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In Vitro to *In Vivo* Extrapolation (IVIVE) of Itraconazole Precipitation using a Biphasic Dissolution Test and Mechanistic Absorption Model

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PURPOSE

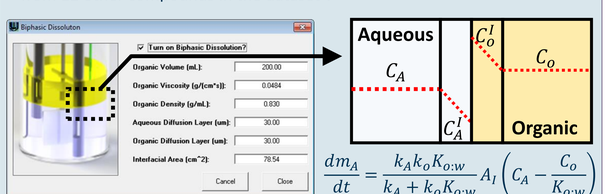
Regulatory agencies have encouraged the use of mechanistic absorption (MAM) and physiologically-based pharmacokinetic (PBPK) modeling to reduce cost and time to market for new and generic drug products. Models require parameterization, and many physicochemical parameters must be determined as a part of the development process. For low solubility weak bases with high solubility in gastric and low solubility in intestinal fluids, precipitation requires evaluation. Simple *in vitro* transfer experiments have been shown to overestimate precipitation *in vivo*. The biphasic test incorporates an absorptive phase to lower supersaturation similar to *in vivo* and to provide more accurate precipitation estimates. In this work, we present an *in silico* model to extract precipitation parameters from a biphasic *in vitro* dissolution test coupled with a MAM/PBPK model to predict precipitation *in vivo*. The goal was to test whether the biphasic *in vitro* assay provides more relevant parameters for *in vivo* extrapolation.

OBJECTIVES

- Utilize *in vitro* dissolution data to predict precipitation kinetics
- Identify the importance of mechanistic absorption modeling in drug development
- Understand mass transfer in the biphasic dissolution test

METHODS

The mechanistic nucleation and growth model parameters were determined by fit to *in vitro* data using a new biphasic dissolution model in DDDPlus™ v6.0 (Simulations Plus, Inc.) and were compared to parameters fit to PK data in Gastroplus™ (Simulations Plus, Inc.). The biphasic model is shown in Figure 1. The experimental data for ITZ *in vitro* precipitation was obtained from the literature[2]. The drug was introduced as a solution to the aqueous phase of 40 mL phosphate buffer @ pH 6.5. The drug transport into 30 mL of decanol was modeled simultaneously to precipitation using the mechanistic nucleation and growth model (Figure 2). A boundary layer thickness of 17.78 mm was the average of the boundary layer determined from 12 other compounds in the dataset[2].



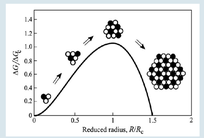
$$\frac{dm_A}{dt} = \frac{k_A k_o K_{o:w}}{k_A + k_o K_{o:w}} A_I \left(C_A - \frac{C_o}{K_{o:w}} \right)$$

m_A	Mass drug in aqueous	$K_{o:w}$	Organic/water partition coefficient
k_A, k_o	Mass transfer coefficient	C_A, C_A^l	Conc. drug in aqueous and interface
A_I	Interfacial area	C_o, C_o^l	Conc. drug in organic and interface

Figure 1: DDDPlus™ Biphasic Dissolution Model

METHODS CONT.

The PBPKPlus™ module in GastroPlus (Simulations Plus, Inc.) was used to model the PK of ITZ and its three metabolites[1]. The Advanced Compartmental Absorption and Transit (ACAT™) model was used to describe the intestinal dissolution, precipitation, and absorption of ITZ after p.o. administration. Human physiologies were generated by the program's internal Population Estimates for Age-Related (PEAR™) Physiology™ module. The biopharmaceutical parameters for both ITZ and its metabolites were either obtained from literature or predicted by ADMET Predictor™ 6.5 (Simulations Plus, Inc.). Tissue/plasma partition coefficients for all the compounds were calculated using the Lukacova method from *in vitro* and *in silico* property estimates. The metabolism series from ITZ to hydroxy-ITZ to keto-ITZ to N-desalkyl-ITZ (CYP3A4 enzyme) was modelled by Michaelis-Menten kinetics with *in vitro* kinetic parameters and built-in expression levels of CYP3A4 in gut and liver. N-desalkyl-ITZ (CYP3A4 enzyme) was modelled by Michaelis-Menten kinetics with *in vitro* kinetic parameters and built-in expression levels of CYP3A4 in gut and liver. The Johnson dissolution model was used for both solution and capsule dosage forms. Particle size for the capsule dosage form was adjusted to 3 µm to account for the formulation effect. The permeability of ITZ was predicted in MembranePlus™ 1.0 (Simulations Plus, Inc). The mechanistic nucleation and growth (MNG) model in GastroPlus was used to account for possible precipitation as ITZ solubility changes in different intestinal regions.



Schmelzer, J. Non-Crystalline Solids (2010) 356

Nucleation Rate:

$$\frac{dN}{dt} = D_{mono} N_A c^2 \left(\frac{k_b T}{\gamma}\right)^{\frac{1}{2}} ln\left(\frac{c}{S}\right) \frac{R^*}{R^* + \lambda} exp\left(-ExpCorr \frac{16\pi}{3}\left(\frac{\gamma}{k_b T}\right)^3 \frac{v_m^2}{ln\left(\frac{c}{S}\right)^2}\right)$$

Growth Rate:

$$\frac{dX_{nc}}{dt} = 4\pi R_p^2 \frac{D_{eff}}{h}(C_b - S_b) \quad where \quad R_p = \left(\frac{4X_{nc}}{3\pi\rho}\right)^{\frac{1}{3}}$$

D_{mono} = Diffusion monomer (cm²/min)
N_A = Avogadro's number
c = Concentration monomer (mol/cm^3)
k_b = Boltzman's constant
T = 310° K
g = Interfacial tension (Newtons/cm)
S = Solubility at the current pH
R^* = Critical radius (cm)
l = Effective radius from Lindfors (cm)
ExpCorr = exponential correction factor
n_m = Molecular volume
ρ = density
X_{nc} = rate of particle growth
R_p = radius of particle
D_{eff} = effective diffusion coefficient
h = diffusion layer thickness
S_b = solubility in the bile micelle media
C_b = bile and free drug concentrations

Figure 2: Mechanistic Nucleation and Growth Precipitation Model

RESULTS

The exponential correction factor of 0.1707 (unitless) and Lindfor's parameter of 0.1984 µm were fit to the *in vitro* data utilizing the DDDPlus biphasic dissolution model. The simulation is shown in Figure 3. The red curve represents the % released of total ITZ 5mg solution dose precipitating down to its estimated crystalline solubility of 0.000189 mg/mL[4]. The green curve represents the % dissolved of ITZ in the organic layer. Initially, the appearance rate is very fast, but reduces dramatically as precipitation occurs. The grey curve represents the precipitate radius in micron. The parameters in Figure 3 were then utilized to predict the *in vivo* PK of ITZ using the GastroPlus PBPK model built by Szeto[1].(See graphs labeled "DDDPlus ppt." The *in vivo* formulations were 200 mg capsule and 100/200 mg solution administered in fasted and fed state[56]. The predictions were compared to the simulation results where the mechanistic nucleation and growth model parameters (0.23 and 0.5 µm for the exponential correction factor and Lindfor's parameter, respectively) were fitted to match the observed PK data in GastroPlus (Figure 4, graphs labeled "G+ Fit ppt.").

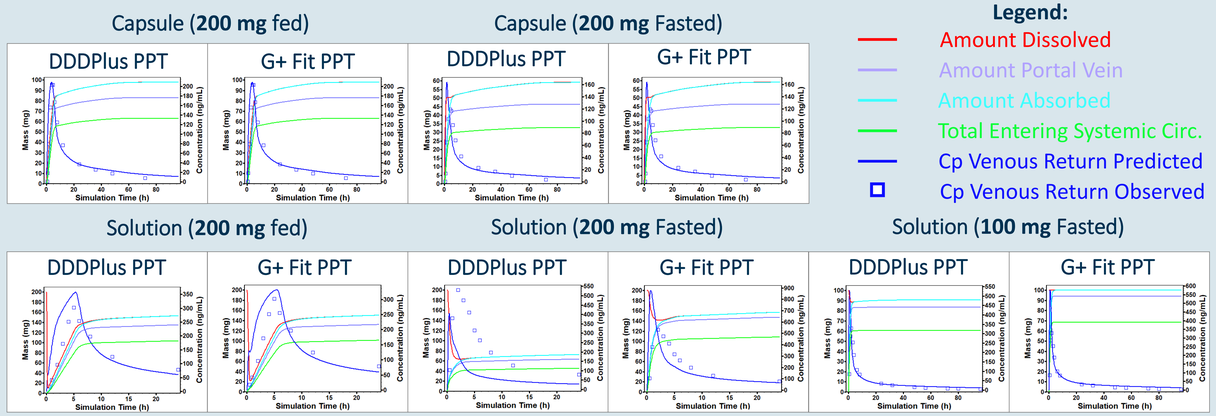


Figure 4: Itraconazole IVIVE Extrapolation of precipitation and pharmacokinetics vs. *in vivo* fitted precipitation parameters.

RESULTS CONT.

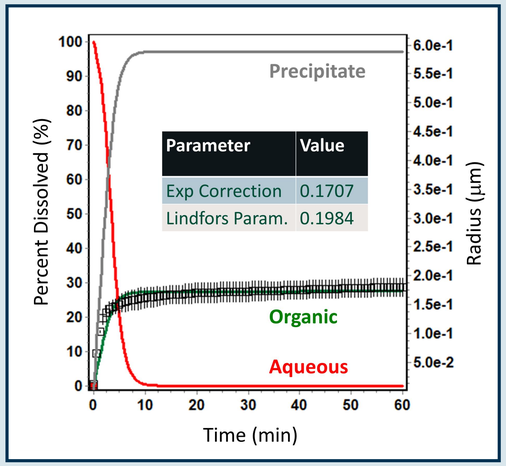


Figure 3: Biphasic Dissolution of ITZ appearance in organic phase (green) and precipitation in the aqueous phase (red). The grey curve is the radius of precipitate in microns.

CONCLUSION(S)

Utilizing *in vitro* precipitation parameters gave reasonable prediction of ITZ PK across all datasets except the 200 mg solution dose in fasted state. For all other doses, the precipitation IVIVE gave results similar to fitting *in vivo* parameters against observed PK profiles. This shows the utility of more advanced absorptive dissolution tests in extraction of precipitation parameters.

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