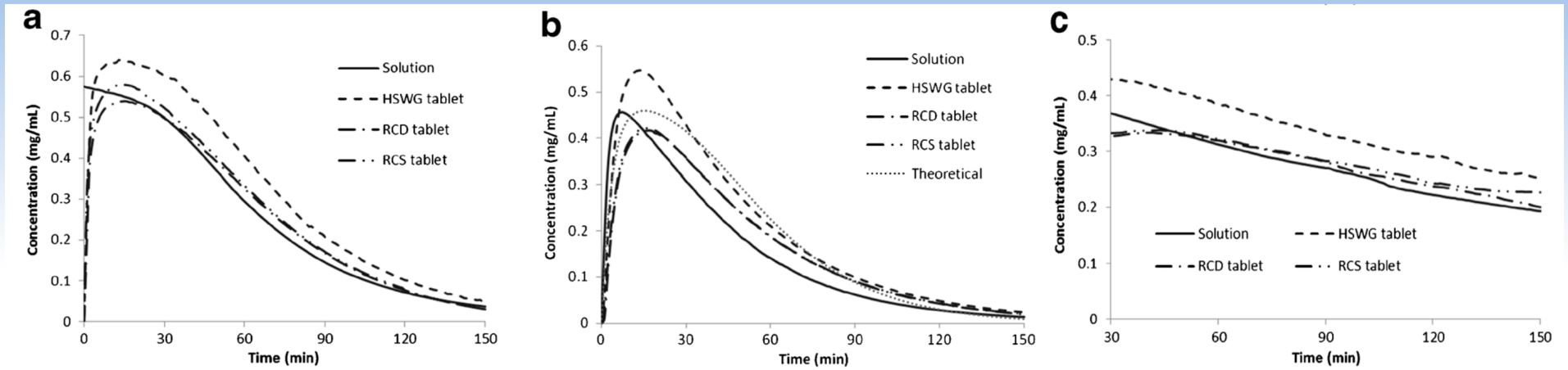
Artificial Stomach Duodenum (ASD) *In Vitro* Dissolution Data for Galunisertib

Stomach | Duodenum | Waste



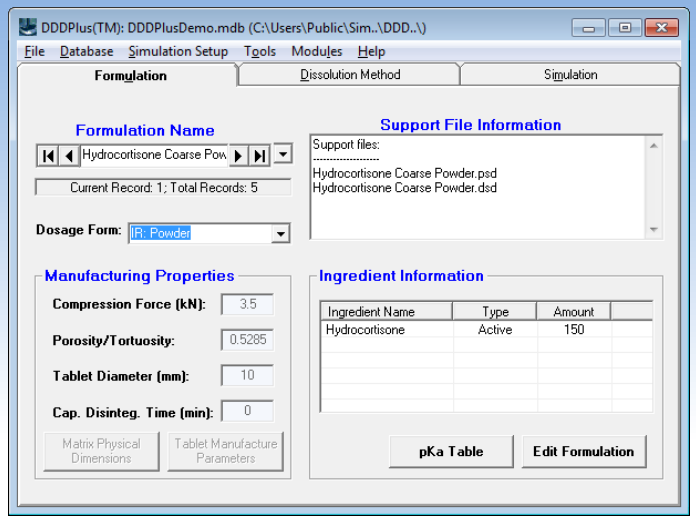
- Can we use a model to determine the precipitation time?
- HSWG tablet concentration higher than theoretical
  - potentially due to pump or volume issues?
  - Supersaturation (not likely – higher than theoretical solution)

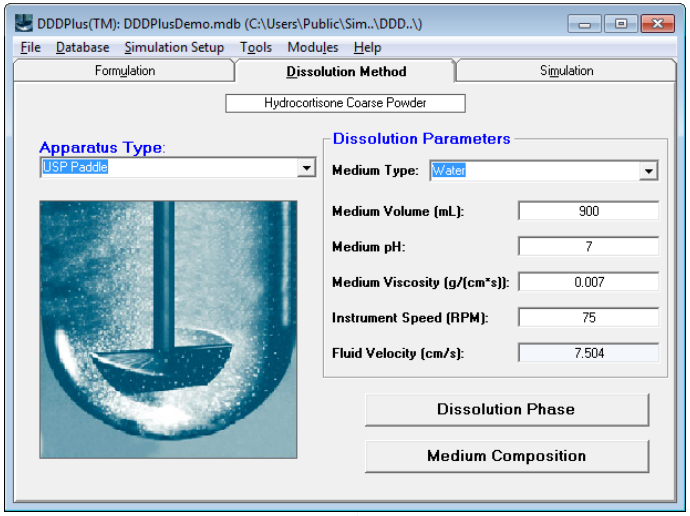
Ding, et al, AAPS Journal, 2015, 17(6), pg. 1395-1406

What is DDDPlus™?

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
- A 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 user defined experimental apparatus and experimental conditions
- Multiple experimental phases to allow for dissolution experiment design
- Micelle-facilitated dissolution through incorporation of surfactants in medium





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ASD Model/Apparatus Setup

DDDPlus(TM): Galunisertib.mdb (C:\Users\Public\Sim..\DDD..\Gal..\)

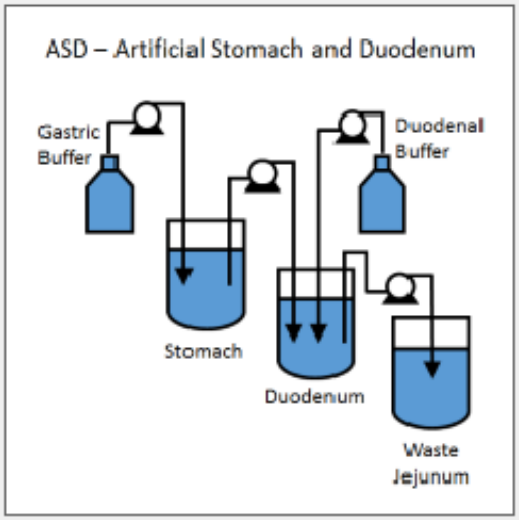
File Database Simulation Setup Tools Modules Help

Formulation | **Dissolution Method** | Simulation

galunisertib HSWG

Apparatus Type:

ASD Artificial Stomach and Duodenum



Medium Composition

Dissolution Parameters

ASD Model galunisertib ASD Setup CDT

Gastric Emptying Time (min): 30.00

Pump Stop Time (min): 150.00

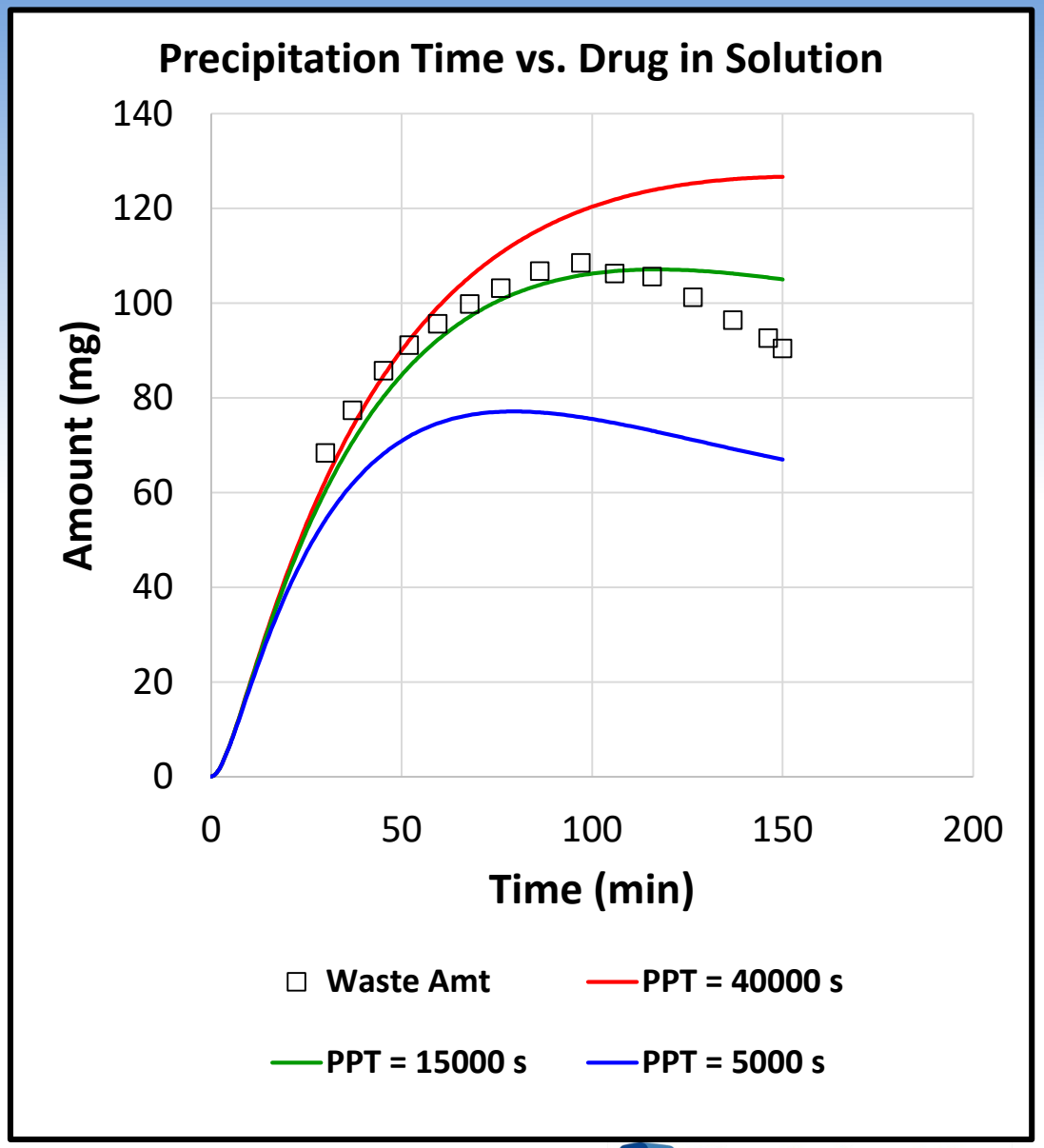
ASD Buffer Setup	
Compartment	Buffer File
Stomach Initial	0.002 N HCL
Duodenum Initial	FaSSIF 6.5
Jejunum Initial	FaSSIF 6.5
Stomach Reservoir	0.01 M Hydrochloric Acid
Duodenum Reservoir	FaSSIF 6.5
Jejunum Reservoir	FaSSIF 6.5

Variable	Stomach	Duodenum	Jejunum
Volume (mL)	250	30	0
pH	1.2	5.5	6.5
Buffer Flow (mL/min)	0	2	0
Dosage Transit Time (min)	30	20	0
Viscosity (Pa-s)	0.0007	0.0007	0.0007
Stirring (rpm)	75	75	75
Fluid Velocity (cm/s)	7.5	7.5	7.5

- Gastric Emptying = 30 min
- Initial Buffer in each compartment
  - 250 mL - 0.002 N HCL
  - 30 mL - FaSSIF
- Reservoir Buffer flow only for Duodenum
  - FaSSIF – 2 mL/min
- Experimental settings for each compartment
- Full pH vs. time calculation in each compartment

ASD Model Prediction – Solution Formulation

- This is a good study to check the reported settings and see if they may be off.
- Perhaps the stomach emptying reported is slightly off. But waste compartment is captured well.
- Waste compartment is key to understanding precipitation time
- T_{precip} = 15000 sec



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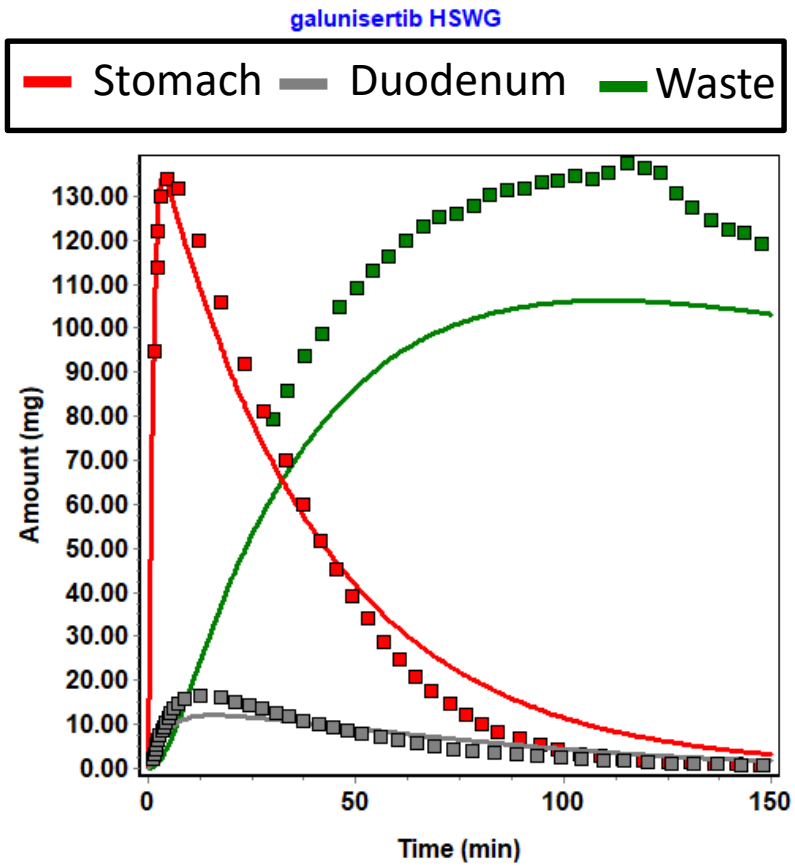
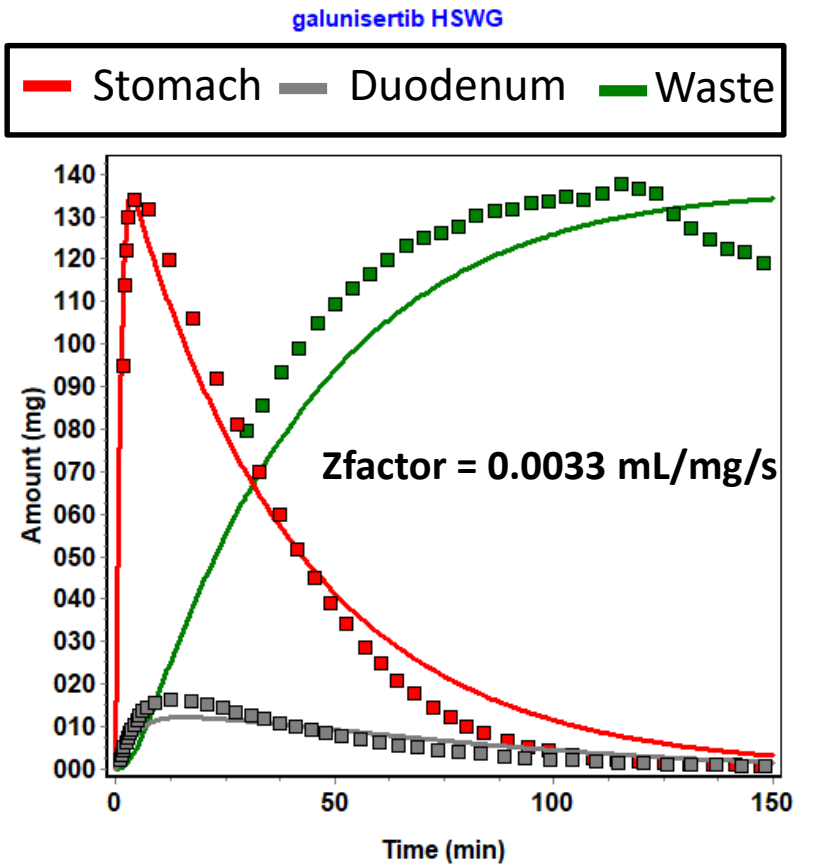
ASD Model Tablets - HSWG

Solution PPT Time = 15,000 sec



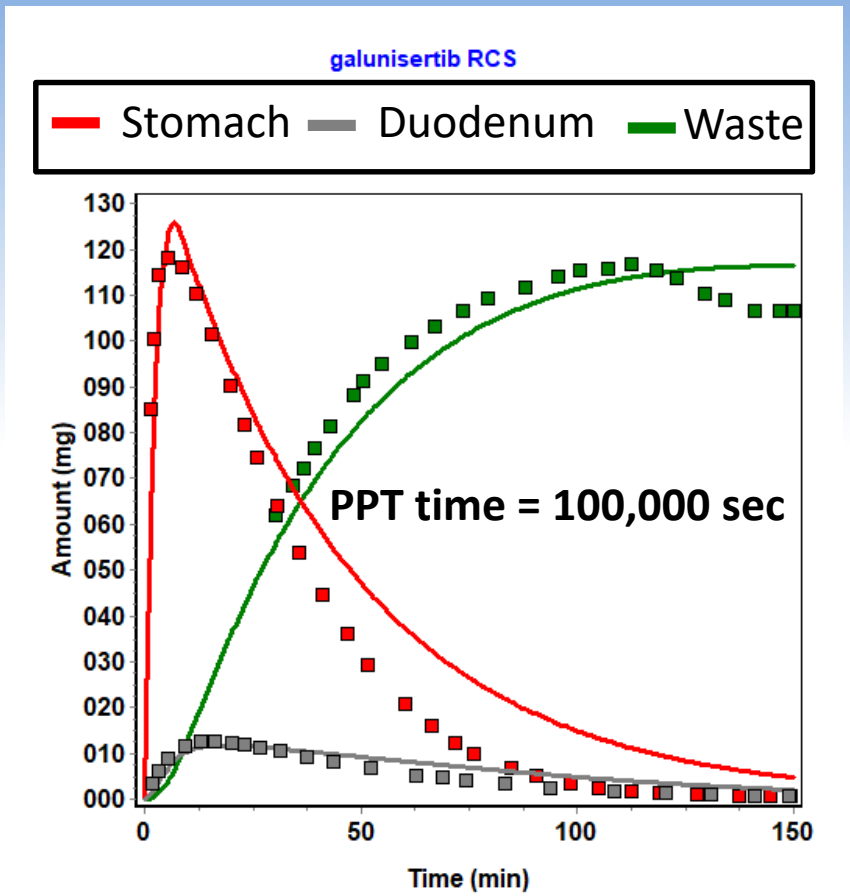
Solution PPT Time = 100,000 sec



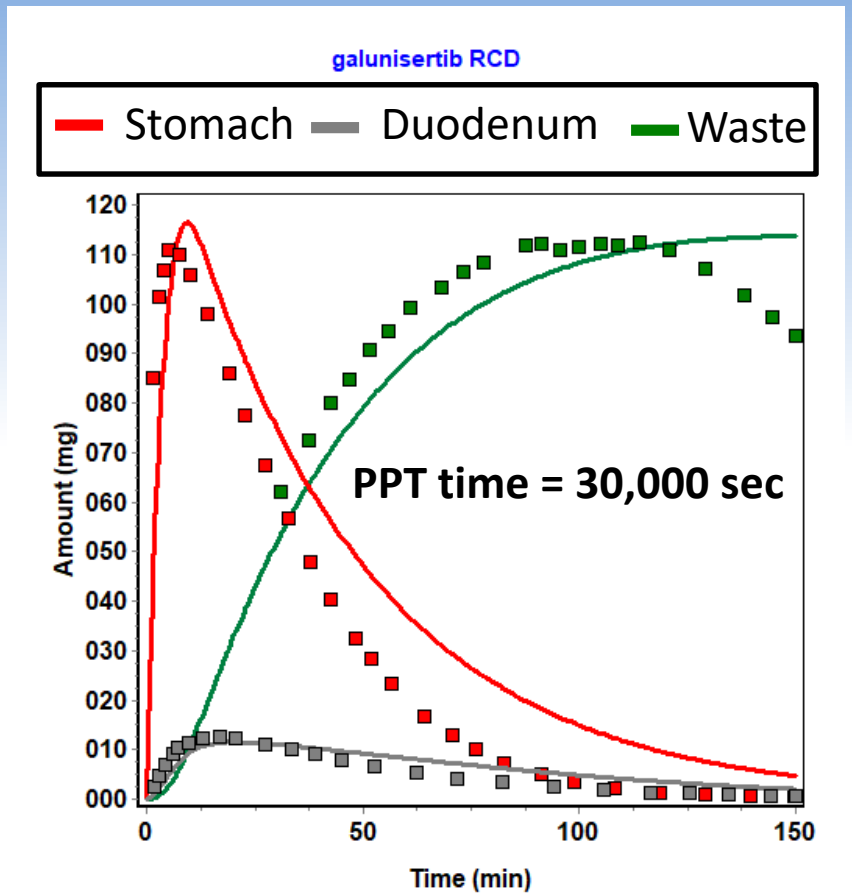
- Granulation process and/or excipients may provide nucleation inhibition. Very little precipitation of the solid dosage forms compared to the solution.
- Single Z-factor value fit is between the values from pH 1.2 and 3.5 USP experiment

RCS and RCD Tablets

Zfactor = 0.00167 mL/mg/s

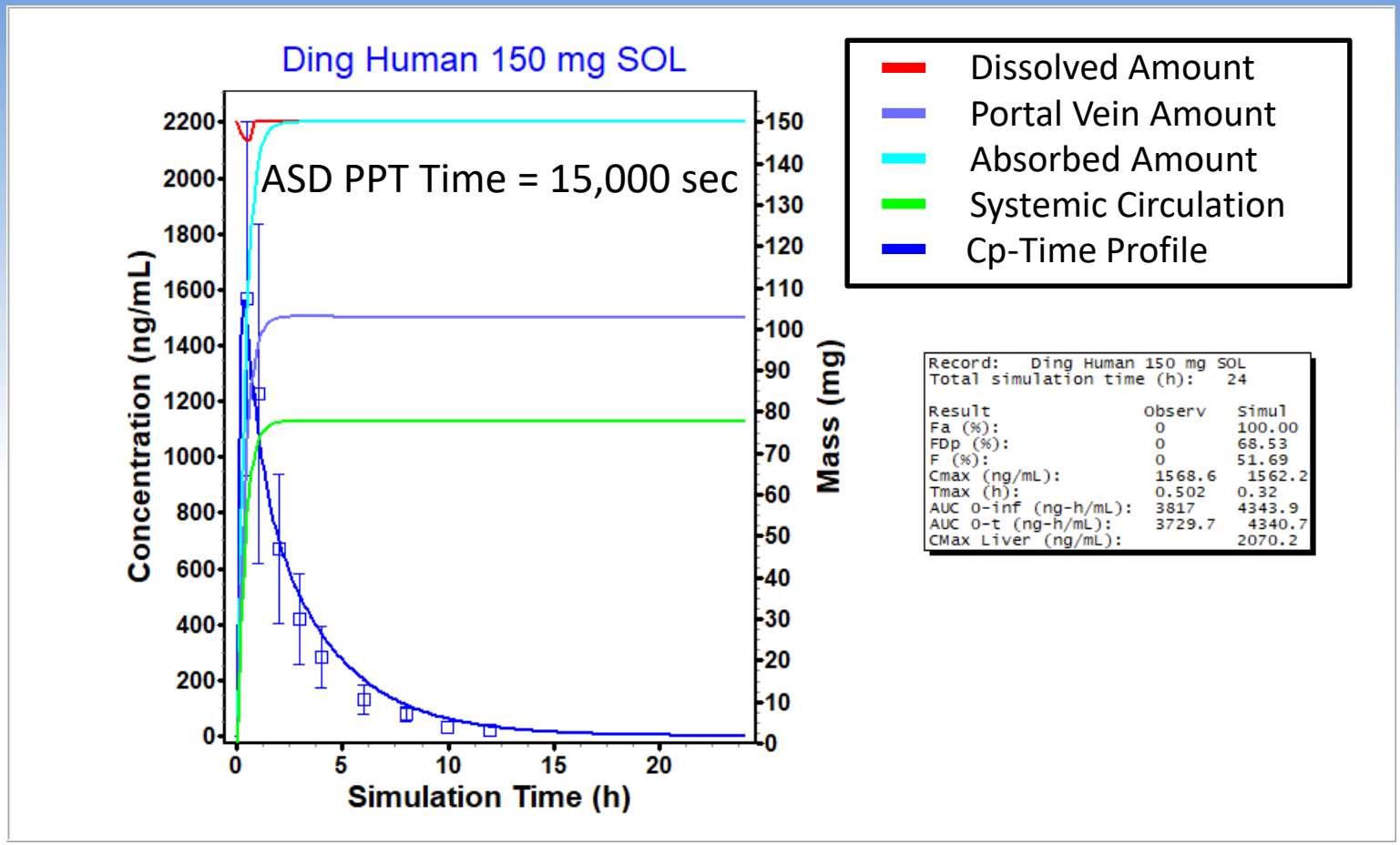


Zfactor = 0.00108 mL/mg/s



- There seems to be some issue with the experimental pump settings not perfectly matching the data which is fairly normal across literature datasets from other groups

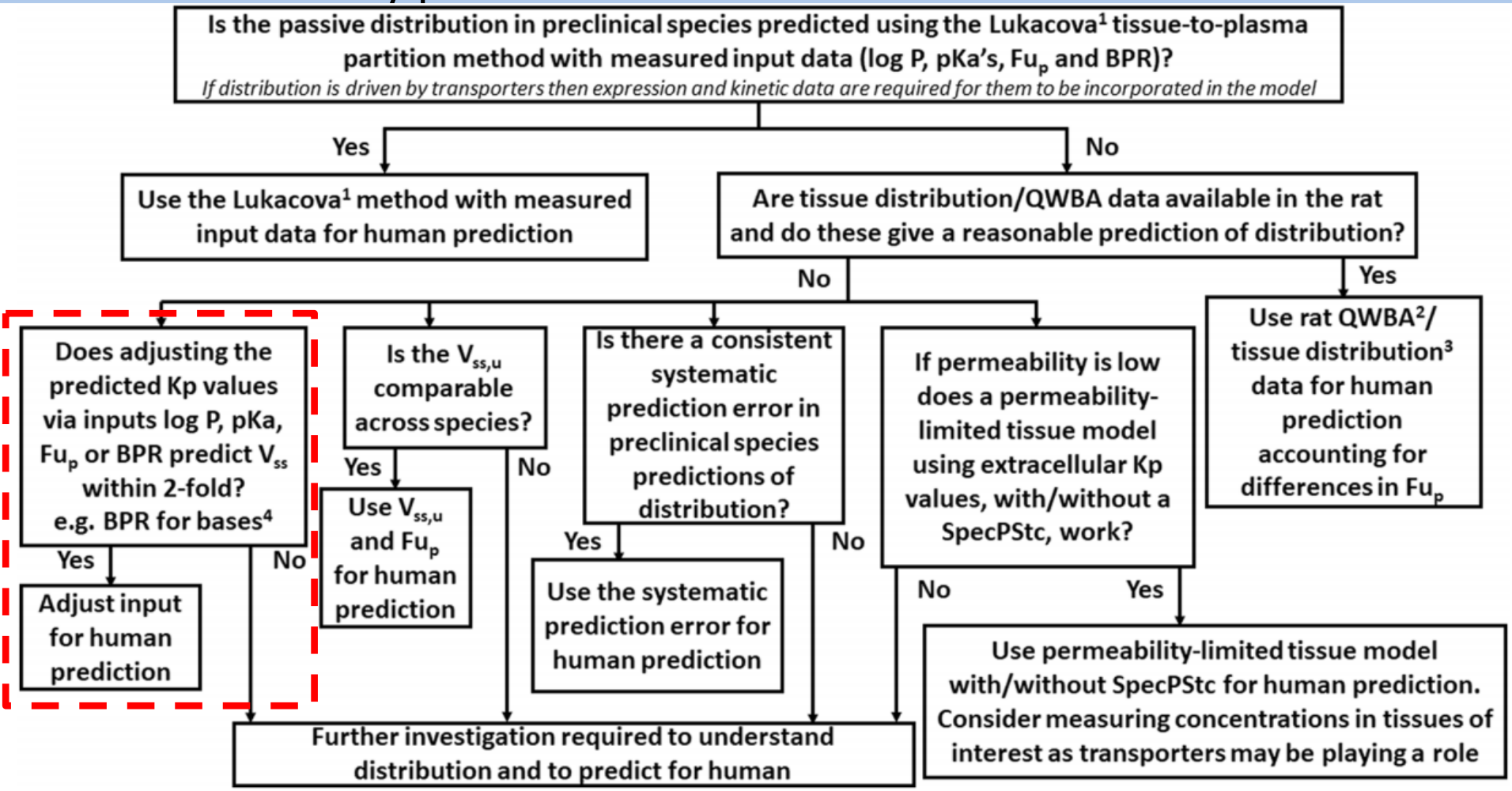
GastroPlus Model 150 mg Solution Dose



- PBBM model describes solution dose well in terms of Cmax and Tmax predicting 60% drug metabolized in gut vs. liver.
- Small amount of precipitation but redissolution is fast.

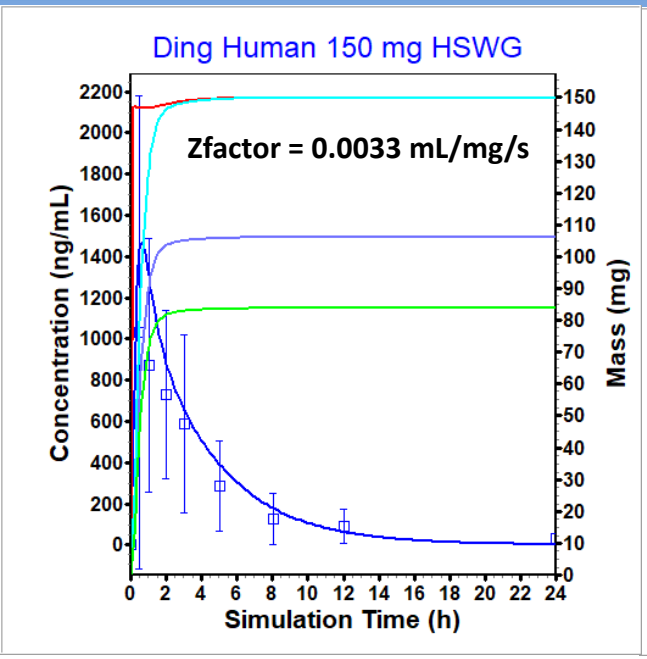
Galunisertib Rat PBBM Model

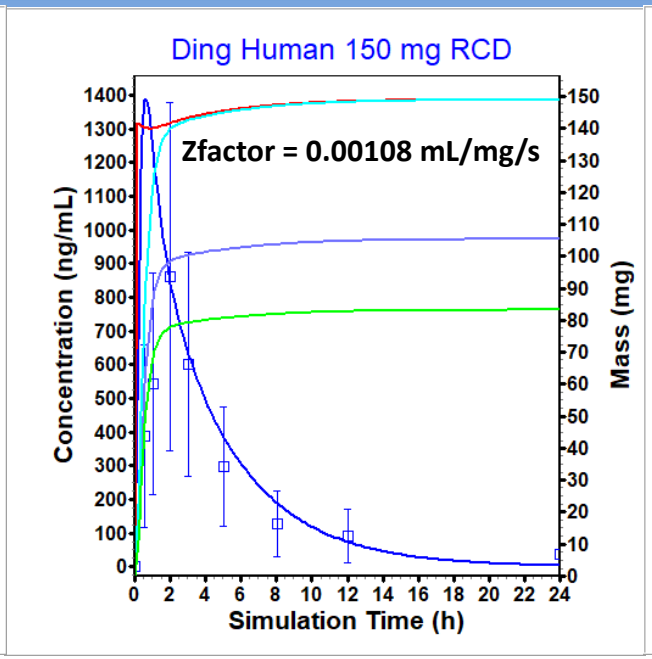
- Same Kp adjustments are able to work for the rat.
- Linear clearance in liver was added using NCA CL that was corrected by predicted %F.

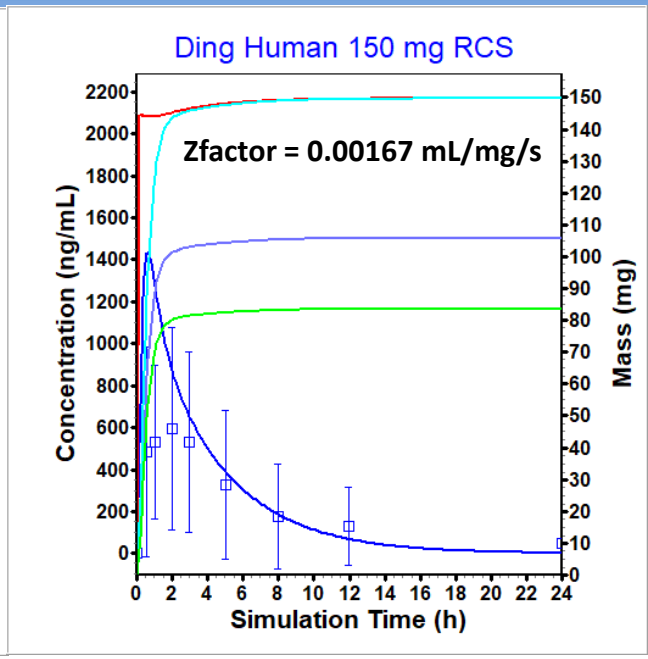


Miller et al., Clinical pharmacokinetics 58.6 (2019): 727-746.

Does ASD *In Vitro* Dissolution Predict *In Vivo* PK?



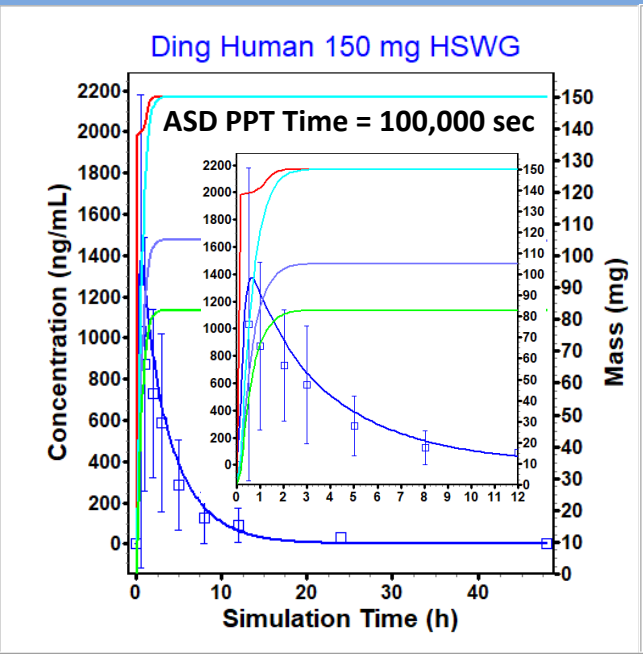


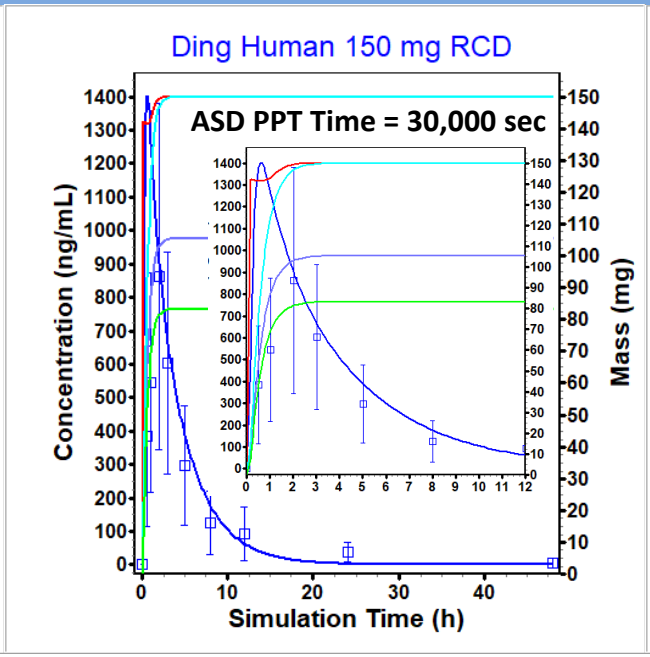


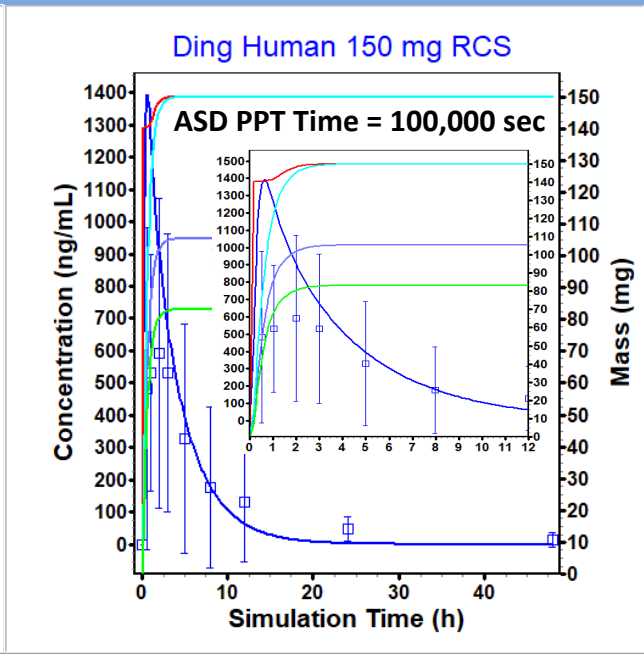
Dissolved Amount | Absorbed Amount | Cp-Time Profile
Portal Vein Amount | Systemic Circulation

- ASD *in vitro* data overpredicts *in vivo* dissolution for all the tablet formulations.

Does USP2 *In Vitro* Dissolution Predict *In Vivo* PK?







Dissolved Amount | Absorbed Amount | Cp-Time Profile
Portal Vein Amount | Systemic Circulation

- Using Z-Factor as a function of pH based on USP2 *in vitro* data, the dissolution *in vivo* is overpredicted.
- While there is *in vitro* differentiation – the resulting rates predict no *in vivo* differences

***In Vitro* Dissolution Z-factor Rates**

pH	HSWG mL/mg/s	RCD mL/mg/s	RCS mL/mg/s
1.2	0.000165	0.000741	0.000468
3.5	0.012	0.0095	0.01
4.5	0.022	0.018	0.016
6.8	0.029	0.014	0.012

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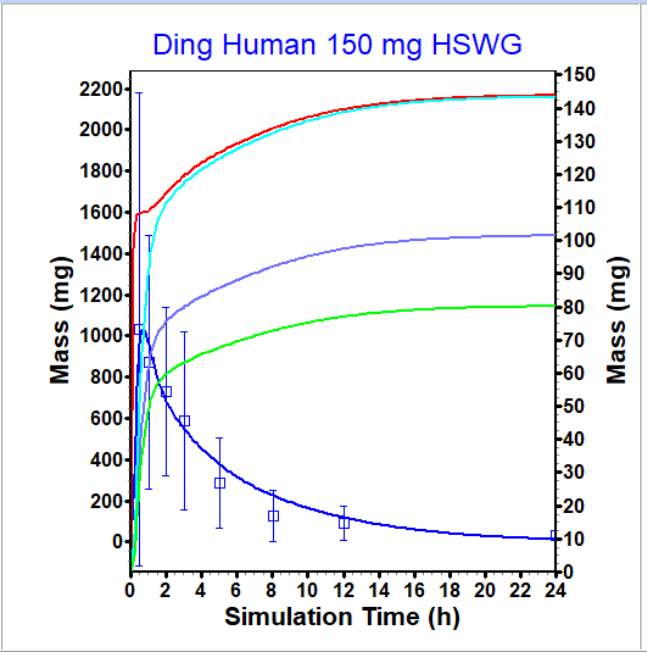
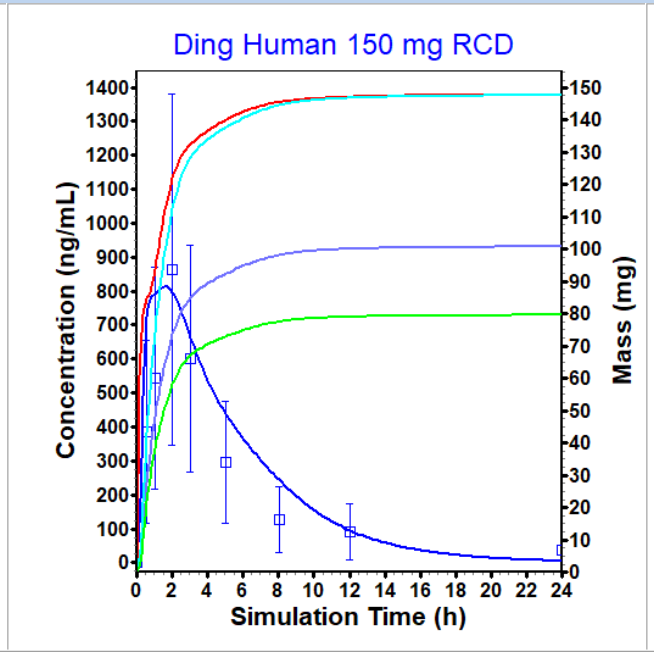
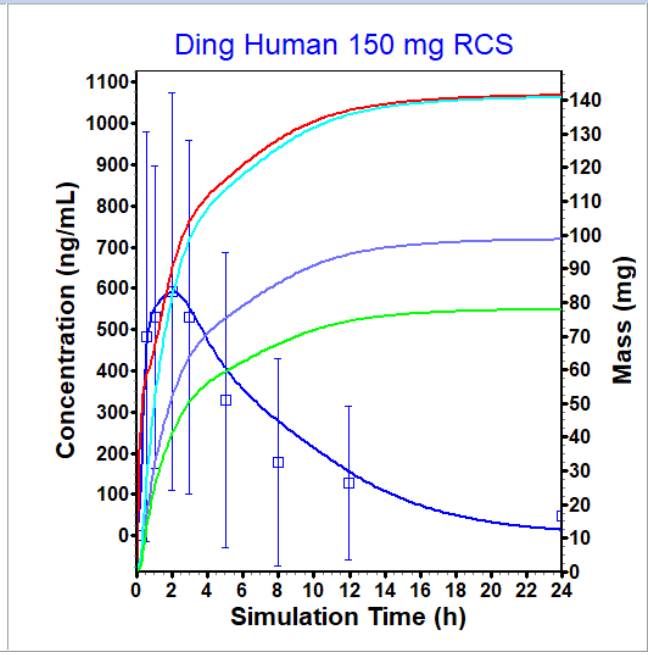
In Vivo Z-factor Dissolution Fit

- *In vivo* dissolution was calculated by optimizing z-factor values at the same pH's as the *in vitro* data
- *In vivo* dissolution is much slower in general than *in vitro*.







Dissolved Amount
Absorbed Amount
Cp-Time Profile
Portal Vein Amount
Systemic Circulation

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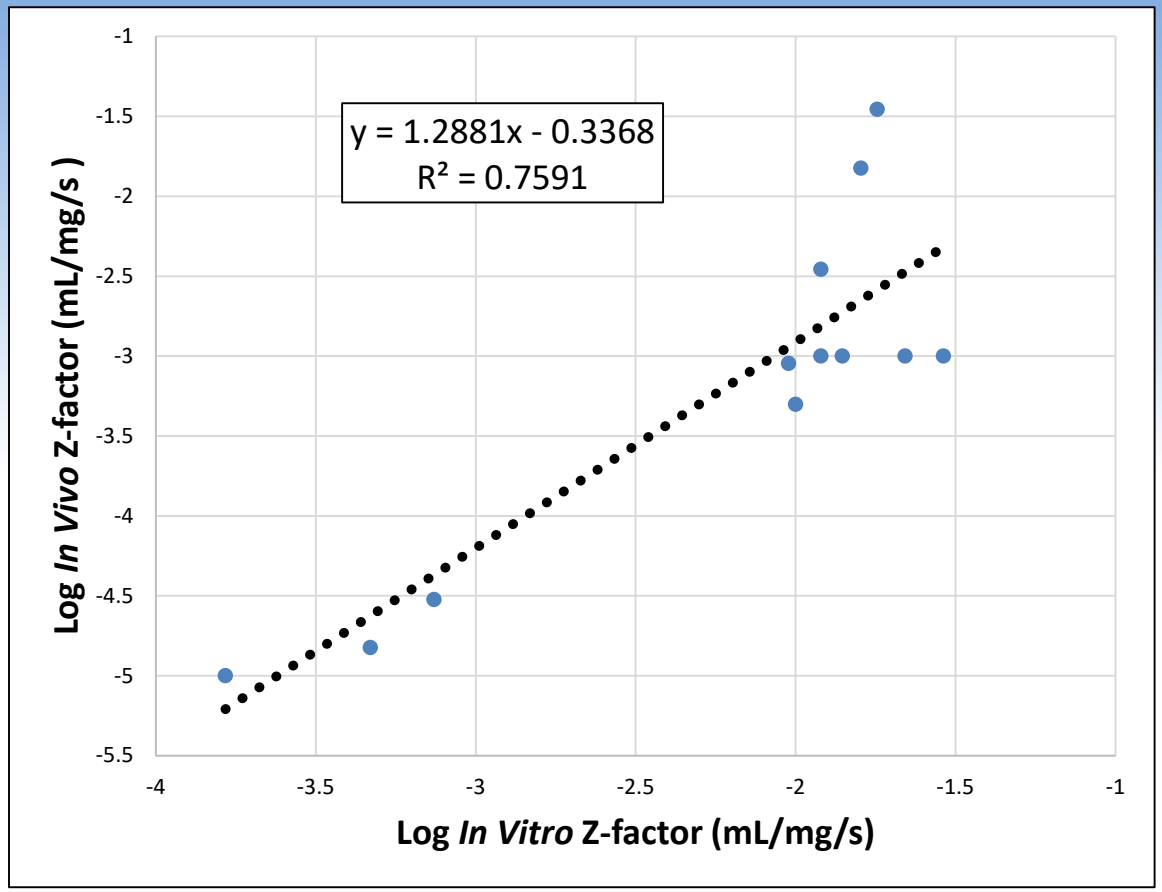
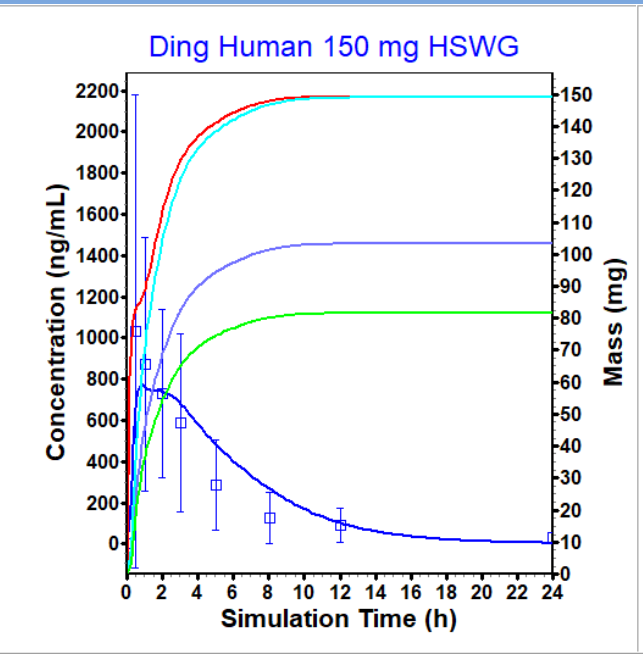
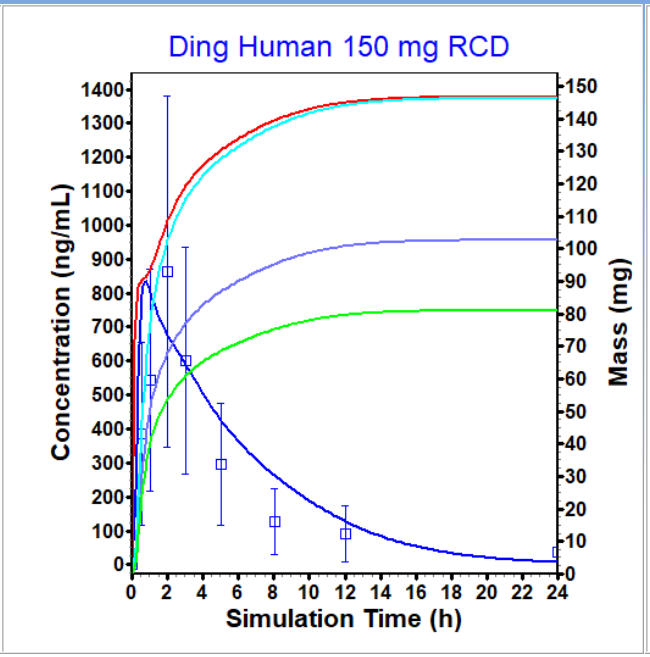
Z-Factor IVIVC

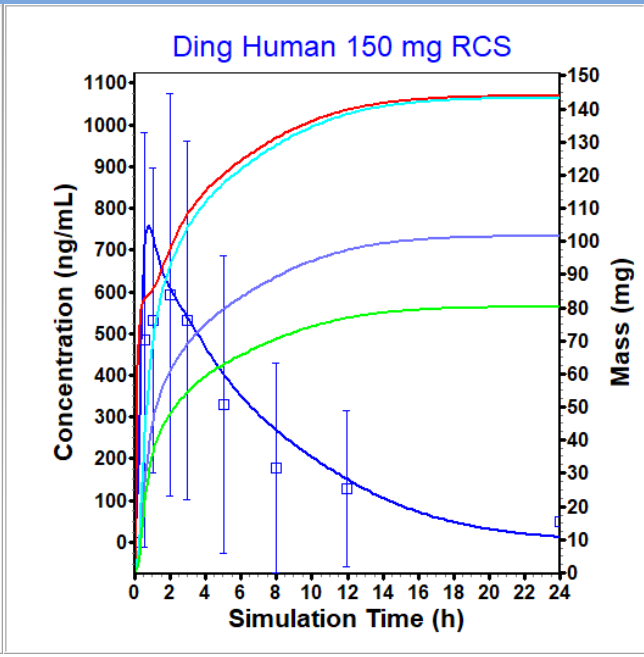


- An IVIVC could be built by using fitted *in vivo* Z-factor values at each pH vs. the *in vitro values*.

Z-factor IVIVC Internal Validation





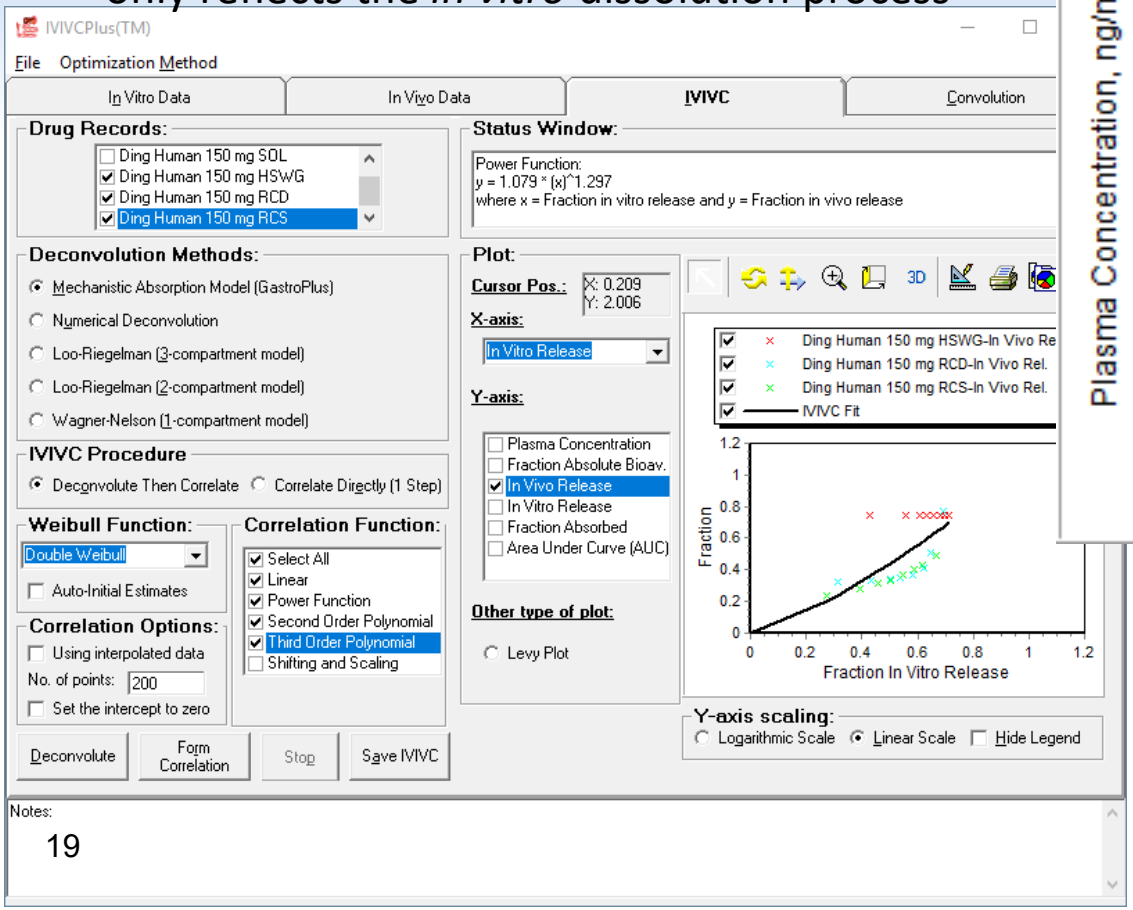


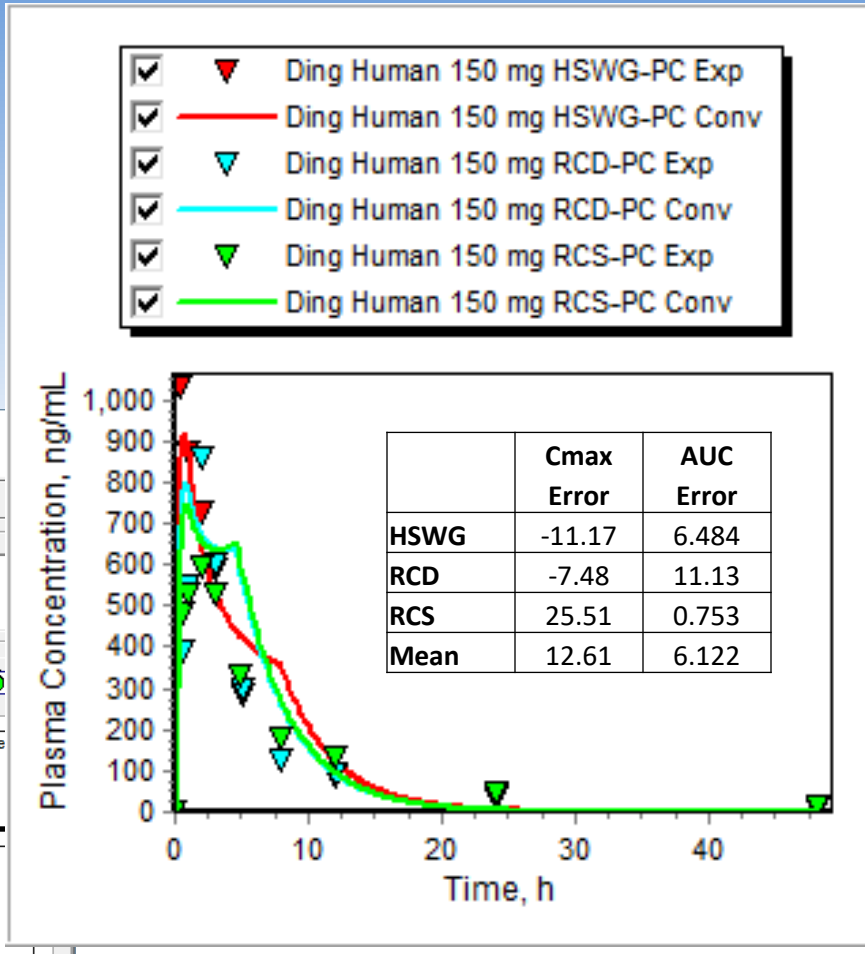
- This result is not good enough to be utilized in any sort of regulatory situation
- This method has been used successfully in other client projects to describe *in vivo* dissolution of IR products.

	Cmax Error	AUC Error
HSWG	-25.16	0.67
RCD	-3.08	4.90
RCS	27.83	-4.96
Mean	18.69	3.51

Mechanistic IVIVC Result

- pH 4.5 dissolution data.
- Mechanistic IVIVC fails to provide good IVIVC
- Results marginally better that Z-factor statistically but profiles don't have correct shape
- May not expect two dissimilar granulation processes to fall on the same IVIVC unless it only reflects the *in vitro* dissolution process





	Cmax Error	AUC Error
HSWG	-11.17	6.484
RCD	-7.48	11.13
RCS	25.51	0.753
Mean	12.61	6.122

- Traditional Wagner-Nelson deconvolution completely fails to describe the data

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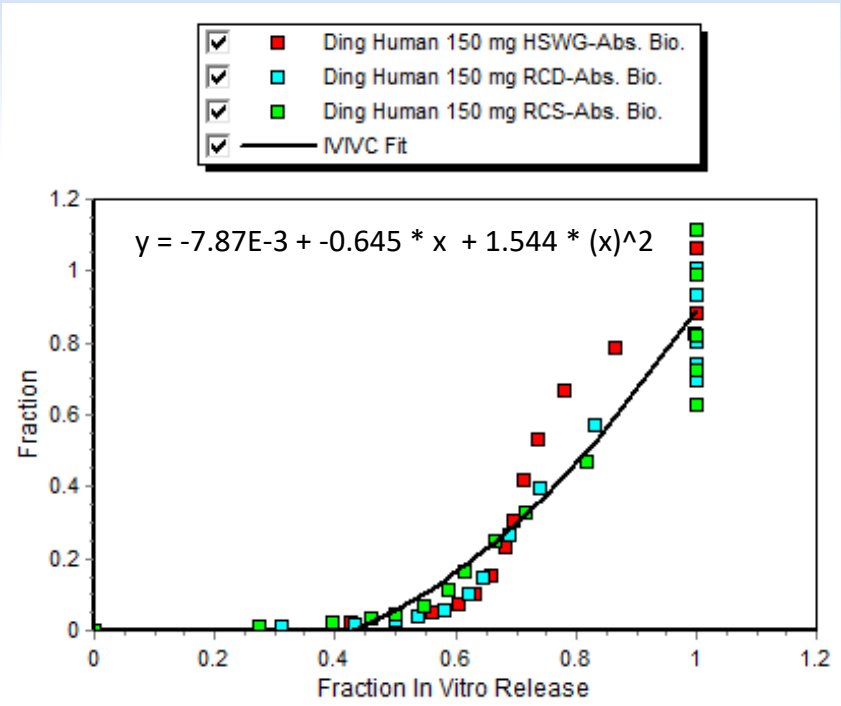
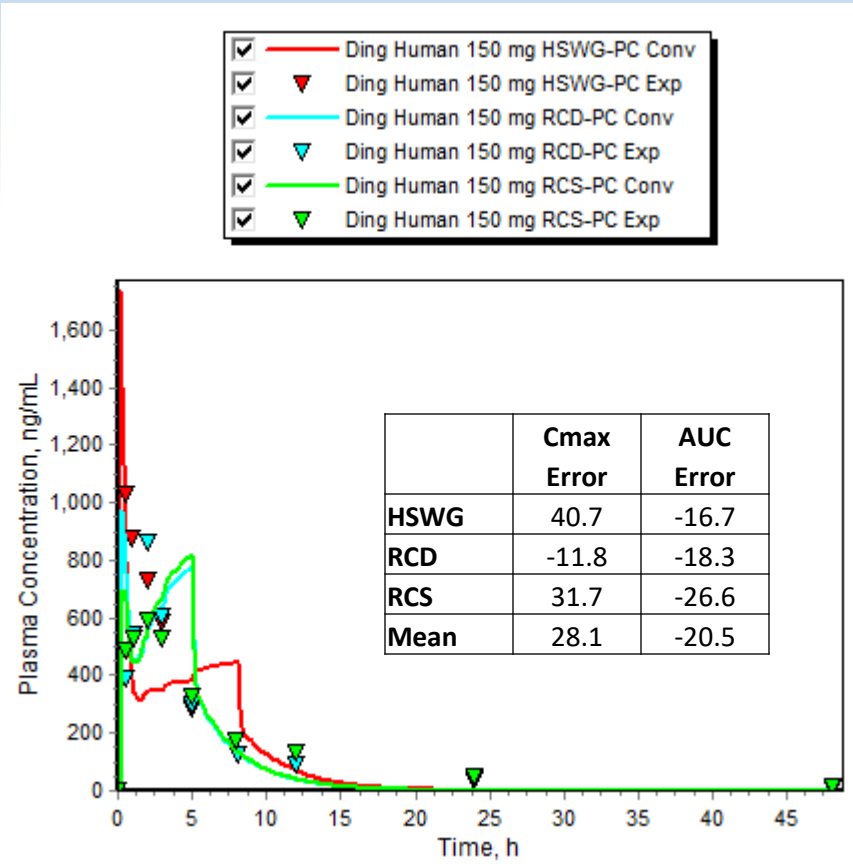
Traditional IVIVC

- Using traditional Wagner Nelson 2 compartment IVIVC method with the dissolution data at pH 4.5 results in very poor results
- Dissolution tests at other pH values are equally poor or worse





	Cmax Error	AUC Error
HSWG	40.7	-16.7
RCD	-11.8	-18.3
RCS	31.7	-26.6
Mean	28.1	-20.5

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Conclusion

- ASD experiment provided accurate precipitation parameters for solution or solid dosage form
  - DDDPlus model provides the ability to extract the relevant information considering all the physical processes.
- Z-factor method was used to extract the dissolution rate for the solid dosage forms and to account for differences in dissolution due to excipients and process but did not provide accurate *in vivo* dissolution predictions likely due to high variability
- IVIVC can be challenging for IR dosage forms when there is a large difference between *in vitro* and *in vivo* dissolution with any method
  - Mechanistic methods seem to provide better statistical results in this difficult scenario over the Z-factor method but the curve shape is off.
  - Both methods fall short due to high variability, but the Z-factor method has been effective in client projects where granule differences cause differing dissolution rates.

Case Study 2: The Irrelevance of *In Vitro* Dissolution in Setting Product Specifications for Drugs Like Dextromethorphan That are Subject to Lysosomal Trapping

ELSEVIER

Journal of Pharmaceutical Sciences

Available online 11 October 2018

In Press, Corrected Proof ⓘ

Pharmaceutics, Drug Delivery and Pharmaceutical Technology

The Irrelevance of *In Vitro* Dissolution in Setting Product Specifications for Drugs Like Dextromethorphan That are Subject to Lysosomal Trapping

Michael B. Bolger [1, 2], Joyce S. Macwan [1], Muhammad Sarfraz [3, 4], May Almukainzi [5], Raimar Löbenberg [3]

⊞ Show more

https://doi.org/10.1016/j.xphs.2018.09.036

Bolger et al. J. Pharm. Sci. (2018)

Study Objectives

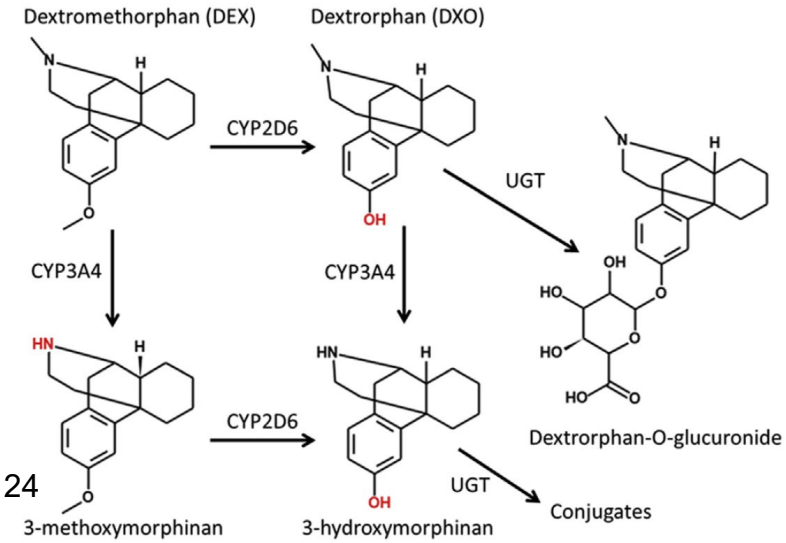
- Build mechanistic human ACAT™/PBPK model for dextromethorphan (**DEX**) and the total concentration of its major metabolite dextrorphan (**DXO**) + DXO β dextrorphan-O-glucuronide (**DXO-O-glucuronide**) in **extensive** (EM) and **poor metabolizers** (PM) using available literature data.
- Use validated model to study the **influence of dissolution rates** on the **sensitivity of C_{max}** and **AUC** for immediate release formulations.

ADME/Physicochemical Properties of DEX and Metabolites

Table 1
Physicochemical and Biopharmaceutical Properties of DEX, DXO, and DXO-O-Glucuronide

Property	DEX	DXO	DXO-O-glucuronide
LogP	3.97[a]	3.26[b]	−0.36[b]
Molecular weight (g/mol)	271.41[b]	257.38[b]	433.5[b]
p*Ka*	Basic 8.91[b]	Acidic 10.21; Basic 8.83[b]	Acidic 3.93; Basic 8.78[b]
Aqueous solubility (mg/mL)	0.0096 at pH 8.87 using GSE[c]	0.31 at pH 9.48[b]	1.35 at pH 6.36 [b]
Diffusion coefficient ($cm^2/s \times 10^5$)	0.76×10^{-5}[b]	0.79×10^{-5}[b]	0.63×10^{-5}[b]
Human jejunal effective permeability (Peff) (×10−4 cm/s)	3.0×10^{-4}[d]	3.48×10^{-4}[b]	0.33×10^{-4}[b]
Unbound percent in human plasma (Fup %)	72%[e]	55%[e]	44%[f]
Fup % correction after lipid binding	32.3%[e]	20.18%[e]	43.96%[b]
Human blood-to-plasma concentration ratio (R_{bp})	1.65[f]	1.22[b]	0.87[b]

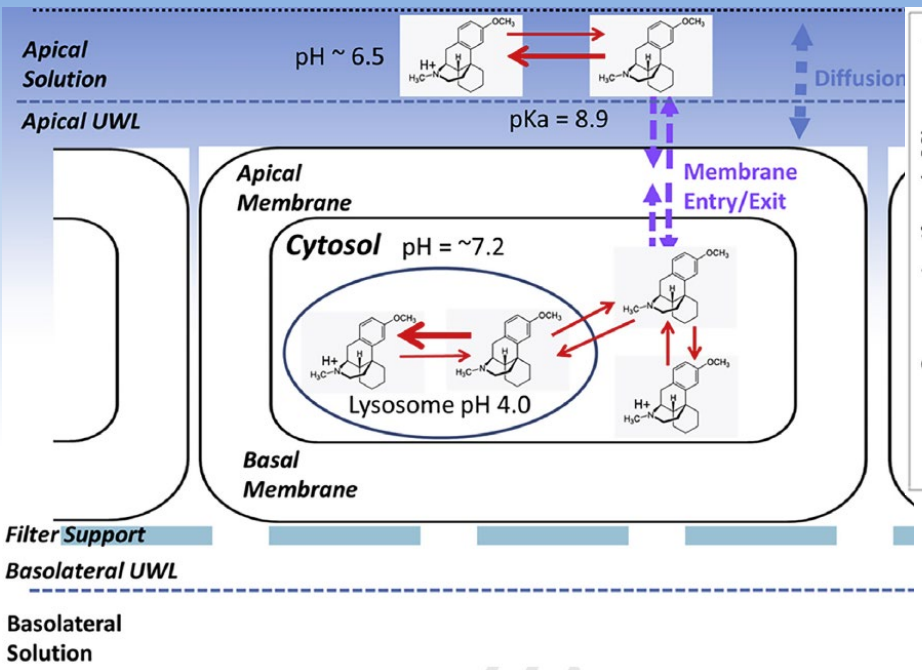
[a] Arellano et al.
[b] Predicted by ADMET Predictor™ 7.1.
[c] Aq. solubility was determined general solubility equation (GSE) as given in Sanghvi et al.
[d] Peff was determined using Caco-2 cell Papp = 1.7×10^{-5} cm/s value from Kanaan et al. with a conversion equation based on the default Absorption Systems Caco-2 calibration (ABSCa).
[e] Fup value used as given by Lutz et al.
[f] Single value fitted to match the clinical data for all formulations and doses.

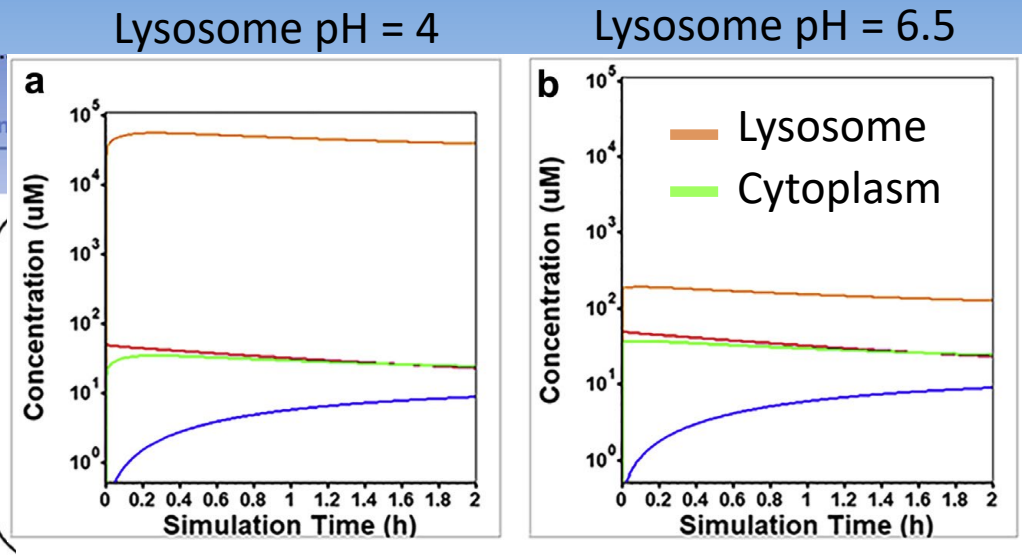


DEX is mainly metabolized by the CYP2D6 enzyme, which is highly polymorphic and hence undergoes different extents of metabolism in different populations.

Calleri etal., J Pharm Biomed Anal. 2004 Sep 3;35(5):1179-89.

MembranePlus Lysosomal Trapping of DEX



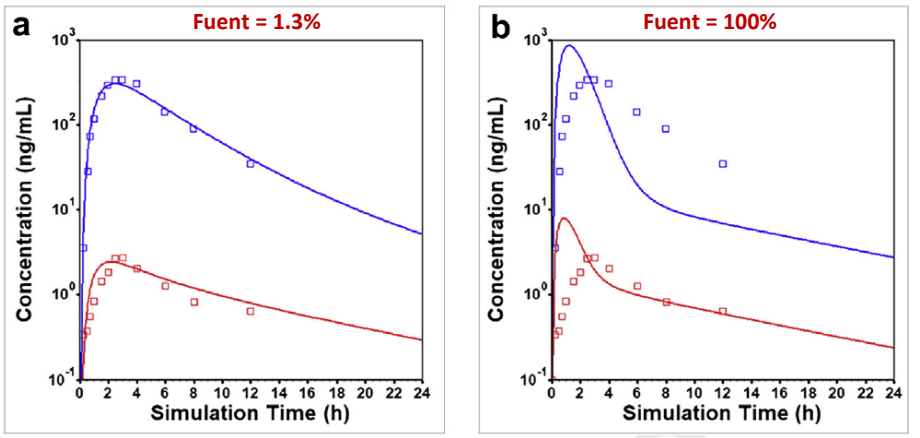


Simulated Caco-2 transwell permeability assay for 50 mM dextromethorphan. (A) lysosomal pH @ 4.0 and (B) lysosomal pH @ 6.5. Concentration in lysosomes (orange lines), cytoplasm (green lines), donor compartment (red lines), and receiver compartment (blue lines).

From the GI lumen (pH ~ 6.5) and the enterocyte cytosol (pH ~ 7.2), DEX (lipophilic nature and high pKa 8.91, LogP 3.97) will readily diffuse across the membrane in its unionized form, while maintaining equilibrium with its ionized form. After diffusion into the acidic environment of the lysosome (pH 4-5), the equilibrium between charged and uncharged DEX shifts in favor of an ionized form of the lipophilic amine (DEX), while limiting the diffusion back into the cytosol and results in temporary trapping of DEX in the lysosomes.

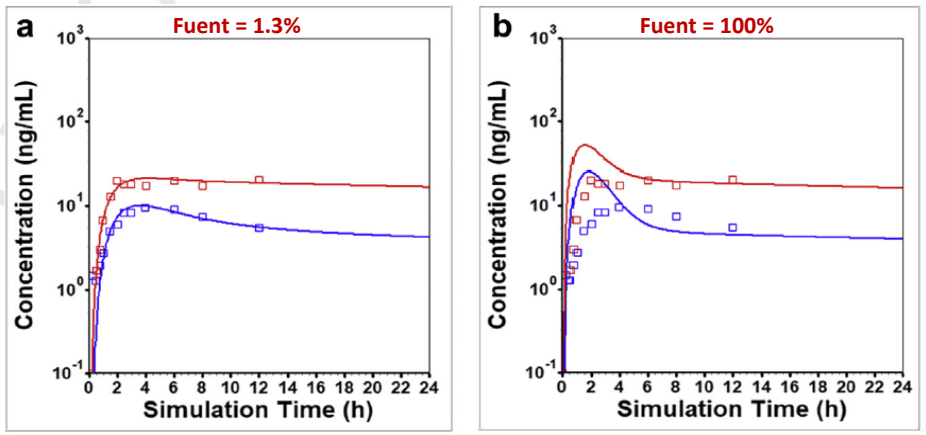
Simulated Plasma Profiles with and without Lysosomal Trapping

Extensive metabolizers



Observed (points) and simulated (lines) mean plasma concentration-time profiles of DEX after a single oral dose of 30 mg IR tablet in healthy volunteers in EM. (a) Fuent = 1.3% and (b) Fuent = 100%. Total DXO (blue) and DEX (red).

Poor metabolizers

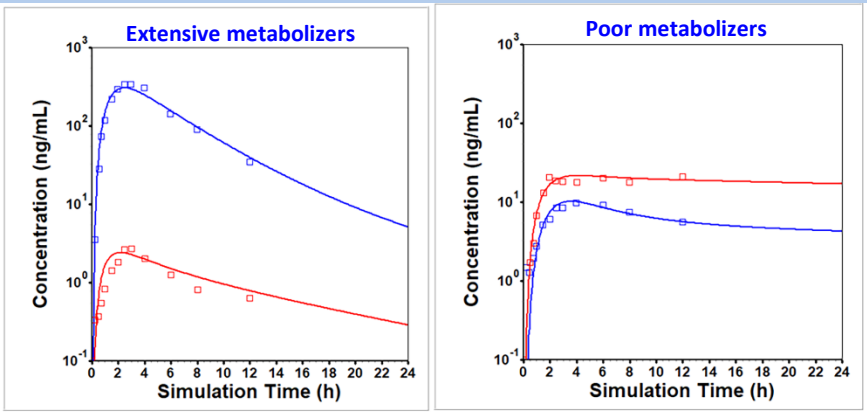


Observed (points) and simulated (lines) mean plasma concentration-time profiles of DEX after a single oral dose of 30 mg IR tablet in healthy volunteers in PM. (a) Fuent = 1.3% and (b) Fuent = 100%. Total DXO (blue) and DEX (red).

Gorski et al., Clin Pharmacol Ther. 2004;75(1):89-100

Model Development and Validation

IR tablet formulation



(A) (B)

Observed (points) and simulated (lines) mean plasma concentration-time profiles of DEX after a single oral dose of 30 mg (23 mg of free base) IR tablet in healthy volunteers using the best PBPK model in (a) EM and (b) PM. Total DXO (blue) and DEX (red).

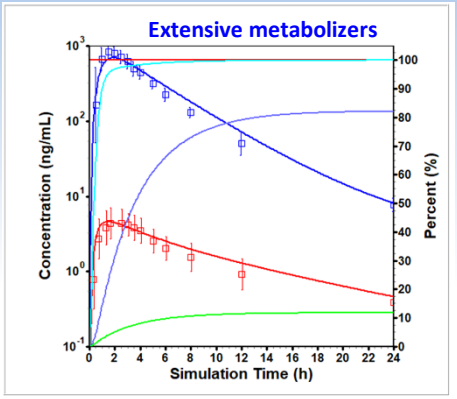
Gorski et al., Clin Pharmacol Ther. 2004;75(1):89-100.

Comparison of the Simulated and Observed C_{max} and AUC, and Absolute Average Fold Error (AAFE)[a] of DEX

Formulation (Dose) (EM/PM)	Obs C_{max} (ng/mL)	Sim. C_{max} (ng/mL)	AAFE [a] C_{max}	Obs. AUC[b] (Ng-h/mL)	Sim. AUC[b] (Ng-h/mL)	AAFE[a] -AUC[b]
IR tablet (30 mg) (EM)	2.71	2.41	0.89	24.5	25.7	1.05
IR tablet (30 mg) (PM)	21	21.7	1.03	208	218	1.05
IR solution (60 mg) (EM)	4.4	4.6	1.05	39.2	45.7	1.17

[a] The absolute average fold error (AAFE) was calculated as 10^{-}(log (Sim./Obs.).
[b] The AUC calculation for the 30 mg tablet and 60 mg solution doses in EM subjects represents AUC(0-inf). The AUC calculation for the 30 mg tablet in PM subjects represents AUC(0-t) because of the very shallow terminal slope and error associated with extrapolation of AUC(0-inf).

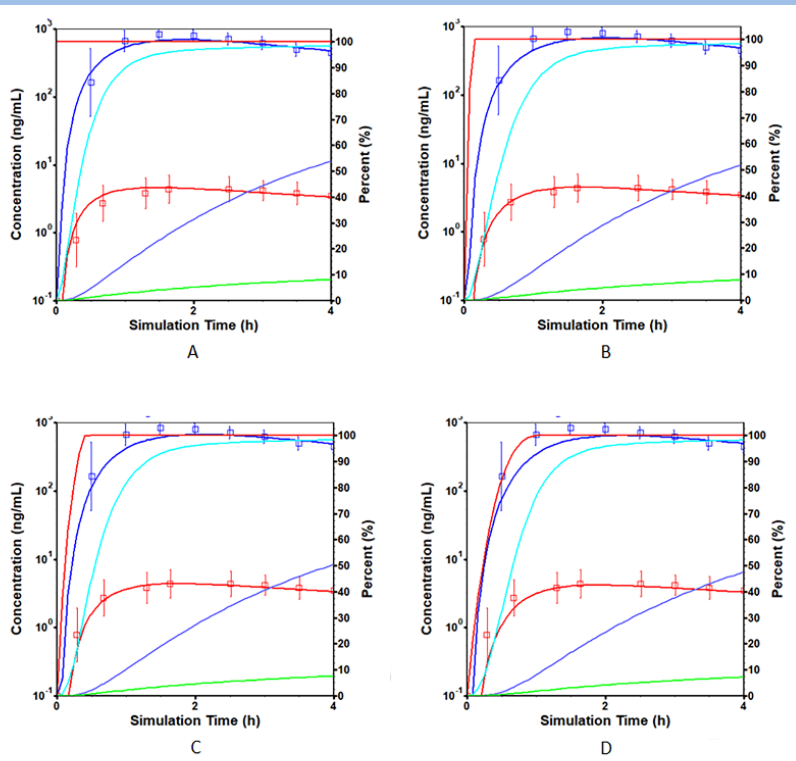
IR solution formulation



Observed (points) and simulated (lines) mean plasma concentration-time profiles of DEX after a single oral dose of 60 mg IR (Extuson, Ferrosan Ab, Malmo, Sweden) solution in EM healthy volunteers. Total DXO (blue) and DEX (red). Solid lines without data points represent cumulative amount dissolved (red), absorbed (cyan), entered portal vein (blue), and entered systemic circulation (green), all shown as mass as a percent of the administered dose (Y-axis on the right).

Silvasti et al., Int J Clin Pharmacol Ther Toxicol. 1987;25(9):493-497.

Testing the Sensitivity of Dissolution Rate on Bioequivalence (BE) for DEX in Extensive Metabolizers



Observed (points) and simulated (lines) mean plasma concentration-time profiles of DEX after a single oral dose of 60 mg IR solution or tablets in EM healthy volunteers. DXO (blue line with points) and DEX (red line with points). Solid lines without data points represent cumulative amount dissolved (red), absorbed (cyan), entered portal vein (blue), and entered systemic circulation (green), all shown as mass as a percent of the administered dose (Y-axis on the right). (a) solution, (b) 25 µm, (c) 50 µm, and (d) 100 µm.

Silvasti et al., Int J Clin Pharmacol Ther Toxicol. 1987;25(9):493-497.

- Starting with the 60 mg solution formulation and then changing to tablet formulations with monodisperse particle sizes of 25, 50, and 100 µm, we tested the BE of each formulation to the clinical data from Silvasti et al.
- Of the 4 formulations tested in this hypothetical *in vivo* dissolution experiment, only the 100 µm formulation (83% at 30 min) had less than 85% dissolved at 30 min. The time required to achieve 85% for the solution, 25, 50, and 100 µm formulations was 0, 0.09, 0.25, and 0.55 h, respectively.
- The simulated PK parameters of DEX for all formulations tested had AAFE >0.8 and <1.25 of clinically observed data.
- These simulations illustrate the lack of sensitivity between dissolution rate and clinical product performance and BE for this class of drug molecule.

Table 6
Comparison of 4 Simulated 60 mg IR Formulations of DEX in EM With Observed C_{max} and AUC of 60 mg IR Solution,[23] and Absolute Average Fold Error (AAFE)[b]

Formulation (Dose) (EM)	Obs C_{max} (ng/mL)	Sim. C_{max} (ng/mL)	AAFE [a] C_{max}	Obs. AUC[b](ng-h/mL)	Sim. AUC[b](ng-h/mL)	AAFE [a] -AUC[b]
IR solution (60 mg) (EM)	4.4[c]	4.6	1.05	39.2[c]	45.7	1.17
IR tablet (60 mg) (EM) 25 µm		4.5	1.02[c]		45.5	1.16[c]
IR tablet (60 mg) (EM) 50 µm		4.4	1.00[c]		45.1	1.15[c]
IR tablet (60 mg) (EM) 100 µm		4.2	0.95[c]		44.4	1.13[c]

[a] The average absolute fold error (AAFE) was calculated as $10^{|}$(log (Sim./Obs.).
[b] The AUC calculation all formulations represents AUC(0-inf).
[c] The BE of each formulation was compared to the solution formulation clinical data from Silvasti et al.

Summary and Conclusions

- The proposed PBPK model was able to describe the Cp-time profiles of DEX and total DXO in extensive and poor metabolizers
- Lysosomal trapping was identified as the main factor for a slow appearance of the drug in plasma. **This delay might be mistakenly used to set slow product dissolution specifications**
- Drug dissolution and rate of entry into the enterocytes are clinically irrelevant for the performance of the drug product for drug like dextromethorphan
- The DEX and DXO plasma levels are not suitable to set product dissolution performance criteria. Rather, it is the knowledge and understanding of the entire drug absorption and disposition processes that should be used to define clinically relevant product specifications

Questions?

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  - Viera Lukacova: Director, Simulation Sciences
  - Haiying Zhou: Team Leader, Simulations Technologies
  - Joyce Macwan, Senior Scientist