Conventional *versus* Physiologically-Based (PB)-IVIVC: Revisiting some successful and failed conventional IVIVC cases with PB-IVIVC

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PURPOSE:

Conventional deconvolution methods, such as Wagner Nelson (WN) and Numerical deconvolution (ND), 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 preferably with the use of IV bolus data as the unit impulse response (UIR). 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, such as the Simcyp Advanced Dissolution Absorption and Metabolism (ADAM) model[1], by virtue of their nature, can estimate *in vivo* dissolution profiles while separately accounting for permeation, GI transit and first pass elimination, potentially simplifying the establishment of IVIVCs and can be used to assess population variability[2]. Here, we apply the Simcyp PB-IVIVC approach to both published successful and failed conventional IVIVC studies. Two model drugs – (i) Metoprolol (high solubility, moderate permeability and high first-pass liver extraction), and (ii) Diltiazem (high solubility, moderate permeability, significant gut-wall and liver first pass metabolism and auto-inhibition of the metabolizing enzyme CYP3A4) - and three published conventional IVIVC models[3-6] were used during this study.

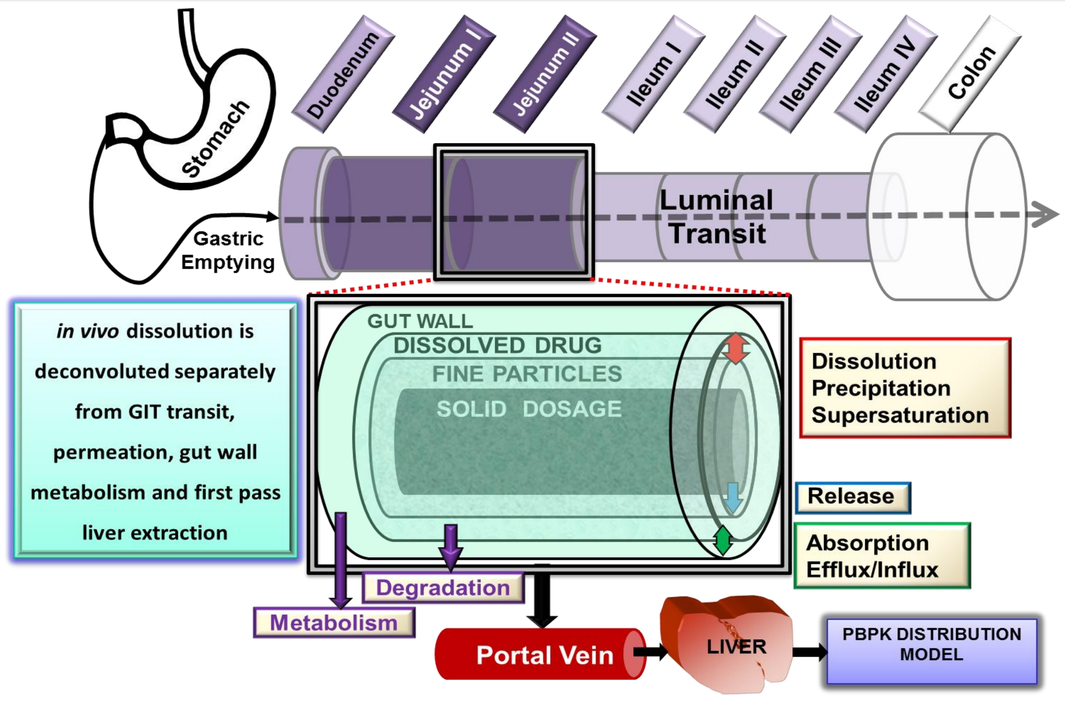

Fig. 1. Simcyp ADAM and PBPK Models

RESULTS AND DISCUSSIONS:

With PB-IVIVC methods the processes involved in oral absorption - *in vivo* dissolution, permeation, gut-wall metabolism and first-pass liver metabolism - can be separated (Figure 2a, Metoprolol and 2b, Diltiazem). When the pure *in vivo* dissolution is correlated with *in vitro* dissolution, simpler and more robust IVIVCs can be established (Figure 3 and Tables 1 & 2). The auto-inhibition of its own metabolism by Diltiazem can also be considered with PBPK models which allow assessment of steady state exposure achieved after sustained periods of multiple-dosing rather than considering only single dose studies.

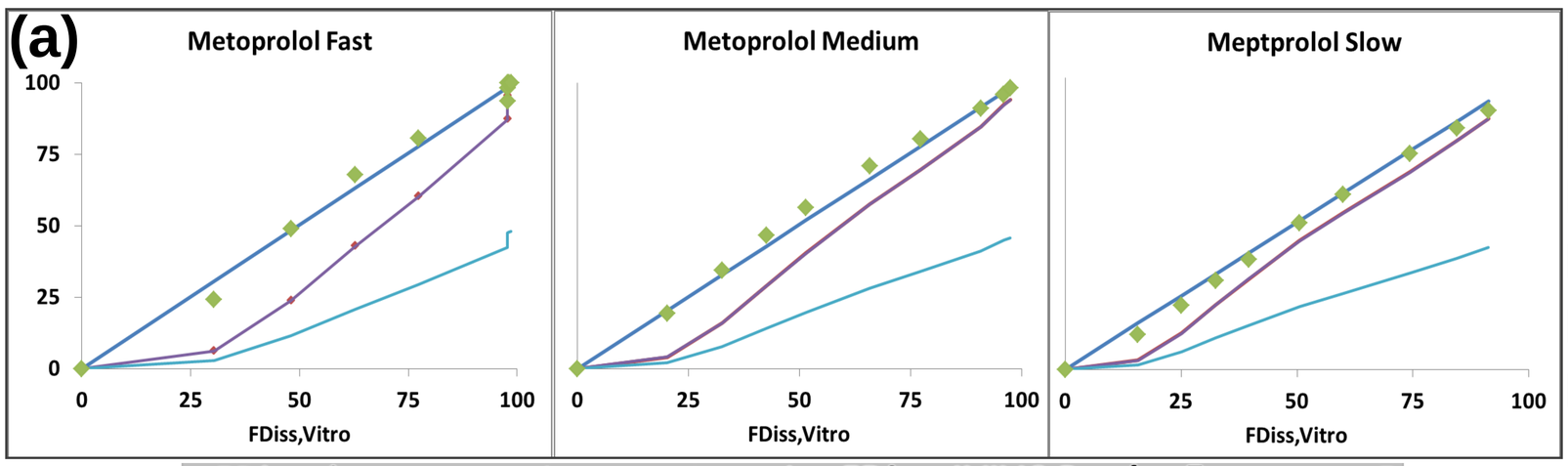

Fig 2. (De)convoluted *in vivo* processes *versus in vitro* dissolution for Metoprolol (top panel) and Diltiazem (lower panel).

Validation	Formulation	%PE in AUC			%PE in Cmax		
		ND	SM	Simcyp	ND	SM	Simcyp
Internal	Fast	4.52	11.4	-0.34	3.97	3.1	-0.86
	Medium	5.22	11.5	6.07	-0.85	1.94	8.07
	Slow	-0.76	9.27	8.18	-5.67	-9.26	1.84
	AAPE	3.5	10.72	4.86	3.50	4.77	3.59
External	I (3 kg)	6.13	NP	1.35	7.53	NP	8.28
	II (50kg)	-2.2	NP	-6.38	-3.17	NP	1.29
	III (3kg Other)	-1.3	NP	-2.81	-11.7	NP	-6.99
	IV (80 kg)	1.3	NP	-1.05	-8.03	NP	0.35
	V (Bead Cap)	2.5	NP	2.91	-23	NP	-9.57
	AAPE	2.69	NP	2.9	10.69	NP	5.30

Table 1. Metoprolol formulations: Internal (fast, medium and slow) and external (I, II, III, IV, V) validation of Simcyp PB-IVIVC and reported conventional models; where ND is Numerical Deconvolution, SM is Semi-mechanistic and NP is Not Performed.

Formulation	%PE AUC		%PE Cmax	
	ND with Quadratic IVIVC	Simcyp with linear IVIVC	ND with Quadratic IVIVC	Simcyp with linear IVIVC
Fast	94.0	12.61	77.8	0.11
Medium	57.2	3.07	75.9	10.69
Slow	47.5	-4.79	65.9	-4.89
Average	66.3	6.82	73.2	5.23

Table 2. Diltiazem formulations : Validation of Simcyp PB-IVIVC and comparison with reported models.

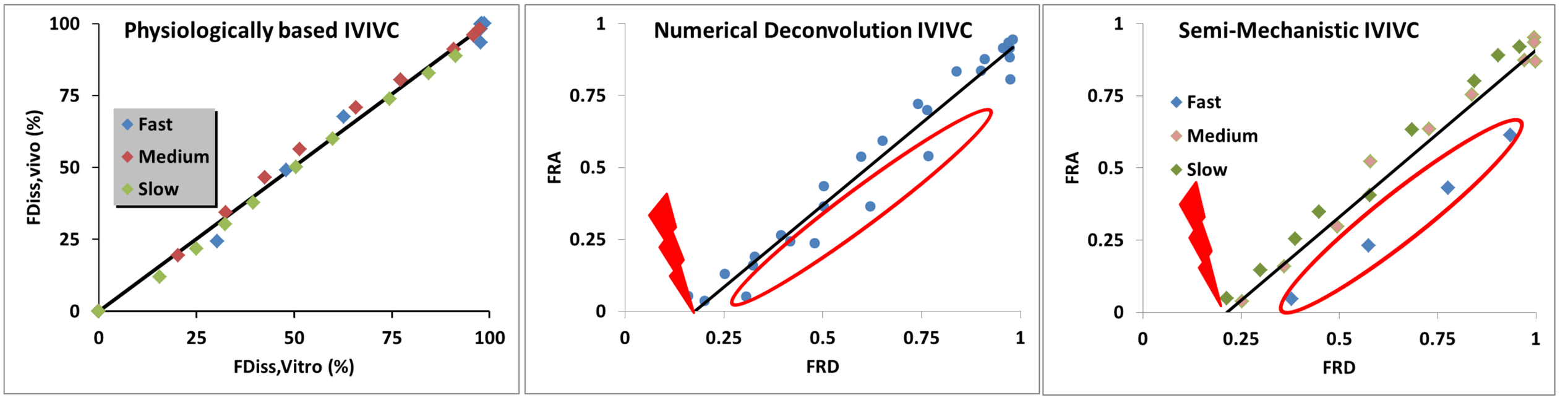

Fig 3. Metoprolol IVIVC plots for the PB, ND and semi-mechanistic methods.

CONCLUSIONS:

PB-IVIVC approaches can be used to deconvolute 'pure' unconfounded *in vivo* dissolution leading to simpler and more meaningful IVIVCs.

REFERENCES: [1] Jamei, M. AAPS J, 11 225 (2009); [2] Patel N. AAPS Annual Meeting and Exposition, Chicago, IL, (2012a,b); [3] Eddington, N. Pharm. Res., 15 466 (1998); [4] Sirisuth, N. Eur. J. Pharm. Biopharm, 53 301 (2002); [5] Mahayni, H. J. Pharm. Sci., 89, 1354 (2000); [6] Sirisuth, N. Biopharm & Drug Disp, 23 1 (2002).