Biopharmaceutic *In Vitro In Vivo* Extrapolation (IVIV_E) Informed PBPK Model of Ritonavir Norvir® Tablet Absorption in Humans Under Fasted and Fed State Conditions

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Introduction

ASDs are complex products where the active pharmaceutical ingredient is molecularly dispersed within the polymer matrix resulting in the disordered state of drug. This amorphization/disruption of the drug crystal lattice significantly improves the solubility and dissolution rate and, as a consequence, leads to improvement in bioavailability.[1]

In this study, we applied a stepwise methodology to model *in vitro* biopharmaceutics experiments to increase confidence in input parameters to a physiologically-based mechanistic absorption model to predict the exposure of ritonavir from Norvir® 100 mg tablet when administered in humans under fasted and fed conditions. The main assumption of the model, supported by *in vitro* experiments, is that ritonavir stays in the amorphous form for the entire duration of absorption from the GI tract.

Methods

An extensive literature search was performed and studies were collected where biopharmaceutical characterization of ritonavir (amorphous form alone) as well as Norvir® 100 mg tablet were reported. The Simcyp In vitro Analysis toolkit (SIVA® V3) was used for the modeling of *in vitro* biopharmaceutic experiments. A PBPK model using ADAM was developed using Simcyp Simulator (V18, Release 1).

Figure 1 demonstrates the approach taken to confirm/obtain key parameters affecting the absorption of amorphous ritonavir such as intrinsic solubility, bile-micelle partition coefficients, formulation disintegration and *in vivo* precipitation parameters. Table 1 lists the absorption related parameters used in the model. Distribution and elimination related parameters were taken from the Simcyp V17 SV-Ritonavir File except V_{max} for CYP3A4/5 was corrected for ISEF values of BD Supersomes.[2]

The approach of sequential modeling of biopharmaceutics experiments to generate absorption related input parameters of the PBPK model was assessed by predicting the clinically observed plasma concentration time profiles of ritonavir following administration of a 100 mg Norvir® tablet in a virtual population (10 trials of 27 individuals). For fed state predictions, increased viscosity of the luminal fluids was also considered.

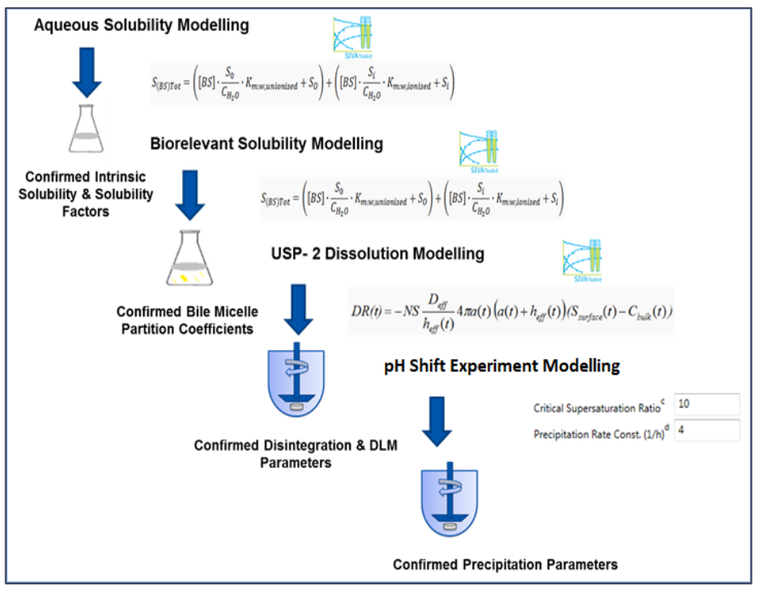


Figure 1. An integrated sequential *in vitro* modelling workflow followed within this research work

Table 1. Model Input Parameters for Ritonavir Norvir® Tablet Formulation

Absorption Related Parameters	Value	Comment/Reference
Formulation	Immediate Release	Amorphous solid dispersion formulation, Norvir® tablet
Particle Handling Method	PPB	
Particle Size (µm) Monodisperse	10	Assumed, as data not available
Intrinsic Solubility (mg/mL)	0.0385	Xu et al 2017[3]
Solubility Factor 1	103.9	Fitted with SIVA 3, Law et al. 2004[4]
Viscosity Model	Yes	To capture negative food effect
logKm:w, neutral	3.894	Fitted with SIVA 3, Xu et al 2017[3]
logKm:w, ion	7.235	Fitted with SIVA 3
Disintegration Profile, Kd	0.017	Fitted with SIVA 3, Ellenberger et al 2018[5]
Precipitation Model	Model 2	
CSR	1	Xu et al 2017[3] ; Ellenberger et al 2018[5]
PRC (1/h)	0.0001	Xu et al 2017[3] ; Ellenberger et al 2018[5]
sPRC (1/h)	1000	Xu et al 2017[3]
Particle heff prediction	Hintz-Johnson	
MechPeff, Ptrans (10-6 cm/s)	1000.6	Predicted, needed to capture negative FE
Peff,man (cm/s) (Jejunum)	7.25	Predicted
Colon Abs Scalar	0.1	Fitted to account P-gp efflux of ritonavir

Results

Fig. 2 shows the results obtained after modeling the *in vitro* disintegration and precipitation parameters of the Norvir® tablet. *In vitro* studies suggest that crystallization is unlikely to occur during absorption timeframes and any precipitate in the simulations was assumed to be to amorphous; the modelling results support this approach. Predicted and Observed C_{max} and AUC_{0-t} parameters were within 1.5 fold for both the fasted and fed states in healthy volunteers (Fig. 3, Table 2). The simulations predicted significant decrease in the effective diffusion coefficient (D_{eff}) of ritonavir in all GI segments in the fed state compared to the fasted state. This is due to the increased apparent viscosity of the luminal fluid and reduction in the free fraction of the drug in the fed state due to increased bile salt concentration, which both influence D_{eff} calculations (Fig. 4).

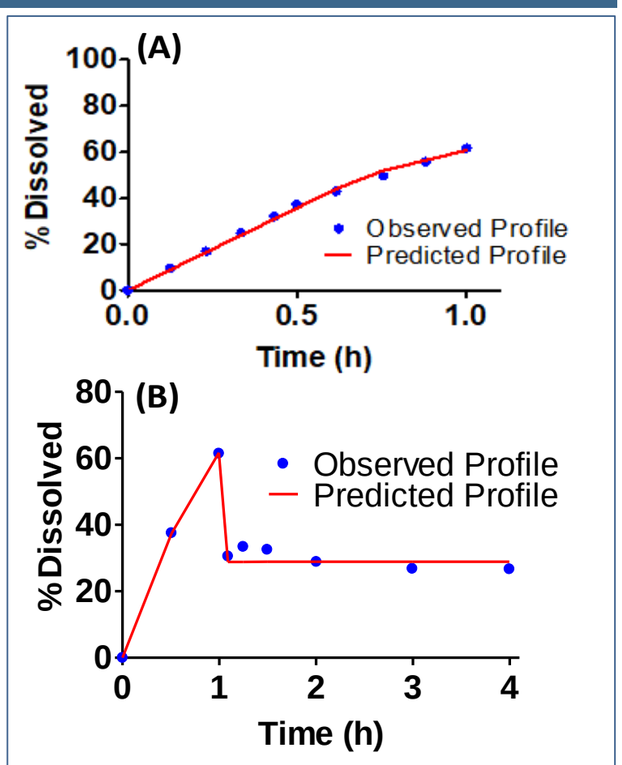


Figure 2. Simulated and Observed[5] in vitro dissolution data (a) 0.1N HCL and (b) pH Shift experiment

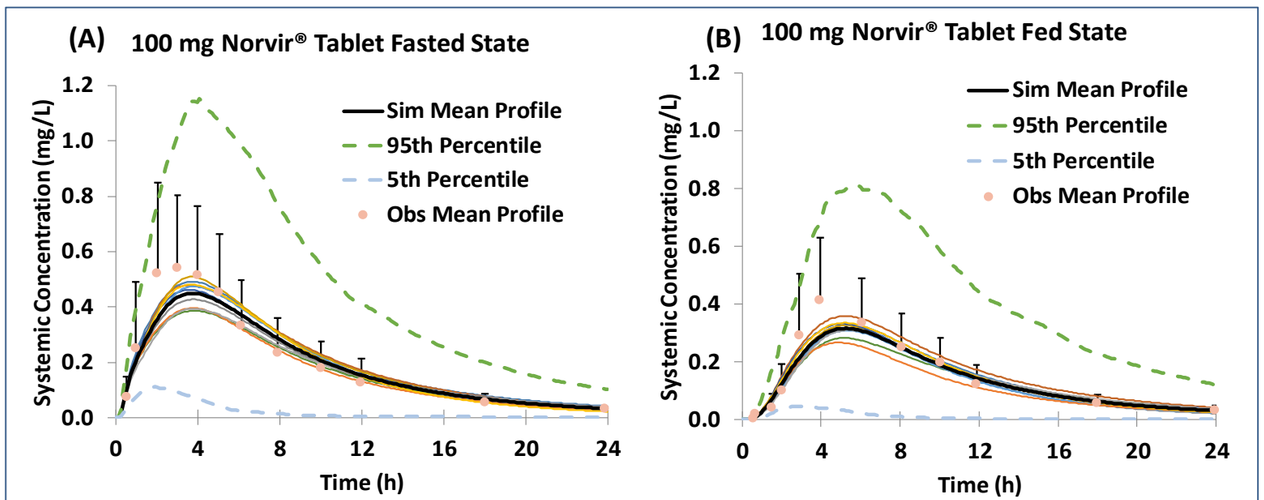


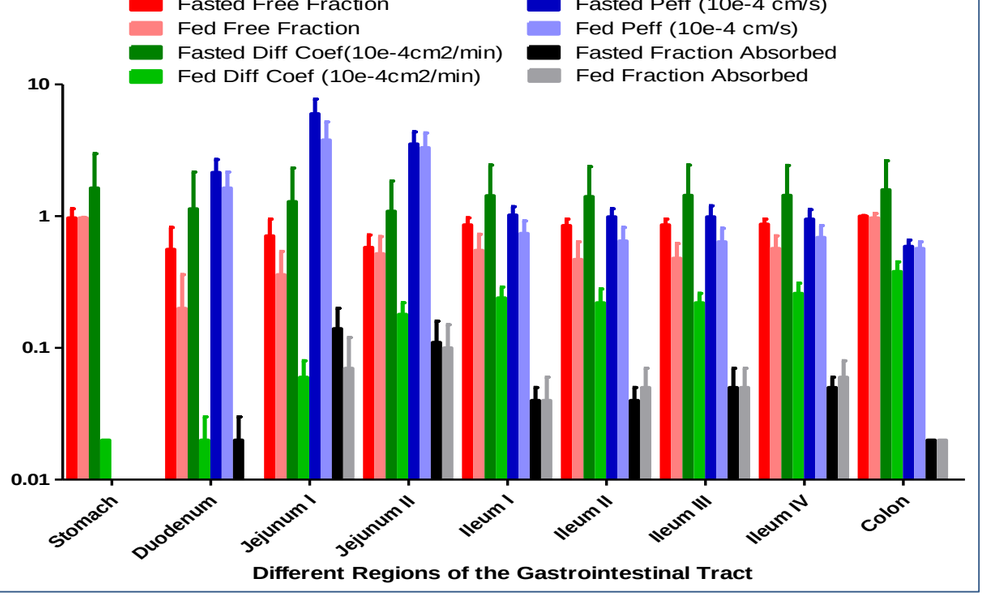
Figure 3. Simulated and Observed plasma concentration time profiles of ritonavir under fasted and high fat fed states. Observed data is reported by Ng et al 2008[6]

Table 2. Simulated and Observed pharmacokinetic parameters (arithmetic means ± S.D.) of ritonavir following administration of 100 mg Norvir® Tablet under fasted and high fat fed state.

PK Parameters	Observed Fasted[6]	Simulated Fasted	Observed Fed[6]	Simulated Fed
C_{max} (µg/mL)	0.6 ± 0.31	0.49 ± 0.30	0.44 ± 0.21	0.34 ± 0.25
T_{max} (h)	3.2 ± 1.2	3.43 ± 1.18	4.8 ± 1.1	4.75 ± 1.37
AUC_{0-t} (µg/mL.h)	4.6 ± 2.0	4.46 ± 3.27	3.5 ± 1.6	3.30 ± 2.86

The MechPeff model, by default, assumes that the unbound (free) fraction of dissolved drug in the luminal boundary layer drives drug permeation through the gut membrane, thereby affecting regional P_{eff}. Thus, consideration of viscosity differences in prandial states and the effect of free fraction of drug on gut wall permeation rate were found able to explain the negative food effect observed for Norvir® tablets (Fig. 3).

Figure 4. Simulated luminal fluid free fraction, diffusion coefficient, effective permeability and fraction absorbed of ritonavir in different segments of the gastro-intestinal tract under fasted and fed states



Conclusions

- Mechanism based modeling of *in vitro* biopharmaceutic experiments can help to build confidence in the quality of the key absorption parameters of a PBPK model.
- Model analysis revealed that in fed conditions decreased Deff as a result of increased viscosity and reduced free fraction resulted in reduced regional Peff (particularly in the duodenum and jejunum I) which could explain the underlying mechanisms of the negative food effects observed with Norvir® Tablet.

References

1. Pang, *Drug Metab Dispos*, 2003, 31:1507. **2.** Koudriakova et al. *Drug Metab Dispos*, 1998, 26:552. **3.** Xu et al, *Mol Pharm*, 2017, 14:3801. **4.** Law et al, *J Pharm Sci*, 2001, 90:1015. **5.** Ellenberger et al, *AAPS PharmSciTech*, 2018, 19:1985. **6.** Ng, et al, *Jour. Intern AIDS Soc*, 2008, 11.

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