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 not been shown to overestimate precipitation in vivo. The benefit of the biphasic test is the absorptive phase that lowers saturation 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. 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 (PARE™) Physiology™ module. The bipharmaceutical 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.

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 literature5. 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 dataset5.

The parameters in Figure 3 were then utilized to predict the in vivo PK of ITZ using the GastroPlus® PBPK model built by Szeto6.(See graphs labeled “DDDPlus®.”) The in vivo formulations were 200 mg capsule and solution administered in fasted and fed state5. 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 Lindfors parameter, respectively) were fitted to match the observed PK data in GastroPlus® (Figure 4, graphs labeled “G+ Fit ppt.”).

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

1. Szeto, et al., AAPS Annual Meeting, 2015, Poster W5237
2. Box, et. al., AAPS Annual Meeting 2016, Poster 24W0130

Figure 1: Mechanistic Nucleation and Growth Precipitation Model

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.

Figure 2: Micromechanical and Growth Precipitation Model