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Establishing an *In Vitro-In Vivo* Correlation (IVIVC) for Tramadol Extended-Release Tablets : Conventional vs. Physiologically Based IVIVC

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PURPOSE

Generally conventional deconvolution methods do not separate multiple processes involved in drug absorption, e.g. GI transit, permeation, and first pass effects that determine *in vivo* systemic input rate from *in vivo* dissolution rate. Physiologically-based pharmacokinetic (PBPK) deconvolution models, on the other hand, can disentangle these processes and estimate *in vivo* dissolution rather than absorption allowing establishment of more robust and transparent IVIVCs. Herein we establish a PB-IVIVC for extended release (ER) tramadol formulations using the mechanistic Simcyp Advanced Dissolution Absorption and Metabolism (ADAM) model[1] and compare the outcomes to conventional IVIVC model.

METHODS

Observed plasma concentrations (Cp)[3], and *in vitro* dissolution profiles of five formulations[2] (including two external validation batches), upper and lower dissolution specifications for target formulation and oral solution (reference) Cp data for tramadol were obtained from the literature[2,3]. Oral solution data were used to estimate disposition parameters and gut permeability. For each ER formulation *in vivo* dissolution profiles were deconvoluted from the corresponding Cp profile using the IVIVC module of the Simcyp Simulator (V13 R2). A level A linear IVIVC between deconvoluted *in vivo* and *in vitro* dissolution profiles was established and validated internally using three formulations and externally using two ER formulations.

Table 1. Comparison between reported and simcyp IVIVC Model

Parameter	Reported IVIVC Model[3]	SimCYP IVIVC Model
Deconvolution Method	Deconvolution by convolution which involved nonlinear regression analysis of convolution integral	Deconvolution using SIMCYP Mechanistic ADAM Model
IVIVC Approach	Semi- Mechanistic IVIVC	Mechanistic PB-IVIVC
Linear Model Parameters	Slope= 0.946 ; Intercept= -1.27	Slope= 0.9678; Intercept= 0.00
GI Residence Time Scaling	Required to account for low bioavailability of slower formulation	Inherently accounted within Mechanistic IVIVC
External Validation	Target formulation only	Target as well as slower formulation
Max %PE for UL & LL-based plasma predictions	Cmax= 25.00%; AUC = 23.35%	Cmax= 8.56%; AUC = 16.86%

RESULTS

Validation	Formulation	AUC0-t (ng/mL.h)			Cmax (ng/mL)		
		Obs	Pred	%PE	Obs	Pred	%PE
	Fast-Formulation	2829.7451	2884.5825	-1.94	161.3640	139.9631	13.26
Internal	Medium Formulation	2746.3562	2518.9773	8.28	126.2574	118.4506	6.18
	Slow Formulation	2331.2512	2245.0901	3.70	103.1680	102.3100	0.83

Validation	Formulation	AUC0-t (ng/mL.h)			Cmax (ng/mL)		
	EXTR Medium Formulation	5270.2065	5607.0176	-6.39	281.9600	273.6927	2.93
External	EXTR Slow Formulation	4662.9282	4673.4829	-0.23	233.0400	231.7150	0.57

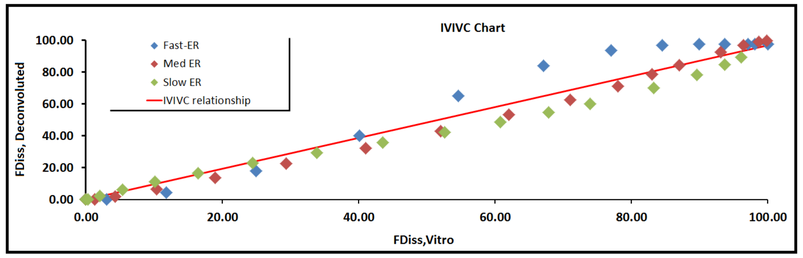

Fig.1. *IVIVC* error level and plot using PB-IVIVC

Prediction	Formulation	AUC0-t (ng/mL.h)			Cmax (ng/mL)		
		Obs- Med	Pred	%PE	Obs- Med	Pred	%PE
Dissolution	LL Disso Specs	2746.3562	2283.3879	16.86	126.2574	117.1461	7.22
	UL Disso Specs	2746.3562	2843.2808	-3.53	126.2574	137.0588	-8.56

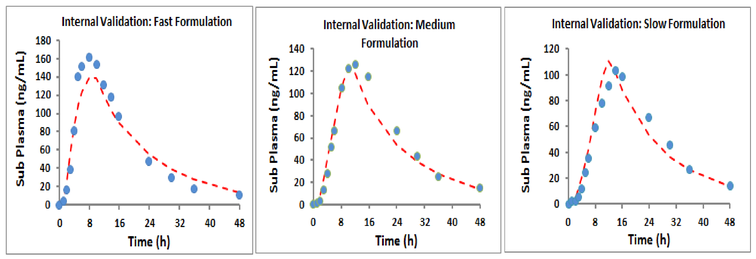

Fig.2. Internal Validation- Observed and IVIVC Predicted plasma concentration profiles of (100 mg) Fast, Medium and Slow Formulations

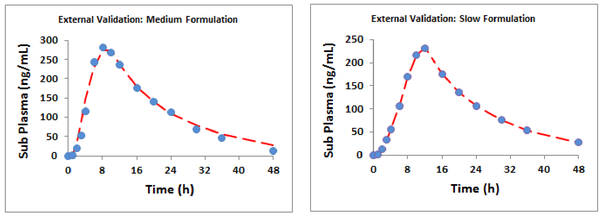

Fig.3. External Validation- Observed and IVIVC Predicted plasma concentration profiles of (100× 2 mg) External Medium and Slow Formulations

DISCUSSION

Figure 4 shows fa (fraction absorbed into the gut wall) over time for three internal formulations. The graphs show the drug absorption is relatively rapid for the fast formulation and complete within 13-14 h, while for the slower formulation it's quite delayed and may even be incomplete across the total transit time of approximately 16-17 hr.

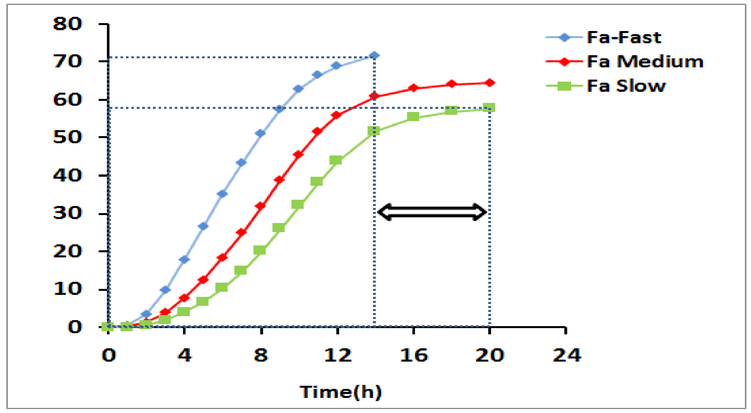

Fig.4. Deconvoluted fraction absorbed (fa) over time for three internal formulations.

The extended absorption of slower and target formulation could be due to the delayed permeation/absorption in the distal part of the GI tract. Conventional IVIVC methods cannot account for lower bioavailability of slower formulation and as a result more complex *in vitro* to *in vivo* relationship (e.g. a time scaling model) is required to obtain good predictions[3]. Although such complex model could fulfil internal validation criteria, it could not describe the dissolution lower and upper limits for a level A IVIVC. Nevertheless, the PB-IVIVC using a simple *in vitro* to *in vivo* relationship is capable of predicting the target as well as external slower formulations.

CONCLUSION

The PB-IVIVC approach improved the predictive performance of the IVIVC model and resulted in a simpler linear IVIVC model unlike the conventional approach that required time scaling.

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