Jeremy Perrier*, Virginie Gualano

PhinC Development, Massy (France)

jeremy.perrier@phinc.fr – Journées du GMP 2021 20 – 22 Octobre Paris, France

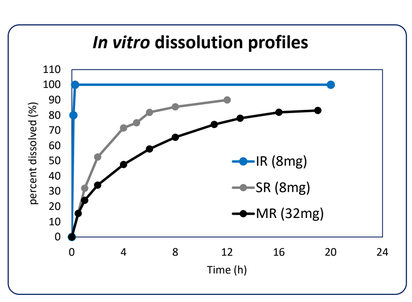
Developing a mechanistic *in vitro-in vivo* relationship (IVIVR) for drug A using Physiologically-based pharmacokinetic modeling

Results

1 - PBPK absorption model

Physico-chemical properties
(MW, solubility, logP, pKa)

***In vitro* ADME**
(Caco-2, Fup, CYP Km/Vmax, CL_{int})



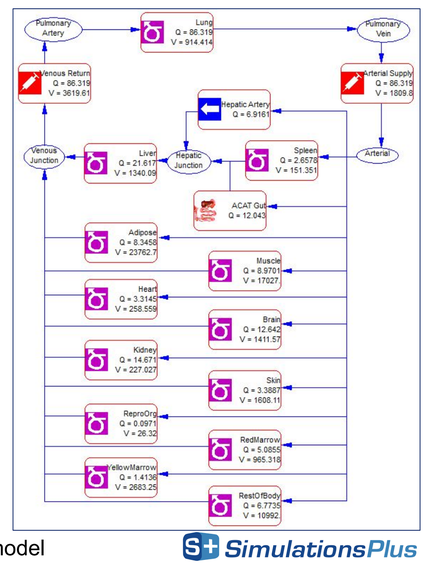


Figure 1. Input parameters and schematic of PBPK model

PBPK model simulations

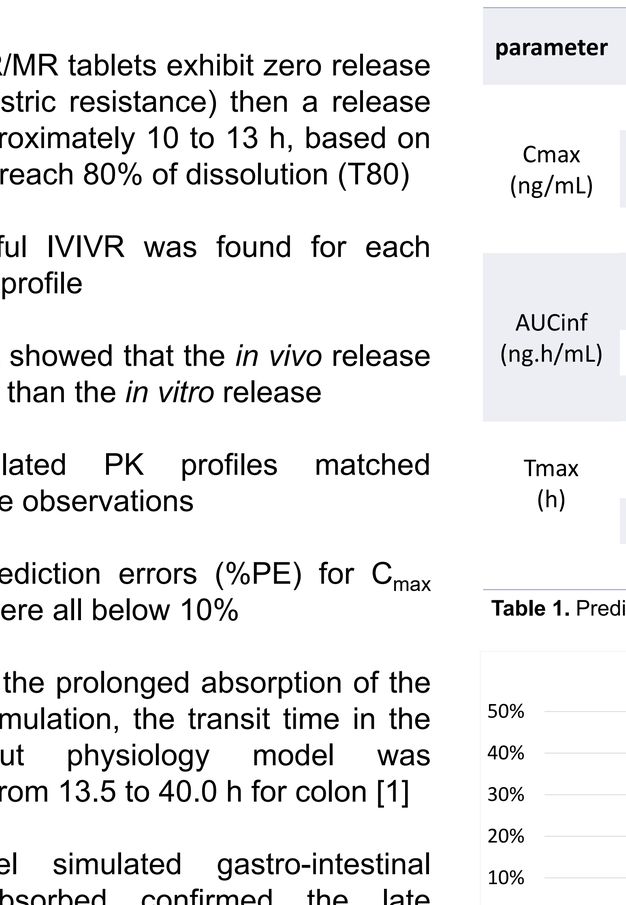


Figure 2. Simulated (line) and observed (symbols) plasma concentration-time profiles after single oral administrations fasted

PBPK model validation

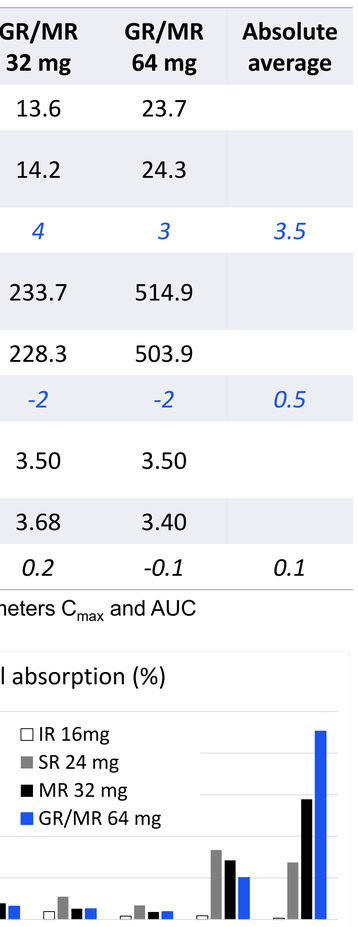


Figure 3. Comparison of simulated *versus* observed PK parameters

2 - Deconvolution and direct correlation (gastro-resistant modified release – GR/MR)

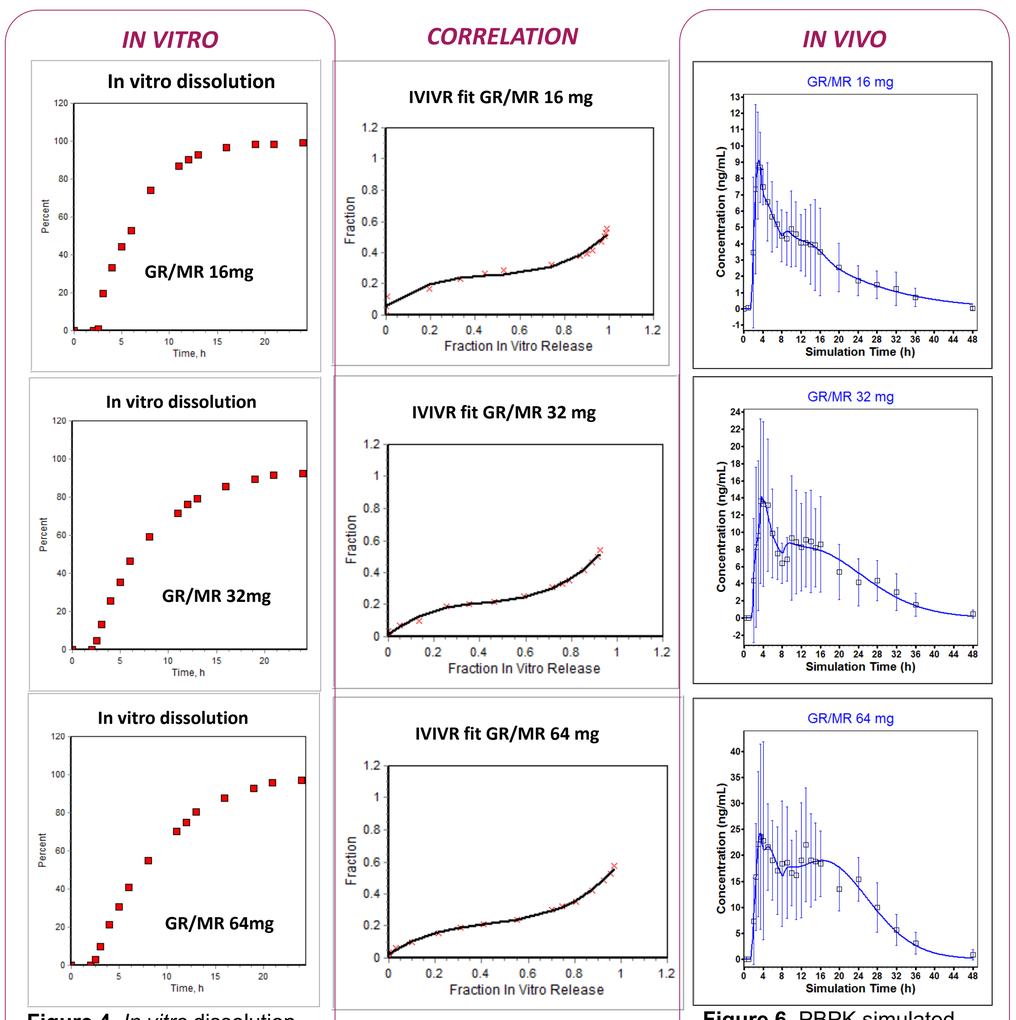


Figure 4. *In vitro* dissolution profiles for each dose

Figure 5. Third order polynomial IVIVR fit

Figure 6. PBPK simulated plasma concentration-time profiles with observed data

- ❑ *In vitro*, GR/MR tablets exhibit zero release for 2 h (gastric resistance) then a release rate of approximately 10 to 13 h, based on the time to reach 80% of dissolution (T80)
- ❑ A successful IVIVR was found for each dissolution profile
- ❑ The results showed that the *in vivo* release was slower than the *in vitro* release
- ❑ The simulated PK profiles matched correctly the observations
- ❑ Percent prediction errors (%PE) for C_{max} and AUC were all below 10%
- ❑ To capture the prolonged absorption of the GR/MR formulation, the transit time in the default gut physiology model was increased from 13.5 to 40.0 h for colon [1]
- ❑ The model simulated gastro-intestinal fraction absorbed confirmed the late caecum and colon absorption of the modified release formulations compared to the immediate release formulations

parameter		GR/MR 16 mg	GR/MR 32 mg	GR/MR 64 mg	Absolute average
Cmax (ng/mL)	observed	8.8	13.6	23.7	
	simulated	9.1	14.2	24.3	
	%PE	*4*	*4*	*3*	*3.5*
AUCinf (ng.h/mL)	observed	113.8	233.7	514.9	
	simulated	117.2	228.3	503.9	
	%PE	*3*	*-2*	*-2*	*0.5*
Tmax (h)	observed	3.00	3.50	3.50	
	simulated	3.20	3.68	3.40	
	difference	*0.2*	*0.2*	*-0.1*	*0.1*

Table 1. Prediction errors for the PK parameters C_{max} and AUC

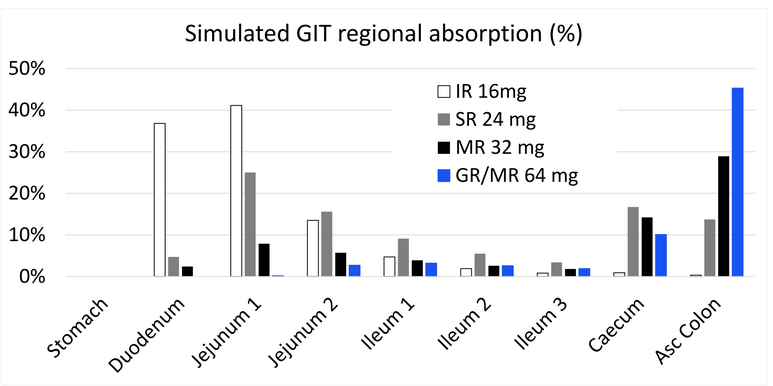


Figure 7. PBPK model simulated gastro-intestinal tract (GIT) regional absorption

Background

- ❑ Drug A is a small molecule with good solubility and permeability (BCS class I)
- ❑ The molecule is extensively metabolized and eliminated in urine and feces
- ❑ IVIVR can be a useful tool to get relevant insight into *in vivo* dissolution and absorption

Objectives

- ❑ 1. To develop a PBPK absorption model for drug A to describe oral absorption in healthy subjects based on data with immediate release (IR), sustained release (SR) and modified release (MR) formulations
- ❑ 2. To develop a mechanistic *in vitro-in vivo* relationship for the specific gastro-resistant modified release (GR/MR) oral formulation

Materials & Methods

- ❑ GastroPlus version 9.7 was used to develop a PBPK absorption model
- ❑ Dissolution and absorption after oral dosing were predicted using the advanced compartmental absorption and transit model (ACAT)
- ❑ IVIVCPlus™ module was used to develop the IVIVR
- ❑ Mechanistic deconvolution one step procedure (Correlate Directly) was used in IVIVCPlus™ module
- ❑ The fitting optimization method set as unity with the concentration-time profile as observation weight
- ❑ Predictability of the IVIVR was evaluated according to the regulatory guidance by calculating the percent prediction errors (%PE) [2]

Conclusions

- ✓ A PBPK absorption model was successfully developed and validated (within 2-folds)
- ✓ Predictability of the IVIVR was evaluated and %PE were below 10%
- ✓ The results confirmed the ability of the IVIVCPlus™ module to adequately characterize the specific MR formulations (GR/MR) and to be further used to develop an IVIVC

References

- ✓ [1] Bouchacha et al. 2012 Colonic response to food in constipation, *Int. J. Colorectal Dis.*, vol. 21, no. 8, pp. 826-833, 2006
- ✓ [2] FDA - Guidance for Industry: Extended Release Oral Dosage Forms: Development, Evaluation and Application of In vitro/In Vivo Correlations. 1997