

Development and Validation of an *In Vitro* and *In Vivo* Correlation Model in the Rabbit for Topiramate Extended Release Capsules

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Laxman, *et al.*: IVIVC of Topiramate Extended Release Capsule

The purpose of this study was to build an *in vitro-in vivo* correlation model for topiramate extended release capsules. Three formulations with different release rates were developed by varying the percent content of the rate controlling polymer ethyl cellulose and pore former hypromellose. *In vitro* dissolution of all formulations was performed by United States Pharmacopeia type I apparatus using multimedia dissolution conditions such as 0.1 N hydrochloric acid pH 1.2 for initial 2 h followed by phosphate buffer pH 6.8 for the rest of 22 h. Total dissolution time was up to 24 h. *In vivo* pharmacokinetic profile of the immediate release suspension and different extended release formulations were investigated in a rabbit model after single oral administration of topiramate at a dose of 10.33 mg/kg. An *in vitro-in vivo* correlation model was established by using two-stage numerical deconvolution approaches. Unit impulse response was obtained from pharmacokinetic profile of immediate release suspension which was used as a reference formulation. A linear correlation model with a time scaling factor was found to be useful to build level A correlation. The developed *in vitro-in vivo* correlation model was validated as per Food and Drug Administration guideline and the % prediction error for maximum concentration observed (C_{max}) and area under the concentration time curve was within acceptable limits of below 15%. The utility of the developed model was evaluated by testing the targeted formulations. The observed % prediction error was 2.61 and -0.43 for C_{max} and area under the concentration time curve, respectively suggesting the usefulness of the present *in vitro-in vivo* correlation model.

Key words: Topiramate, extended-release capsule, *in vitro-in vivo* correlation

Topiramate (TPM) is a second generation broad spectrum antiepileptic drug used in the treatment of a migraine, tonic clonic seizures and partial seizures^[1,2]. The usual therapeutic dose of TPM was 50-400 mg divided in twice/day basis. The once a day extended release (ER) formulation was developed to reduce dose frequency, maintain steady plasma levels, minimize the concentration-related adverse effects and better accumulation ratio for effective management of antiepileptic therapy^[3]. Lambrecht *et al.* reported smaller peak trough ratio for TPM-ER formulation than twice a day immediate release (IR) formulation suggesting that plasma peak trough variation could be reduced by using once a day ER formulation^[4].

Often, the development of ER formulation with desired dissolution and plasma concentration profiles is time

consuming and costly. *In vitro-in vivo* correlation (IVIVC) enlighten the mathematical relationship between an *in vitro* release of a dosage form and relevant *in vivo* response which will reduce the number of *in vivo* trials^[5]. IVIVC for TPM tablets were reported earlier at the clinical level^[6]. During the initial ER formulation development, IVIVC using a preclinical animal model would be beneficial in the speedy development of bioequivalent formulation at low cost. Numerous reports were available for applicability of preclinical animal species for testing IVIVC such

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as Beagle dogs for propranolol ER tablets^[7]; rats for exenatide microspheres^[8]; rabbits for glipizide tablets and flurbiprofen capsules^[9,10] and cynomolgus monkey for RO-X tablets^[11]. Among the preclinical animal models reported, rabbits were easy to handle, convenient for the administration of solid dosage forms and cost-effective animal model. Previous reports were also suggested the better correlation between the rabbits and humans for rank order of maximum concentration (C_{max}) and area under curve (AUC) of different formulations^[12]. Thus, the present work was aimed to establish rabbit as a preclinical animal model for IVIVC of TPM.

Three different ER formulations of TPM were developed and optimized as per FDA guideline in order to establish a level of correlation. Further, these ER formulations were subjected for *in vitro* dissolution studies. The *in vivo* release profile was accomplished by using preclinical pharmacokinetic studies in New Zealand (NZ) rabbits. Finally, the obtained fraction of drug dissolved was correlated to a fraction of drug absorbed by using suitable linear correlation model, which could be useful to accelerate the development of generic formulations of TPM. Once IVIVC model was developed, it was also used to check the percentage (%) variation limit allowed in the dissolution of marketed formulation.

MATERIALS AND METHODS

TPM (purity $\geq 98\%$), diclofenac (internal standard, IS), ethylcellulose and hypromellose were purchased from Sigma Aldrich, St Louis, MO, USA. HPLC grade methanol, *n*-hexane, ethyl acetate and formic acid were purchased from Merck Pvt. Ltd. (India). Ultrapure water was collected from a Milli-Q PLUS PF water purification system.

Analytical and bioanalytical method development of TPM:

To estimate TPM concentration in dissolution media and plasma, a liquid chromatography-mass spectrometry (LC-MS/MS) method was developed. API 3200 mass spectrometer (Applied Biosystems, MDS Sciex, Toronto, Canada) coupled with a Waters HPLC system (Milford, USA) consisted of a quaternary pump (600), auto sampler (717) was utilized for analysis. The chromatographic separation was achieved on Waters Symmetry-Shield C_{18} column (5 μ , 4.6 \times 150 mm) using methanol: 0.1% formic acid (95:5 v/v) as the mobile phase at a flow rate of 0.75 ml/min.

The LC-MS/MS system was operated with an electrospray ionization (ESI) source in negative polarity mode. The most abundant fragment ions of (m/z 338.16/77.96) and diclofenac (IS) (m/z 294.00/250.00) were chosen in the MRM acquisition for better sensitivity and selectivity. Compound-dependent parameters such as declustering potential -90 and -16 V; entrance potential -10 and -8 V; collision energy -70 and -10 eV and collision cell exit potential -10 and -20 V were set for TPM and diclofenac, respectively. All raw data were processed with PE SCIEX analyst software (Version 1.4.2) from applied biosystems.

Calibration standards were prepared by spiking 10 μ l of working stocks solution into 90 μ l of rabbit plasma or dissolution media to obtain a concentration range of 6.25-1600 ng/ml. The quality control (QC) samples of four different concentrations (6.25, 15, 300, 1400 ng/ml) *viz.*, lower limit of quantification (LLOQ), low quality control (LQC), middle quality control (MQC) and high quality control (HQC), were prepared in five replicates.

Liquid-liquid extraction method was used for extraction of analytes from rabbit plasma or dissolution media. Plasma or dissolution samples (100 μ l) were taken in 5 ml polypropylene tubes, then 10 μ l of IS (2 μ g/ml final concentration) was spiked into the tubes and mixed on cyclomixer (Spinix Tarsons, Kolkata, India) for 15 s. After that 3 ml of extraction solvent (*n*-hexane and ethyl acetate, 50:50 v/v) was added. The samples were then vortexed and centrifuged for 10 min at 4000 rpm at 5° by Sigma 3-16K (Frankfurt, Germany) centrifuge. The organic layer (2.5 ml) was collected and evaporated to dryness under vacuum in SpeedVac concentrator (Savant Instrument, Farmingdale, USA). The dried residue was reconstituted with 100 μ l of methanol followed by vortexing for 30 s. The samples (20 μ l) were injected through an auto sampler into the LC-MS/MS system for analysis.

Development of different formulations of TPM:

The development of IVIVC correlation requires two or more formulation with different release rates. Three preliminary prototypes of ER granules FS-01 (slow), FM-05 (medium) and FF-08 (fast) were developed with different concentrations of the rate controlling polymers ethylcellulose and hypromellose. The formulated ER granules were filled in capsules. The 0.5% w/v, carboxymethyl cellulose (CMC) suspension of TPM was used as reference IR treatment. The marketed Trokedni XR-200 mg ER capsules (manufactured

by Catalent Pharma Solutions) were used as targeted formulation.

***In vitro* dissolution study:**

The *in vitro* release behavior of ER TPM capsules were studied using USP type I apparatus, i.e., the basket method rotating at 100 rpm. The TPM capsules were placed in 900 ml of dissolution media (0.1 N HCl, pH 1.2 for two hours, followed by phosphate buffer, pH 6.8) and maintained at 37°. The dissolution samples (10 ml) were collected at the predetermined time intervals up to 24 h and filtered through membrane filter (0.45 µm). The drug was extracted from the dissolution media by using earlier explained LLE method. LC-MS/MS was used to quantify the amount of drug released. At least six capsules of each formulation were accomplished to calculate the mean and standard deviation (SD) of % dissolved.

Dissolution profiles of the three ER formulations were subjected to similarity factor (f_2) test. According to FDA guideline, *in vitro* release rates of different formulations should differ by at least 10% for IVIVC. When dissolution profiles shows 10% average difference then it gives $f_2=50^{[13]}$. We require the f_2 value below 50 to discriminate *in vitro* release profiles^[14,15]. *In vitro* dissolution data were analyzed using Hill, Weibull, double Weibull and Makoid-Banakar models. Different dissolution models were evaluated based on the various criteria including closeness of the fit between observed and predicted value coefficient of variation of the estimated parameters for all models akaike information criterion (AIC) and Schwarz's Bayesian criterion (SBC) for representation of goodness of fit plot of observed fraction dissolved vs. predicted fraction dissolved for the percent prediction error (%PE) in the validation of the IVIVC model.

***In vivo* pharmacokinetic study:**

Per oral pharmacokinetic studies were performed in male NZ rabbits. The study was conducted in accordance with current legislation on animal experiments as per Institutional Animal Ethics Committee at CSIR-Central Drug Research Institute (IAEC approval no IAEC/2014/155). Previously rabbit has also been used as a preclinical animal model for TPM pharmacokinetic studies^[16]. The rabbits were housed in restraining cages and kept in hygienic conditions at a temperature of 23-25°, relative humidity of 50-70% and 12-12 h light-dark cycle. Prior to the experiment, rabbits were fasted overnight (12 h) with free access to

water. The rabbits were divided into the five different groups based on the administered formulations (n=3, in each group, weight range 2.5-3.2 kg): group-A, slow release formulation FS-01; group-B, medium release formulation FM-05; group-C, fast release formulation FF-08; group-D, marketed formulation and group-E, 0.5% w/v CMC suspension of TPM. Capsules filled with TPM granules were administered orally at a dose of 10.33 mg/kg body weight to rabbit followed by distilled water to swallow the capsule. For reference treatment, 0.5% w/v CMC suspension of TPM was administered to rabbits. In all cases, the same dose strength was given to the rabbit. Blood samples (0.4 ml) were collected from the marginal ear vein of each rabbit in heparinized microcentrifuge tubes at 0.25, 0.5, 0.75, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 12.0, 24.0, 48.0, 72.0 and 96.0 h post dosing. Plasma was collected by centrifuging the blood samples at 4000 rpm for 10 min and stored at -70±10° until the analysis.

Development of IVIVC model:

IVIVC was performed in various stages including the development of correlation model, validation of the model and utilization of the same for *in vivo* prediction of targeted formulation. The present work is based on the two-stage numerical deconvolution method. It involves the deconvolution in first stage to explore the time course of *in vivo* absorption. In the second stage, correlation was built between the *in vitro* drug release and *in vivo* drug absorption. In current study unit impulse response (UIR) is generated by using oral pharmacokinetic profile of TPM suspension^[17]. Three preliminary formulations FF-08, FM-05, FS-01 were considered for the building of IVIVC model. Fraction of drug absorbed was estimated using the 'deconvolution through convolution' method (WinNonlin IVIVC Toolkit™, Version 6.3, Pharsight, CA, USA) from the observed pharmacokinetic profile for each formulation. The IVIVC model was developed by using a fraction of the drug absorbed and that of a fraction of drug dissolved. On the basis of developed IVIVC model, predicted fraction of drug absorbed was estimated from the observed fraction of drug dissolved^[18]. Levy plot was considered as a primary attempt for selection of correlation model. Two levy plots were considered during a model development, i.e., fraction of drug absorbed (Fabs) vs. fraction of drug dissolved (Fdis) and *in vivo* absorption time (T_{vivo}) vs. *in vitro* dissolution time (T_{vitro}). In order to attempt level A correlation, the following linear correlation models were applied. Model 1: $Fabs=AbsScale \times Diss$, Model

2: $F_{abs} = AbsScale \times Diss (T_{scale} \times T_{vivo})$, Model 3: $F_{abs} = AbsScale \times Diss (T_{scale} \times T_{vivo} - T_{shift})$, Model 4: $F_{abs} = AbsScale \times [Diss(T_{scale} \times T_{vivo} - T_{shift}) - AbsBase]$.

These models take consideration of time scaling factor (T_{scale}), absorption scale factor ($Abs\ Scale$), time scale shift (T_{shift}) and absorption baseline ($AbsBase$). Selection of the model was based on the consideration of multiple parameters including the Akaike information criteria (AIC) and Schwarz's Bayesian criterion (SBC), correlation coefficient (R^2), the fit between observed and predicted value, %PE limit for internal validation as per FDA.

Validation and prediction of IVIVC model:

The IVIVC model can be validated by using the internal and/or external predictabilities. The internal predictability involves the use of the same formulation to define the IVIVC model^[15]. In this study, FM-05 and FF-08 were used as internal formulation. Additional formulation FS-01 with different release rate was prepared for external predictabilities. The %PE (Eqns. 1 and 2) of the IVIVC model was calculated with respect to maximum concentration observed (C_{max}) and area under the concentration time curve (AUC). FDA regulatory guidance suggests that the %PE values for C_{max} and AUC should be less than $\pm 15\%$ for each formulation and below $\pm 10\%$ for the average. The application of the established IVIVC model was evaluated by the prediction of targeted formulation. Eqns.: %prediction error (PE) for $C_{max} = \frac{C_{max}(observed) - C_{max}(predicted)}{C_{max}(observed)} \times 100$ and %prediction error (PE) for $AUC = \frac{AUC(observed) - AUC(predicted)}{AUC(observed)} \times 100$.

Evaluation of IVIVC for simulated dissolution profiles:

The simulation of dissolution profiles was carried out for the marketed formulation to check variation window allowed for dissolution. Dissolution profiles for marketed formulation were simulated in both ways, i.e., increase or decrease of 1, 3, 5, 7, 9 and 11% fraction of dissolution from the marketed formulation. These simulated dissolution profiles were tested for the $\pm 10\%$ PE bounds as per FDA guidelines for C_{max} and AUC.

Bioequivalence testing for the simulated profiles:

The simulated dissolution profiles of the marketed formulation were prepared by varying the fraction of dissolution by 5, 11, 17, 20 and 25% in either ways, i.e., increase or decrease. The developed IVIVC model was utilized to predict the *in vivo* performance of these

simulated dissolution profiles. Bioequivalence was tested between the simulated and marketed *in vivo* profiles.

RESULTS AND DISCUSSION

Accuracy and precision were within acceptable limits for the developed LC-MS/MS method. The recovery of analytes was calculated from the spiked plasma samples of QCs. The absolute mean percent recoveries were 70.92 ± 2.60 , 74.82 ± 4.04 and 73.66 ± 3.64 , respectively at LQC, MQC and HQC concentrations. Negligible matrix effect was observed as the calculated concentrations were within acceptable range of $< \pm 15\%$ (106.1 to 108.3%). Therefore, ion suppression or enhancement from rabbit plasma was negligible.

The similarity factors (f_2) of FM-05 vs. FF-08, FM-05 vs. FS-01, and FS-01 vs. FF-08 formulations were 49, 47 and 35, respectively. These values indicated that the dissolution profiles were sufficiently diverse to proceed for IVIVC. Observed raw data for dissolution did not show any lag time (fig. 1). Hill, Weibull, double Weibull and Makoid-Banakar models were evaluated for parameterizing the dissolution data. Hill equation was finalized on the basis of low AIC-105.84, low SBC-102.43 and good R^2 0.9980 compared to the other dissolution model (Table 1). Hill Eqn. 3 parameterizes dissolution profile better than other models, indicates the probability of sigmoidal cumulative drug release profile. Fig. 2 shows how good the observed dissolution data correlates with predicted data. Eqn. 3:

$$F_{d\ pred}(t) = \frac{Fd, \infty t^\alpha}{MT_d^\alpha + t^\alpha}$$

Where, M_d^α Mean dissolution time, α -Exponent

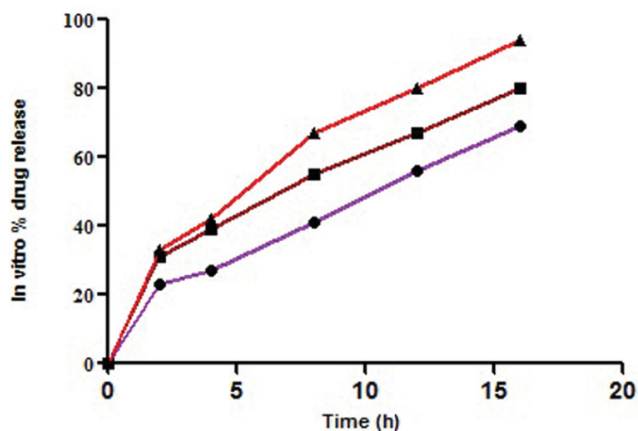


Fig. 1: Mean *in vitro* dissolution profiles of TPM ER formulations.

-●- FS-01, -■- FM-05, -▲- FF-08

referred as slope or sigmoidity factor $F_{d,\infty}$. The amount of drug released at time infinity.

The mean dissolution time (M_d^a) for FS-01, FM-05, FF-08 and marketed (MKT) formulation was found to be 65.17, 39.46, 27.21 and 24.30 min, respectively. Fraction dissolved at infinity ($F_{d,\infty}$) has the value of 2.48, 2.15, 2.32 and 1.90 for FS-01, FM-05, FF-08 and MKT, respectively.

The *in vivo* pharmacokinetic profile for slow, medium and fast ER formulation was shown in fig. 3. Specific rank orders for these formulations were maintained same as *in vitro*. Therefore the data were fulfilled the primary requirement for assessment of IVIVC. Ideally, for generating unit impulse response (UIR), i.v. bolus as reference data is preferred because it did not show any absorption phase. In the current context, we used IR suspension as reference data, so it requires the elimination of absorption phase, which was done by ‘strip K_a ’ option^[18]. Then the obtained UIR is representative of only disposition kinetic. Polyexponential Eqn. 4 gives average UIR of the IR data without ‘strip K_a ’. This equation has absorption as well as disposition component. Maziar kakhi *et al.* reported an Eqn. 5 with the assumption of first-order absorption process which describes only disposition

phase of the pharmacokinetic profile (‘stripping K_a ’). UIR will now explains hypothetical dose normalized i.v. bolus data and it always remains positive^[18]. The obtained pharmacokinetic parameters for reference formulation were presented in Table 2. UIR values obtained from polyexponential Eqn. 5 were well fitted with observed IR *in vivo* pharmacokinetic profile (fig. 4). Eqns. 4 and 5:

$$g_{IR}(t) \text{ without strip } K_a =$$

$$H(t-t_{lag}) D \sum_{i=1}^n A_i e^{-\beta_i(t-t_{lag})}$$

$$g_{IR}(t) \text{ with strip } K_a =$$

$$H(t-t_{lag}) K_a D \sum_{i=1}^n \frac{B_i}{\lambda_i - K_a} \left[e^{-K_a(t-t_{lag})} - e^{-\lambda_i(t-t_{lag})} \right]$$

Where, g_{IR} -unit impulse response (UIR) (ng/ml), A_i -

TABLE 1: SUMMARY OF MODEL PERFORMANCE AND SELECTION FOR MEAN *IN VITRO* DISSOLUTION PROFILES OF TOPIRAMATE ER CAPSULES

Model	Parameter		
	AIC	SBC	Weighted correlation (R^2)
Hill	-105.84	-102.43	0.9980
Weibull	-105.79	-101.86	0.9979
Double Weibull	-99.09	-92.27	0.9979
Makoid-Banakar	-104.00	-100.60	0.9978

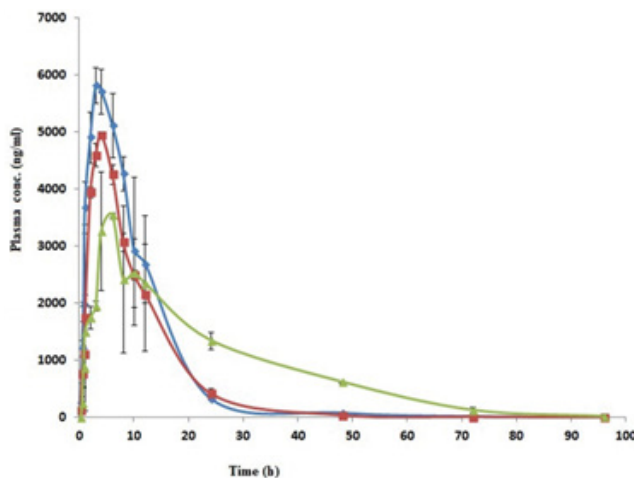


Fig. 3: Mean *in vivo* plasma concentration time profiles of TPM after single oral administration. Single oral administration of TPM ER formulations -♦- FF-08, -■- FM-05, -▲- FS-01

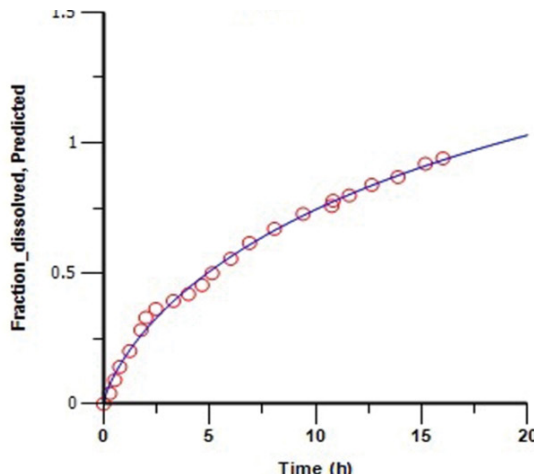
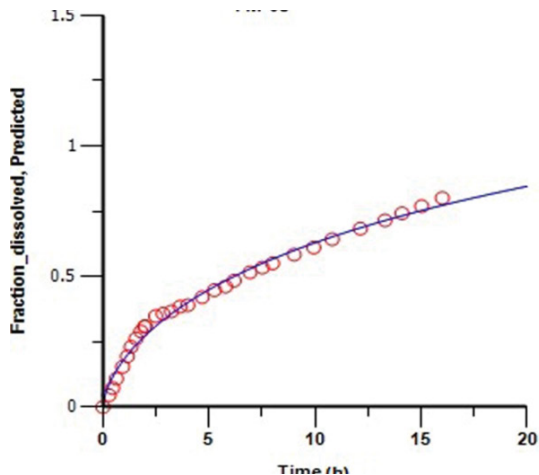


Fig. 2: *In vitro* dissolution model fitting of TPM ER formulations. o Observed ; — predicted

TABLE 2: SUMMARY OF PARAMETERS FOR OPTIMIZED IVIVC MODEL AND IR REFERENCE FORMULATION

	Parameter	Estimate	Standard error	% coefficient of variation (CV)	95% CI (lower-upper)
Optimized IVIVC model	AbsScale	1.69	0.0036	0.21	1.684-1.698
	Tscale	1.71	0.0303	1.77	1.648-1.768
IR reference formulation	Ka	1.53	0.22	15.00	1.03-2.02
	A1(ng/ml)	764.54	59.63	7.80	635.71-893.3
	Alpha (1/h)	0.20	0.25	12.55	0.146-0.255

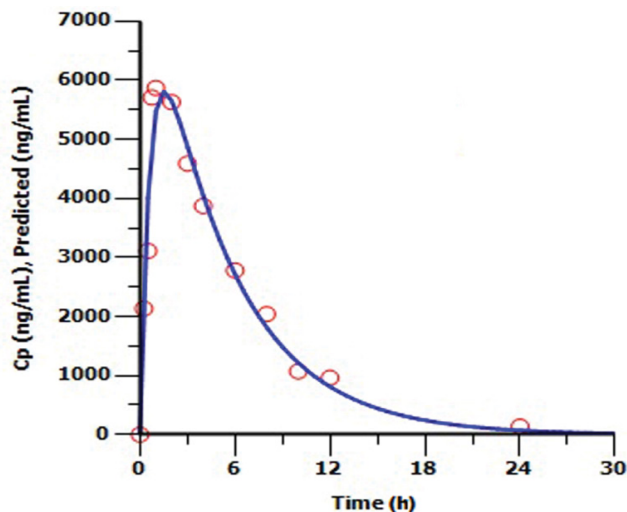


Fig. 4: Polyexponential fit of average UIR.

○ Observed ; — predicted

pre exponential coefficient in polyexponential model for IR data (ml^{-1}), B_1 -pre-exponential coefficient in the polyexponential model for hypothetical dose normalized i.v. bolus data (ng/ml), D-Dose, H-Heaviside step function, B_1 and λ_1 : exponent in polyexponential UIR of IR data and dose normalized i.v. bolus data, respectively. K_a : first-order absorption rate constant ($\text{ml}/\text{ng}\cdot\text{h}$) t_{lag} : initial time lag (h).

Levy plot of F_{diss} vs. F_{abs} gives preliminary information about which correlation model should be considered for IVIVC^[19,20]. Levy plot (fig. 5) shows the deviation of the data points from the regression line, therefore AbsScale should be utilized to minimize this deviation. Levy plot of T_{vitro} vs. T_{vivo} (fig. 6) shows time taken for a percentage of dissolution and the same percentage of absorption. Visual observation of this plot reveals the need of time scaling in correlation model for time correction. Linear correlation models mentioned earlier were screened for all formulations. AIC and SBC criteria help to choose the best model for efficiently exploring the *in vitro-in vivo* correlation by giving the quality of each model in comparison with other. AIC and SBC value for model 2 were low as compared to another model, i.e., -168.40 and -161.78 which indicates the goodness of fit (Table 3). Regression for model 3 and model 4 was better than

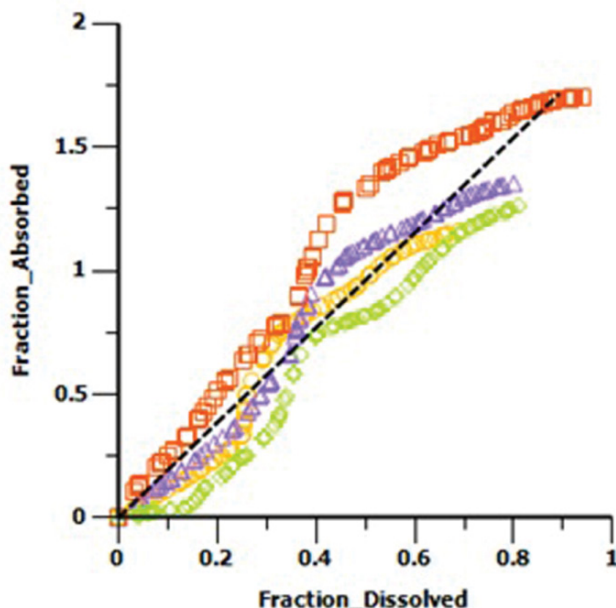


Fig. 5: Levy plot of fraction dissolved vs fraction absorbed for TPM formulations.

$R_{\text{sq}}=0.9728$, intercept=0, Slope=1.923, levy plot; ● F_{abs} vs F_{diss} FS-01; ▲ F_{abs} vs F_{diss} FM-05; ○ F_{abs} vs F_{diss} FF-08; ◆ F_{abs} vs F_{diss} targ; ---- regression

the model 2. But, only regression criteria will not make them superior models. The additional criterion considered was %PE for C_{max} and AUC. Except model 2, remaining models failed either internal validation or prediction. *In vivo* dissolution cut-off time (T_{cutoff}) was not considered for the development of model because mean t_{max} was less than 24 h for all formulation. Linear correlation model 2 with the time scale (T_s) and absorption scale (A_s) were finalized to build IVIVC model. The obtained value of A_s (1.69) and T_s (1.71) were used to build the IVIVC (Table 2) Eqn. 6.

$$F_{a \text{ pred}}(t_{\text{vivo}}) = [(1.69)F_{d \text{ pred}}] [(1.71)t_{\text{vivo}}]$$

Where $F_{a \text{ pred}}$ -the predicted counterpart of $F_{a \text{ obs}}$, $F_{d \text{ pred}}$ -the predicted fraction dissolved.

The %PE of C_{max} and AUC for internal and marketed formulation were shown in Table 4. The average %PE for the all internal formulation was below 10%, satisfying the internal validation criterion. Fig. 7 shows the plot of observed and predicted TPM plasma

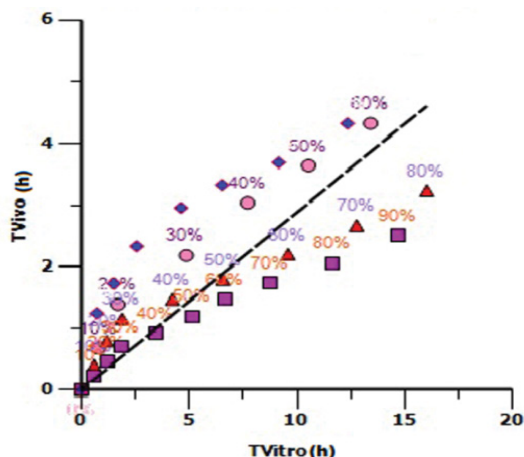


Fig. 6: Levy plot of *in vitro* versus *in vivo* times for a given fraction absorbed or dissolved from TPM formulations. $R_{sq}=0.05651$, intercept=0, slope=0.2883, levy plot, ● FS-01; ▲ FM-05; ■ FF-08; ◆ targ

TABLE 3: SUMMARY OF LINEAR CORRELATION MODELS

Parameters	Model-1	Model-2	Model-3	Model-4
R2	0.9428	0.9869	0.9870	0.9871
AIC	905.94	-168.40	-166.42	-166.34
SBC	912.55	-161.78	-156.50	-153.11

TABLE 4: PREDICTION ERRORS (%) ASSOCIATED WITH C_{max} AND AUC FOR INTERNAL TPM ER FORMULATIONS AND MARKETED FORMULATION

Formulation	C_{max}	AUC
% PE for internal formulation		
FM-05	-6.64	1.99
FF-08	-12.82	0.62
Average of internal formulation	9.73	1.31
% PE for marketed formulation		
Marketed formulation	2.61	-0.43

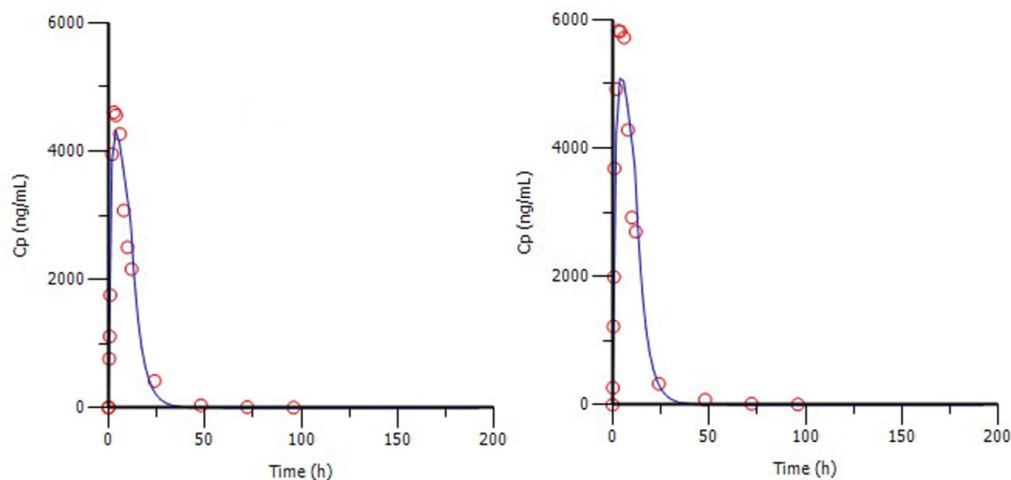


Fig. 7: Mean observed and predicted TPM plasma concentrations versus time profiles. (A) FM-05 and (B) FF-08, observed values represented by symbols and predicted by solid line

concentrations for the formulation FM-05 (fig. 7A) and FF-08 (fig. 7B). It indicates the good correlation between observed and predicted value, suggesting the better model fitting. Although formulation FF-08 shows comparatively high %PE for C_{max} , i.e., -12.82, it satisfies the FDA requirement of individual %PE (below 15%). The formulation FS-01 gave the high %PE of -36.32 for AUC value so it was not considered for validation. The targeted formulation was utilized to verify the usefulness of the validated model. Initially, *in vitro* dissolution profile of the targeted formulation was fitted into the Hill dissolution model which was used to build IVIVC model. Fig. 8 shows the observed F_{diss} values were close to the predicted values indicating that Hill model was suitable to fit the dissolution data. IVIVC models were then applied to predict the pharmacokinetic profile of targeted formulation. Fig. 9 shows model predicted pharmacokinetic profile which was very close to the observed pharmacokinetic

profile indicating the applicability of the model. The %PE of targeted formulation for C_{max} and AUC was found to be 2.61 and -0.43 (within acceptable limit). The established IVIVC level A correlation confirms the usefulness of proposed IVIVC model. Level A correlation is quite imperative since it represents a point to point correlation between *in vitro* dissolution and the *in vivo* input rate of the drug from the formulation^[21].

The developed IVIVC model could also predict *in vivo* profile of targeted formulation in initial stage so as to decline the failure rate of bioequivalence. This preclinical pharmacokinetic approach might be useful for the initial stages of development of ER formulation where several numbers of trials were required to set the formulations for IVIVC. If these trials were performed in animals, then it will ultimately reduce the optimization trials, human use, cost, as well as time.

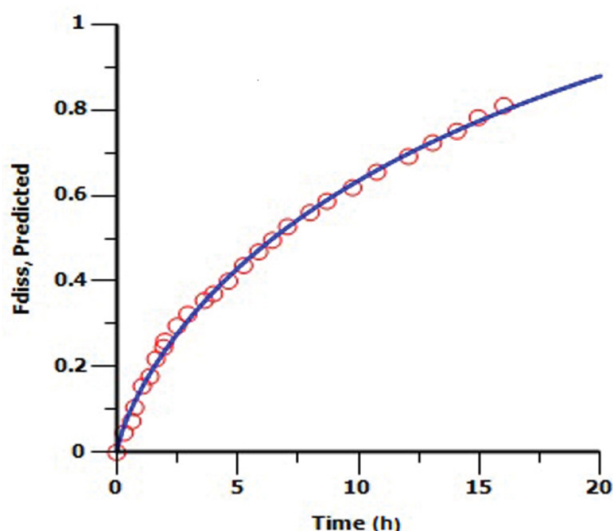


Fig. 8: *In vitro* dissolution profile of targeted formulation.
 ○ Observed ; — predicted

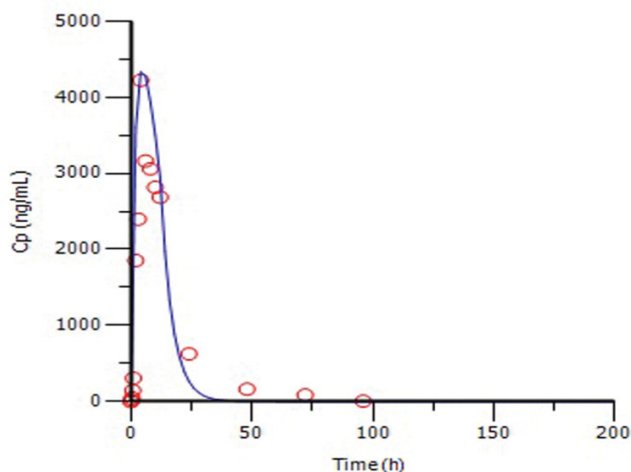


Fig. 9: The plot of observed and IVIVC model predicted profile of marketed formulation.
 ○ Observed ; — predicted

IVIVC for simulated dissolution profiles of the marketed formulation were evaluated for the %PE by using the developed IVIVC correlation model. The result suggests that as the % variation in the fraction dissolution increases or decreases the %PE for C_{max} and AUC also changes. It was observed that up to 7% change in the fraction dissolution, %PE passes the FDA criteria for $\pm 10\%$. Above the 7% variation in the marketed dissolution profile, %PE for C_{max} and AUC fall outside the error bound of $\pm 10\%$. So the presented IVIVC correlation model allowed the $\pm 7\%$ of variation window in the fraction dissolution of marketed formulation.

Bioequivalence was observed up to 17% changes in the fraction dissolution of marketed formulation. Above

20% change in the fraction dissolution, it fails to show the bioequivalence to the marketed formulation.

In conclusion, the present work established a preclinical IVIVC model for TPM extended release capsules. A mathematical model with time scaling factor found helpful to perform IVIVC, which could be used as preliminary information for further development in clinical IVIVC. Hill equation was found suitable for parameterization of *in vitro* dissolution data. Deconvolution through convolution approach was used to build level A correlation which might be expected in human. It was also observed that targeted formulation was fitted in the proposed IVIVC model with acceptable %PE of 2.61 and -0.43 for C_{max} and AUC. These studies were also provided the setup of a preclinical pharmacokinetic animal model for IVIVC. Further, with the help of the physiological-based pharmacokinetic modelling and *in vitro-in vivo* extrapolation methods, preclinical pharmacokinetic profile of different formulations could be extrapolated to humans^[22,23]. Finally, the preclinical IVIVC of TPM would provide cost reduction in formulation development as the numbers of trials for expected *in vivo* profile were reduced due to simulated IVIVC model. The presented preclinical IVIVC of once daily extended release capsule gives expected *in vivo* release; however, further studies in human were needed to prove the utility of the developed model. This model also proved useful to set the limit of variation in the dissolution.

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