Mechanistic Deconvolution Using the ADAM Model: Part 1. Establishing Mechanistic IVIVC for Controlled Release Formulations of the High Extraction BCS Class I Drug Metoprolol: Comparison with Conventional IVIVC Models.

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PURPOSE

Conventional deconvolution methods for establishing *in vitro-in vivo* correlations (IVIVCs) estimate the rate of input of drug into the systemic circulation from observed plasma drug concentrations (Cp) of the oral formulation with the use of IV Bolus data as unit impulse response. These methods do not separate the multiple mechanisms that determine *in vivo* input rate – transit time, gut wall permeability, gut wall metabolism, and hepatic first-pass metabolism – from *in vivo* dissolution rate. Alternatively, mechanistic, physiologically-based pharmacokinetic (PBPK) deconvolution models can be used to estimate *in vivo* dissolution profiles while separately accounting for permeation, GI transit and first pass elimination, potentially simplifying the establishment of IVIVCs. Here, we present a case study using the Simcyp Advanced Dissolution Absorption and Metabolism (ADAM)[1] model to establish a mechanistic IVIVC for a high first pass extraction, BCS Class I drug, metoprolol, and compare the results with reported conventional and semi-mechanistic IVIVC approaches[2,3].

METHOD:

Clinical Cp and *in vitro* dissolution profiles for slow, medium and fast Controlled Release (CR) formulations and an oral solution of metoprolol were obtained from the literature[2]; using the solution study *in vivo* disposition and gut wall permeability values were estimated. For each CR formulation *in vivo* dissolution profiles were deconvoluted from the corresponding Cp profile (Fig. 2) using the Simcyp ADAM model (Fig 1). The IVIVC between deconvoluted *in vivo* dissolution profiles and *in vitro* dissolution profiles was then established and validated using all three formulations (Fig. 3) or using the Fast and Slow CR formulations to establish IVIVC with the Medium CR formulation for external validation (Fig. 4).

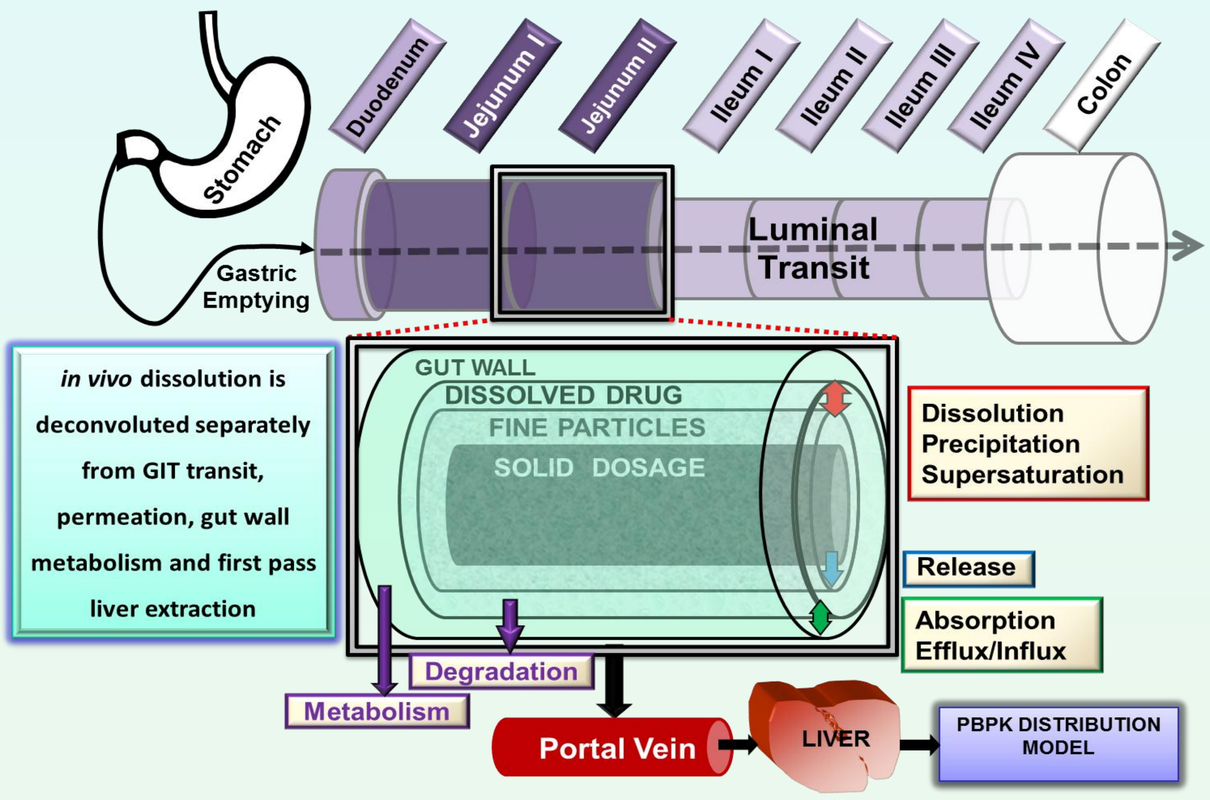


Figure 1. Simcyp ADAM Model

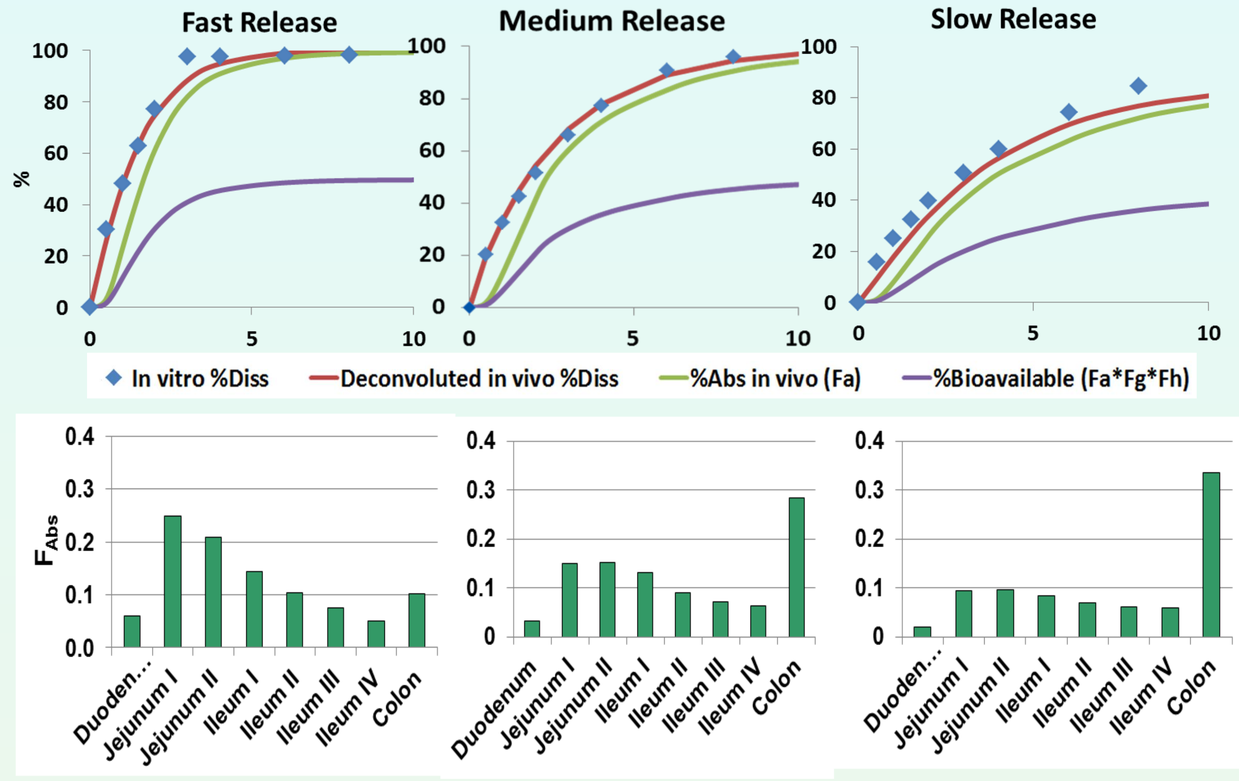
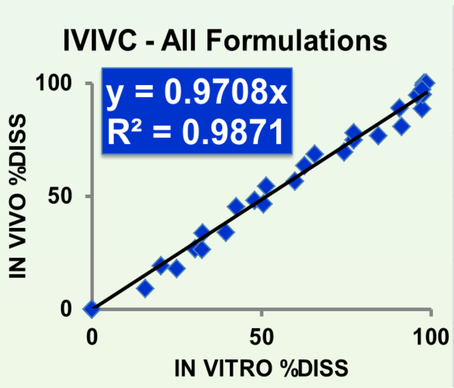
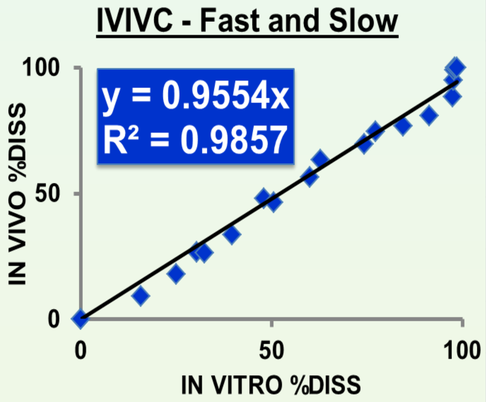


Figure 2. Deconvolution of three CR formulations of metoprolol using ADAM model



	Cmax (ng/mL)			AUC (ng/mL*h)		
	Obs	Pred	%PE	Obs	Pred	%PE
Fast	118.68	122.79	-3.46	821.65	842.18	-2.50
Medium	90.39	93.12	-3.02	846.29	856.60	-1.22
Slow	63.48	64.34	-1.35	685.72	753.12	-9.83
Mean			-2.61			-4.52



	Cmax (ng/mL)			AUC (ng/mL*h)		
	Obs	Pred	%PE	Obs	Pred	%PE
INTERNAL VALIDATION						
Fast	118.68	120.58	-1.60	821.65	828.99	-0.89
Slow	63.48	63.31	0.27	685.72	746.83	-8.91
Mean			-0.66			-4.90
EXTERNAL VALIDATION						
Medium	90.39	88.54	2.04	846.29	853.47	-0.85

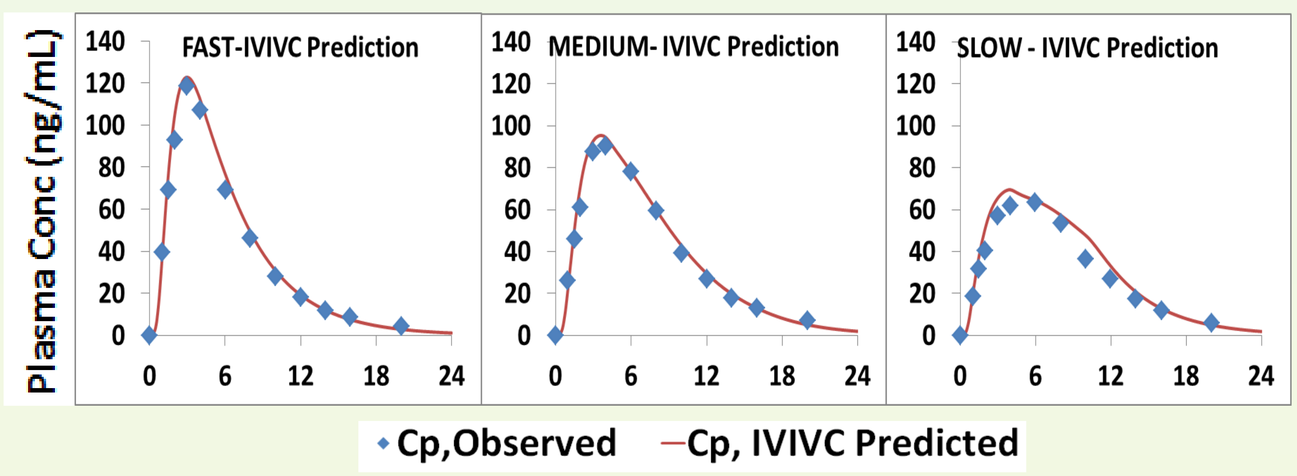


Figure 3. Establishment and Validation of IVIVC using all three formulation

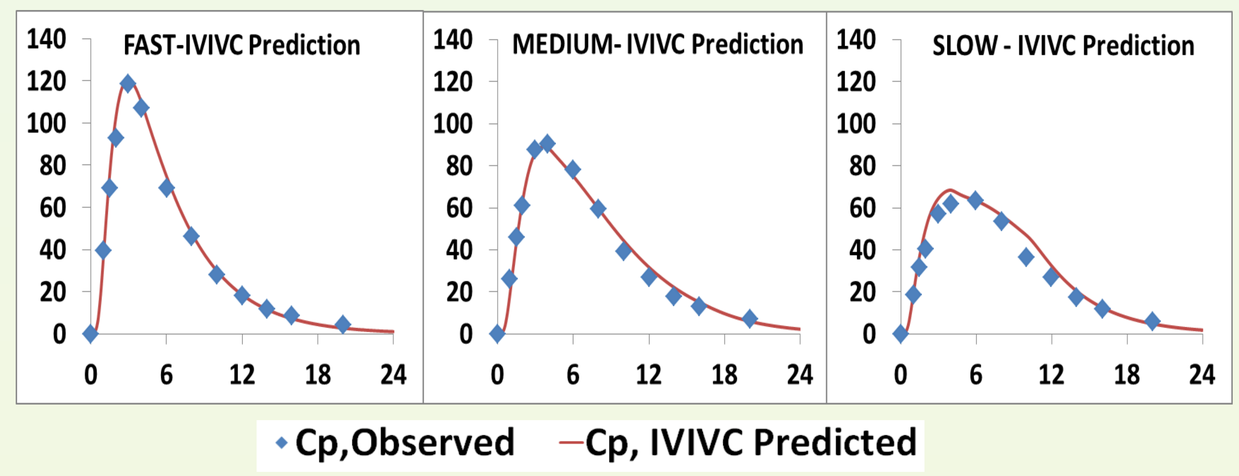


Figure 4. Establishment and Validation of IVIVC using Fast and Slow Formulations and Medium as External

RESULTS:

On the basis of the results summarised in Figs. 3 and 4 both correlation and predictive performance of the mechanistic IVIVC was better than the reported numerical deconvolution-based[2] and alternative semi-mechanistic parent/metabolite differential equation-based[3] IVIVC models.

CONCLUSION:

A novel, physiologically based deconvolution approach to the establishment of IVIVCs has been developed for a BCS Class I, high first pass extraction drug. Further validation of the presented mechanistic IVIVC approach is required using drugs with a wider range of ADME properties.

REFERENCES: **1.** Jamei *et al.* (2009) AAPS J 11(2), 225; **2.** Eddington *et al.* (1998) Pharm Res 15(3), 466; **3.** Sirisuth and Eddington (2002) EJPS 53, 301