In Vitro To *In Vivo* Extrapolation (IVIVE) Of Itraconazole Precipitation Using A Biphasic Dissolution Test And Mechanistic Absorption Model

Poster Number **515**

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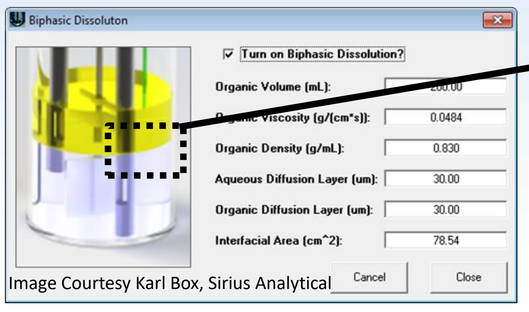
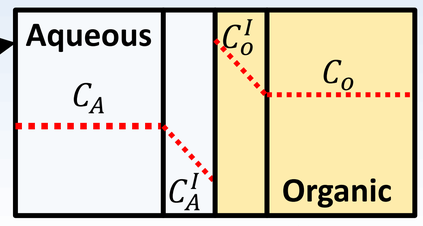
Introduction

Regulatory agencies have encouraged the use of mechanistic absorption (MAM) and physiologically-based pharmacokinetic (PBPK) modeling to reduce both costs and time to market for new and generic drug products. The models require parameterization, and as such, many physicochemical parameters must be determined as a part of the development process. For low solubility weak bases that have high solubility in gastric and low solubility in intestinal fluids, precipitation is an important aspect that needs to be evaluated. Previous simple *in vitro* transfer experiments have been shown to overestimate precipitation *in vivo*. The benefit of the biphasic test is the absorptive phase that lowers supersaturation in a manner similar to *in vivo* and may provide more accurate precipitation estimates. In this work, we present a biphasic *in vitro* dissolution test coupled to an in silico model using classical nucleation theory that allows for the extraction of precipitation parameters of itraconazole (ITZ). The goal was to test whether or not the absorptive *in vitro* assay provides precipitation parameters that are more relevant *in vivo* and can be used in the GastroPlus™ MAM to predict the pharmacokinetics (PK) of ITZ.

Methods

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.

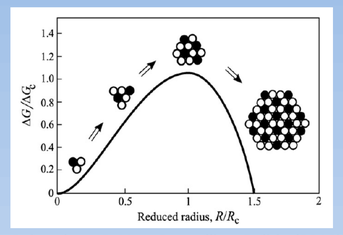




$$\frac{dm_A}{dt} = \frac{k_A k_o K_{o:w}}{k_A + k_o K_{o:w}} A_I \left(C_A - \frac{C_o}{K_{o:w}} \right)$$

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

Figure 1: DDDPlus™ Biphasic Dissolution Model



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 (cm^2/min)
N_A = Avogadro's number
c = Concentration monomer (mol/cm^3)
k_b = Boltzman's constant
T = 310° K
γ = Interfacial tension (Newtons/cm)
S = Solubility at the current pH
R^* = Critical radius (cm)
λ = Effective radius from Lindfors (cm)
ExpCorr = exponential correction factor
v_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

The mechanistic nucleation and growth model parameters were determined by fit to the PK data in GastroPlus and from the *in vitro* data using a new biphasic dissolution model in DDDPlus™ v6.0 (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 μm was the average of the boundary layer determined from 12 other compounds in the dataset[2].

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 solution administered in fasted and fed state[5]. 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.").

Results

The exponential correction factor of 0.152 (unitless) and Lindfor's parameter of 0.33 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.

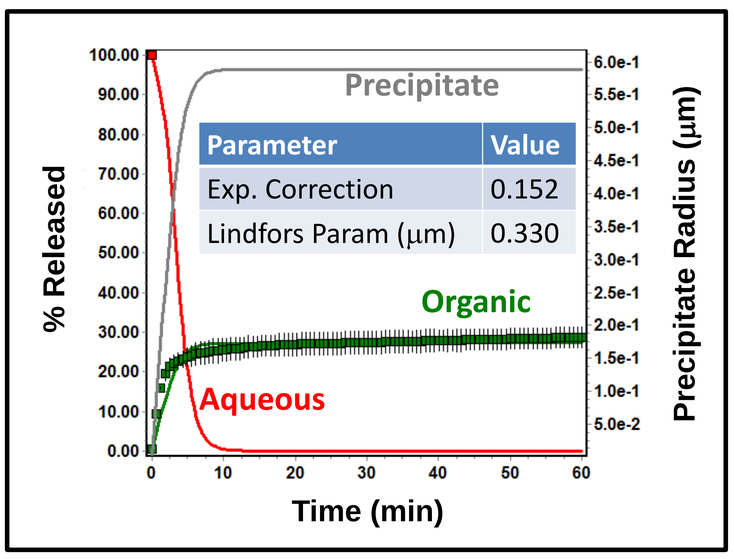


Figure 3: Biphasic Dissolution of ITZ appearance in organic phase (green) and precipitation in the aqueous phase (red). The grey curve represents the calculated average radius of precipitate in microns.

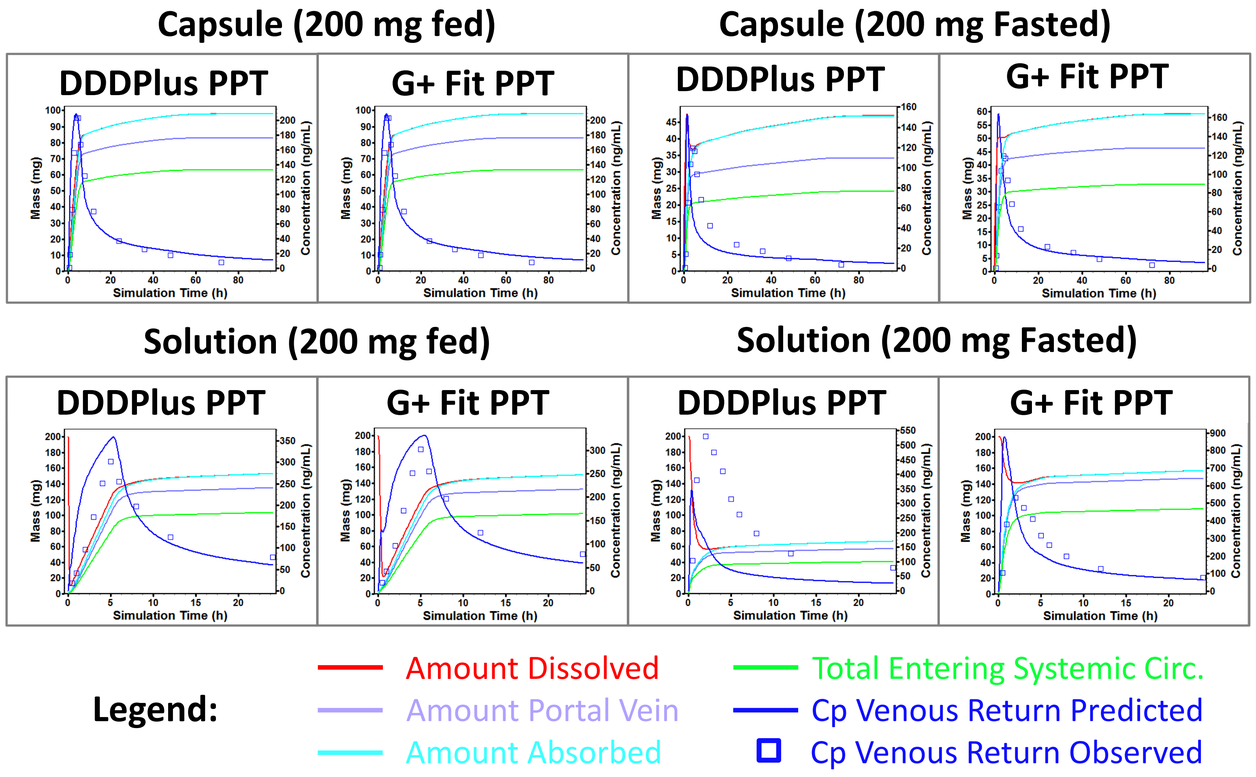


Figure 4: Itraconazole IVIVE Extrapolation of precipitation and pharmacokinetics vs. *in vivo* fitted precipitation parameters.

Conclusions

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.

References

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