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Application of Physiologically-Based Absorption Modelling in the Development of an In Vitro-In Vivo Correlation (IVIVC) for Topiramate Controlled Release Matrix Tablets

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PURPOSE

The deconvolution of plasma profiles to '*in vivo* dissolution' rather than 'absorption' using mechanistic physiologically-based (PB) oral absorption models can result in more predictive IVIVC models that take into account both critical physiological variables and formulation attributes influencing drug absorption characteristics[1-2]. The PB modelling approach thus has far-reaching consequences in several areas of drug product development including IVIVC, dissolution specifications setting and virtual bioequivalence assessments[3]. Herein we present a case study where the Simcyp Advanced Dissolution Absorption and Metabolism (ADAM) model was used to establish a PB-IVIVC for controlled release (CR) formulations of topiramate and the results compared with reported conventional IVIVC approaches[4].

METHODS

Observed plasma concentration time (Cp) profiles, *in vitro* dissolution profiles of four formulations (slow, medium and fast release formulations including an additional batch for external validation), and oral multiple dose immediate release (IR) formulation (as reference) data for topiramate were collated from the literature[4]. Disposition PBPK model parameters were estimated using the reference formulation and its predictive performance verified against observed PK profiles reported in the literature for oral IR and intravenous dosing from other clinical studies. A single stage PB-IVIVC was then developed using the PB-IVIVC module of the Simcyp Simulator (V14 R1) and validated internally as well as externally. The performance of the PB IVIVC is assessed using the absolute percent prediction errors (APPE) for the actual and predicted C_{max} and AUC values and compared with those obtained using numerical deconvolution (ND) IVIVC reported in the literature.

A PBPK Model- Constructed Using Relevant Drug Physchem and Disposition Parameters in Simcyp® V14.1

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Model Verification- Performed for its predictive performance using Clinical Study Dataset of Different Dosage Forms, Formulations & Food-Drug Interaction Conditions

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Internal Validation- A Single Stage IVIVC Method Developed Using Mechanistic ADAM Model and Validated Internally Using Three Different Formulations

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External Validation- Established IVIVC Model was then Tested for Additional Formulation that was not Part of Internal Validation Dataset for External Predictability

Fig.1. General Stepwise Workflow

RESULTS

Table 1. Internal and External Validation Results of PB-IVIVC

Validation	Formulation	AUC (ng/mL.h)			Cmax (ng/mL)		
		Obs	Pred	%PE	Obs	Pred	%PE
Internal	Formulation-A	123424.75	112660.66	8.72	2670.19	2474.59	7.33
	Formulation-B	138426.22	128430.62	7.22	3156.50	3169.09	-0.40
	Formulation-C	108065.14	98139.56	9.18	2081.22	2241.75	-7.71
	Overall Internal %PE			8.38			5.15

Validation	Formulation	AUC (ng/mL.h)			Cmax (ng/mL)		
		Obs	Pred	%PE	Obs	Pred	%PE
External	EXTR- Formulation	110598.60	101793.59	7.96	2186.93	2318.78	-6.03

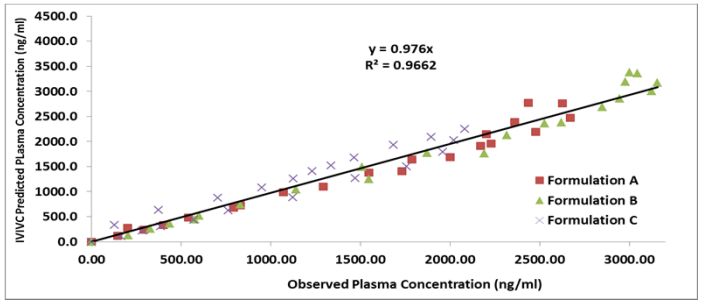

Fig.2. *Observed vs IVIVC predicted plasma concentration* plot for all the three formulations

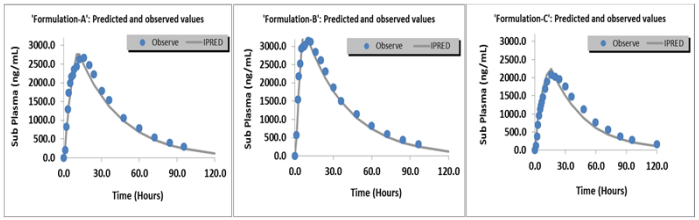

Fig.3. Internal Validation- Observed and IVIVC Predicted plasma concentration profiles of (200 mg) Formulation A, B and C

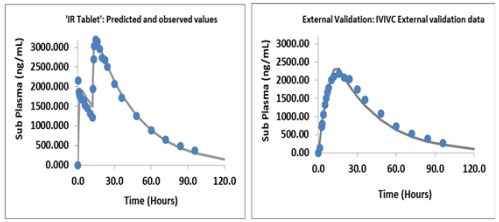

Fig.4. Observed and IVIVC Predicted plasma concentration profiles of (100× 2 mg) External and IR Tablet (200 mg) Formulation

DISCUSSION

A PBPK model developed for IVIVC was initially verified and confirmed for its predictive performance against observed PK profiles of intravenous (IV) infusion, oral immediate release (IR) formulations, modified release dosage forms and also for food-drug interaction studies reported in the literature. Such performance verification of the model for the doses/formulations from clinical studies other than the ones that used in IVIVC establishment, help to ensure that the developed PBPK model is robust and improves confidence in predictive performance of the model for new dissolution profiles.

The PB-IVIVC approach resulted in a simple linear correlation. When observed *vs.* IVIVC predicted plasma concentration plots were compared, the scatter of data points was found narrower with all formulations, distributed uniformly around line for the PB method with R^2 value of 0.966 against 0.946 of that of ND method. The maximum APPE (MAPPE) using PB-IVIVC were 7.7% (Cmax) and 9.2% (AUC) vs. 13.5% (Cmax) and 12.6% (AUC) obtained by the conventional ND method[4]. The predicted PK profile of the slower formulation over-estimated exposure with the ND method whereas the PB-IVIVC based method, due to consideration of physiologically relevant GI residence time, was much more predictive. This is also reflected in higher APPE for AUC 10.4% against 8.4% of PB-IVIVC. The reported ND method did not demonstrate the validity of the model with external dataset. The external validation of the PB-IVIVC based model was undertaken and resulted in less than 10% APPE for C_{max} and AUC.

CONCLUSION

The PB-approach improved the predictive performance of the IVIVC model and resulted in a simpler linear IVIVC. More case studies with various drugs and different formulations needs to be generated to spread awareness of the PB-IVIVC approach and improve confidence in such methodology.

REFERENCES

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