W4230

PBPK Modeling for Predicting the *In Vivo* Performance and Product Quality of Tacrolimus and Itraconazole Amorphous Solid Dispersions in Humans

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1 Purpose

- Amorphous solid dispersions (ASDs) are a promising category of supersaturating drug delivery systems that have attracted considerable research interest as an effective means of improving oral absorption of poorly water-soluble drugs.
- The objective of the study aims to establish a physiologically-based pharmacokinetic (PBPK) model to simulate the *in vivo* PK profiles of poorly water-soluble tacrolimus and itraconazole ASD products in humans. With such models, the impact of crystallization of amorphous products during storage on pharmacokinetics can be evaluated.
- By taking into account the kinetic interplay of dissolution, supersaturation, and precipitation of amorphous pharmaceuticals, we attempt to use this model to gain mechanistic insights on:
  (1) The *in vivo* performance (*e.g.* bioavailability enhancement), and
  (2) Product stability (*e.g.* effect of drug recrystallization on the resulting PK profiles).

2 Method

- GastroPlus (version 8.6 00034, Simulations Plus Inc. Lancaster, CA) based on the ACAT (Advanced Compartmental Absorption and Transit) simulation model (see Fig. 1) was used to perform PBPK modeling for the *in vivo* PK profiles of tacrolimus and itraconazole (see Table 1 for their properties) for ASDs.
- The software enables the introduction of supersaturation and precipitation kinetics, estimated by the physicochemical properties of drug molecules (*e.g.* molecular structure, equilibrium solubility, interfacial tension, etc.) based on classical nucleation theory. The results of *in silico* predictions were validated by the *in vivo* clinical observation available in the literature. The PK profiles of tacrolimus and itraconazole under different scenarios were simulated to evaluate the impact of drug recrystallization on the *in vivo* performance.

Advanced Compartmental Absorption and Transit (ACAT) Model

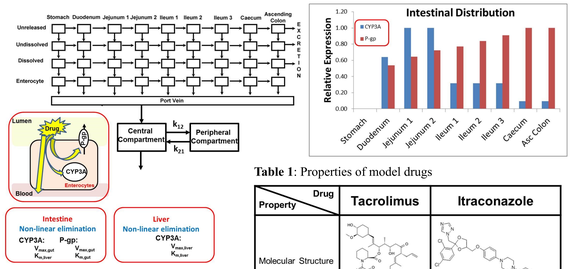


Figure 1: PBPK absorption modeling using GastroPlus based on Advanced Compartmental Absorption and Transit (ACAT) model

Table 1: Properties of model drugs

Property \ Drug	Tacrolimus	Itraconazole
Molecular Structure		
Indication	Immunosuppressant	Antifungal
MW (g/mol)	804.02	705.64
LogP	3.64	5.21
pKa	0.28 (weak base)	0.54, 2.47, 3.88 (weak base)
Water Solubility	5 μg/ml	0.004 μg/mL
Blood-Plasma Ratio	15-52	1.4
Elimination	CYP3A4 and P-gp	CYP3A4 (Both parent drug and metabolite can be inhibitors)

3 Results

Optimization and validation of PBPK models for tacrolimus and itraconazole

- Convert blood concentration of tacrolimus (clinical data collected in Ref. 1) to plasma concentration by using an erythrocyte-to-plasma ratio of 68 (Ref. 2) and the equation on the right.

$$C_P(t) = \frac{C_B(t)}{1 - HCT + HCT\frac{C_{RBC}(t)}{C_P(t)}}$$

- Optimize and validate the PBPK models for tacrolimus and itraconazole by using parameters reported in literature or optimizing the parameters against the reported clinical data.

* Optimized
** Assuming f_U in microsome calculated in Ref. 5)
*** Estimated interfacial tension

Table 2: Parameters for the PBPK models

Parameters \ Drug	Tacrolimus	Itraconazole
V_c	8.361 L/kg*	1.398 L/kg*
K_{12}	0.317 h^{-1}*	0.31 h^{-1}*
K_{21}	0.079 h^{-1}*	0.054 h^{-1}*
Effective Permeability (P_{eff}) Duodenum Jejunum Ileum Caecum and colon	(Ref. 3) 4.77 x 10^4 cm/s 4.77 x 10^4 cm/s 2.38 x 10^4 cm/s 1.69 x 10^4 cm/s	16.1 x 10^4 cm/s (Ref. 6)
Protein binding, f_U Adjusted plasma f_U	27% (Ref. 4) 3.3042% (Ref. 4)	3.15% (Ref. 7) 0.09821% (Ref. 7)
CYP3A4/3A5 K_m V_{max} $V_{max,hepatic}$ SF $V_{max,gut}$ SF	(Ref. 4 and 5) 3.135 mg/L** 0.348 mg/s/mg 8 2.3	(Ref. 8) 2.75 μg/L (assume f_U=100%) 0.024 mg/s/mg 1.8 1
P-gp K_m V_{max} $V_{max,gut}$ SF	 80.4 mg/L* 0.005* 1*	
Precipitation model: Homogenous nucleation based on classical nucleation theory (CNT)		
Interfacial tension	0.02 J/m^2***	0.0296 J/m^2 (Ref. 9)
Surface integration factor	6.5 μm*	10 μm*
Exponential correction factor	0 (crystalline) 1 (amorphous)	0 (crystalline) 1 (amorphous)

3.1 Tacrolimus

- Simulate the PK profiles of different amount of amorphous/crystalline tacrolimus (0.5 to 5 mg) by enabling/disabling the precipitation kinetics (exponential correction factor 1/0 in GastroPlus). The resulting PK profiles and intestinal distribution of amorphous/crystalline tacrolimus are shown in Figs 2 and 3.

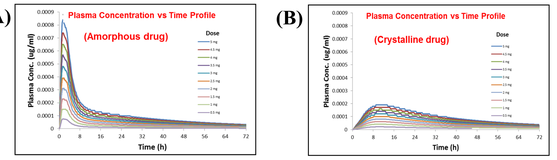


Figure 2: Simulation of pure (A) amorphous and (B) crystalline tacrolimus using the established model

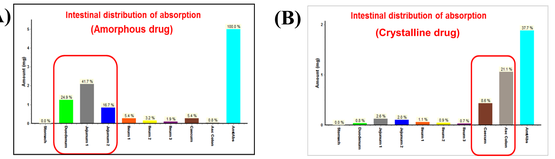


Figure 3: Intestinal distribution of absorption for pure (A) amorphous and (B) crystalline tacrolimus.

- Combine the amorphous and crystalline PK profiles for an amorphous-crystalline composite. The effect of tacrolimus crystallinity on the resulting composite PK profiles is shown in Fig. 4.

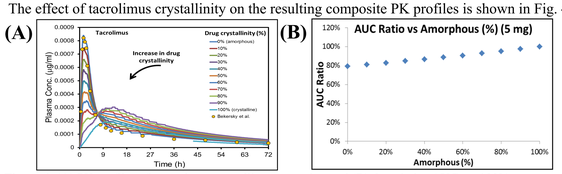


Figure 4: (A) PK profiles of amorphous-crystalline composites and (B) the relative AUC vs. 100% amorphous tacrolimus.

- Examine the effect of "average" kinetic solubility of tacrolimus on the resulting PK profiles (See Fig. 5).

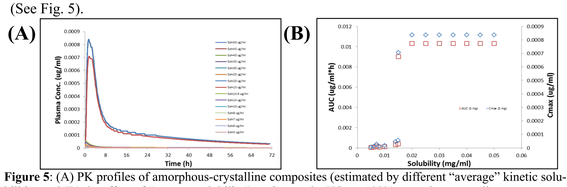
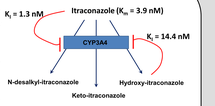


Figure 5: (A) PK profiles of amorphous-crystalline composites (estimated by different "average" kinetic solubilities and (B) the effect of "average solubility" on C_{max} and AUC vs. 100% amorphous tacrolimus.

3.2 Itraconazole

- Itraconazole has a self-inhibition metabolism (see picture on the right). GastroPlus may under-estimate the PK profiles due to lack of simulating this drug-drug interaction (Ref. 5).



- Simulate the PK profiles of different amount of amorphous/crystalline itraconazole (10 to 100 mg) by enabling/disabling the precipitation kinetics (exponential correction factor 1/0 in GastroPlus). The resulting PK profiles of amorphous/crystalline itraconazole are shown in Fig. 6.

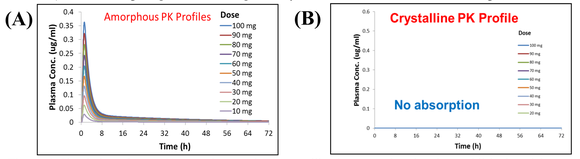


Figure 6: Simulation of pure (A) amorphous and (B) crystalline itraconazole using the established model

- Combine the amorphous and crystalline PK profiles for an amorphous-crystalline composite. The effect of itraconazole crystallinity on the resulting composite PK profiles is shown in Fig. 7.

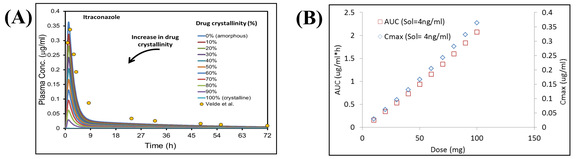


Figure 7: (A) PK profiles of amorphous-crystalline composites (with clinical data from Ref. 10), (B) the relative AUC vs. 100% amorphous itraconazole

- Examine the effect of "average" kinetic solubility of itraconazole on the resulting PK profiles (See Fig. 8).

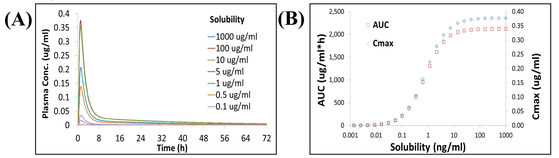


Figure 8: (A) PK profiles of amorphous-crystalline composites (estimated by different "average" kinetic solubilities and (B) the effect of "average solubility" on C_{max} and AUC vs. 100% amorphous itraconazole.

4 Discussion

- The predicted PK profiles of tacrolimus and itraconazole ASDs as a function of drug crystallinity are shown in Figs 4A and 7A, respectively. The predicted *in vivo* PK profiles of tacrolimus ASD (*i.e.* 0% crystallinity) agree well with observed clinical data.
- The prediction for itraconazole ASD by the software slightly overestimates the actual clinical data due to the inability to incorporate the inhibition of metabolism of each other between itraconazole and its metabolite hydroxy-itraconazole for CYP3A4.
- The simulation results showed the ASD formulations of both tacrolimus and itraconazole had a significantly higher bioavailability compared to that of their crystalline counterparts, and a similar PK trend that the higher drug crystallinity present in the ASD formulations, the lower the bioavailability. The PK simulation results also suggested that approximately 50% drug crystallinity leads to 11% and 55% decrease in AUC for 5-mg tacrolimus and 100-mg itraconazole, respectively. This indicates that the oral bioavailability of both ASD products is sensitive to recurrence of crystallization affecting product stability.

5 Conclusion

The newly developed PBPK model based on GastroPlus simulated the absorption improvement of tacrolimus and itraconazole by their ASD formulations. This model provides a showcase how exploratory PBPK modeling and simulation can be utilized to predict the impact of product stability (*i.e.* drug crystallinity) on *in vivo* performance (*i.e.* systemic exposure) during early pharmaceutical development.

6 Disclaimer & References

Disclaimer: Opinions expressed in this poster are those of the authors and do not necessarily reflect the views or policies of the FDA.

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