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Development and execution of a novel strategic statistical tool to determine *in-vitro in-vivo* correlation for sustained release capsules of metoprolol tartrate in humans

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The aim of this present study was to develop and formulate sustained release coated metoprolol tartrate matrix granules and to design an in-vitro in-vivo correlation (IVIVC) tool based on bioavailability data available from human volunteers. USP apparatus II, paddle type was used for generation of in-vitro drug release data for each formulation. The similarity factor (f2) was determined using dissolution data parameters of the formulations. Twenty-four healthy male volunteers participated in the two-way crossover bioequivalent study where the volunteers were treated in a completely randomized fashion. The percent drug dissolved in the dissolution test and percent absorbed data shows a 'level A' IVIVC was achieved with a good linear regression relation. Different release rate formulation including Fast, Moderate and Slow release formulations exhibited an excellent covenant between the three dosage forms.

Key words: Sustained-release capsules, metoprolol tartrate, bioavailability, in-vitro in-vivo correlation (IVIVC), humans.

INTRODUCTION

An *in-vitro in-vivo* correlation (IVIVC) has been distinctly explained by United States Pharmacopoeia (USP, 1998) and the Food and Drug Administration (FDA). The definition has been described as "a predictive mathematical model describing the relationship between an *in-vitro* property of a dosage form and *in-vivo* response" (Center for Drug Evaluation and Research [CDER], 1997). Designing an IVIVC for an extended-release tablet is a salient feature to facilitate formulation development and serves as a tool in quality control during

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pharmaceutical product manufacture. The formulation scientist typically uses IVIVC tests to determine lot-to-lot variability, and shelf life of the formulation. In addition, the formulation can be used to predict *in-vivo* absorption (that is, bioavailability) of the drug after minor modification in formulation development processes (Jerome et al., 1990). A properly designed IVIVC could substantially enhance product quality (Russell, 1997). The *in-vitro* dissolution curve is usually produced by an appropriate dissolution test and in-vivo absorption parameters are frequently measured by deconvolution technique using various established model (e.g. Wagner-Nelson or Loo Regelman) or model-independent (e.g. DeMons) methods (USP Subcommittee on Biopharmaceutics, 1988; Gibaldi et al., 1982). Different types of *IVIVC* levels correlation have been also explained by the FDA (FDA, 2017). The most important and useful of these is Level A correlation. Generally, this kind of correlation is linear and considered as most useful from a regulatory perspective. The FDA guidance explains the various procedures of assessment of prediction error internally and externally. Internal validation indicates how well the model can be used to determine the correlation. In case of External validation, IVIVC model can be used for the formulation which was not used in the development of that particular model (CDER, 1997; Mandal et al., 2007).

Validated IVIVC model, and thus, classification of bio relevant dissolution procedure can help in reducing the number of human volunteers during the formulation development of generic formulations, their final approval by the various agencies, and various post-approval changes (Ziad and Michael, 1990). Determining a correlation between the *in-vivo* drug absorption data and *in-vitro* dissolution release data of a sustained release formulation is an important criterion for drug development. For this reason, IVIVC can be used for the of various extended-release dosage forms Grbic et al., 2011).

In the present study, matrix granules with various rate of release of MT have been prepared using various combinations of HPMC and EC as core matrix. Eudragit® RL and RS in different ratios were selected to coat the granules. Hence, the idea of this study was to develop an IVIVC for three matrix sustained release MT capsules. The validity of the correlation was determined through the concept of external predictability.

MATERIALS AND METHODS

Metoprolol tartrate (around 98 to 101% purity) was received as donation sample from Torrent Laboratories, India. Other excipients, hydroxy propyl methyl cellulose (HPMC K100M), Ethyl Cellulose (EC) (Ethocel*FP Premium, 7 cps viscosity grade), HPMC E5 and dicalcium phosphate (DCP), Eudragit® RS and RL were given as gift sample by Dhara Life Science Pvt. Ltd. India. All belonged to standard of Pharmacopoeial grade (USP/NF). Acetonitrile (HPLC grade) and methanol (HPLC grade) were procured from M/s. Qualigens Fine Chemicals, Mumbai, India. Immediate release tablets of metoprolol tartrate (Metolar 25 tab) were purchased from Cipla limited, India. Acetonitrile (HPLC grade) and methanol (HPLC grade) were procured from M/s. Qualigens Fine Chemicals, Mumbai, India. Immediate release tablets of metoprolol tartrate (Metolar 25 tab) were purchased from Cipla Ltd., India.

Development of formulations and study of dissolution

Three capsules formulation filled with three different release fast (C1-F), moderate (C1-M) and slow (C1-S) SR coated granules containing 100 mg metoprolol tartrate were formulated and developed by using three different ratios of HPMC K100M, ethyl cellulose, dicalcium phosphate by the technique of wet granulation methodology followed by coating with three different range of Eudragit® RS/RL at concentration 25% coating level. These formulations were designed to release metoprolol tartrate at three distinct rates reflected moderate, slow, and fast as described subsequently. Different batches of granules (C1-F, C1-M and C1-S) were formulated with the composition shown in Table 1. Proportion of release retardant (HPMC K100M, ethyl cellulose) was increased in C1-M and C1-S subsequently to obtain fast, medium and slow release of the drug. DCP was used as filler and it was added in decreasing proportion to adjust the weight of increasing proportion of release retardants in these three formulations. All the ingredients were mixed in a double cone blender for 15 min. HPMC E5 (7.5%, w/w) solution was mixed properly to the powder mixture as binder to form a lump. The granules were obtained after passing through sieve (12 mesh size) and then dried adequately at 60°C for 30 to 45 min. The dried granules were then passed manually through 12 mesh screen to remove the lump. The matrix granules in particle size range of 14 to 20 mesh was selected for coating.

The next step granules were first spray coated (5% weight-gain) with an aqueous ethanolic solution of HPMC K100M to form intermediate layer. These granules were again coated with blends of Eudragit® RS and RL along with plasticizer, triethyl citrate (5% w/w) in a fluidized bed coater with different ratios to obtain formulations with different release rate. All the dispersions were plasticized overnight. The process parameters were as follows: preheating temperature 35°C for 2 min, inlet temperature 35 to 40°C, outlet temperature 32 to 34°C, product temperature of 32±2°C, spray rate 2 to 3 g/min, atomization pressure 1.2 bar, nozzle diameter of 1.2 mm, volumetric flow rate of air 100 m^3/h. After coating, the granules were fluidized for 10 min and subsequently cured for 24/48 h at 40°C and 15% relative humidity. They were sieved with 12 to 22 mesh to remove both agglomerate and fine powder (Sabahuddin et al., 2010).

These formulations were designed (Table 1) to release metoprolol tartrate at three distinct rates reflected moderate, slow, and fast (Sabahuddin et al., 2010). The composition of different type of formulation to give different range of release pattern is shown in Table 1.

In vitro drug release study

The drug release properties of the moderate, slow, and fast formulations were evaluated by the following dissolution testing methodologies USP apparatus I, pH 0.1(N) HCL at 50 rpm. Dissolution test was studied on six tablets and the quantity of drug released was calculated by validated reverse phase high performance liquid chromatography (HPLC) method at 223 nm. All dissolution samples were analyzed at the following times: 0, 0.5, 1, 2, 2.5, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 12, 18 and 24 h. Figure 1 shows release characteristics of moderate, slow, and fast release formulations.

Dissolution profiles were constructed and were compared by the determination of similarity factor (f_2) according to equation of Henry

Table 1. Composition of fast, medium and slow release formulations of metoprolol tartrate 100 mg.

Composition	Formulations					
Matrix ingredients	C1-F		C1-M		C1-S	
	%	Amount (mg)	%	Amount (mg)	%	Amount (mg)
MT	20	100	20	100	20	100
HPMC K 100M	20	100	25	125	30	150
Ethyl cellulose	20	100	25	125	30	150
DCP	32.5	162.5	22.5	112.5	12.5	62.5
HPMC E5	7.5	37.5	7.5	37.5	7.5	37.5
Coating ingredients*						
HPMC K 100M	5	25	5	25	5	25
Eudragit® (RS+RL)	25	(115+10)	25	(118.5+6.5)	25	(122+3)
TEC	5	25	5	25	5	25
Total	-	675	-	675	-	675

***Percentage based on core granule, (25/500) × 100 = 5.

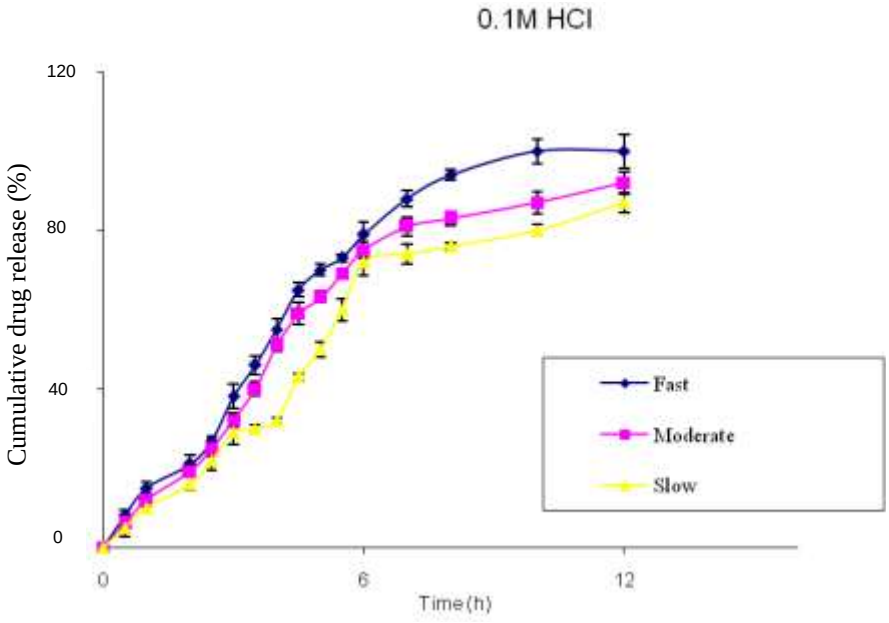

Figure 1. Cumulative mean release of Metoprolol tartrate versus time profile for fast, moderate and slow release formulations.

and Moore (1996).

$$f_2 = 50\log\left[\{1+(1/n)\sum_{i=1}^{n}(Ri-Ti)^2\}^{-0.5}\right]*100$$

where n is the sampling number, Ri and Ti are the percent of drug released from the reference and test products at each time point i. f_2 is a measure of similarity between two dissolution profiles. f_2 value greater than 50% represents equivalence of the two curves and when the percent error is zero (that is, f_2=100) test and drug reference profiles are identical.

Bioavailability study of the formulations on healthy human volunteers

Ethics review procedure

Ethics review procedure. The *in vivo* study was executed as per guidelines of Drugs Control General of India (DCGI, New Delhi). These guidelines complied with the requirements of the US Code of Federal Regulations (Title 21, Part 56), the Declarations of Helsinki and the Canadian MRC Guidelines. The informed consent form and protocol were submitted to the 'Institutional Ethical Committee of Jadavpur University, India' prior to the initiation of the bioavailability

study. The study was not started until the approval of the Ethical Committee had been received.

Design of experiment

Formulations were analyzed utilizing a typical two-period, randomized, two-way complete crossover design in 6 normal healthy, male, human volunteers. There were 2 dosing sessions with a 7 days washout period between the two sessions. Blood samples were obtained at fourteen time points from pre-dose (0 h) until 24 h post dose (0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 8, 10, 12, 18, and 24). The drug plasma samples were stored at -20°C until assayed. The pharmacokinetic parameters for metoprolol tartrate were analyzed by 'zero-moment non-compartmental method'. The maximum plasma concentration (Cmax) and time to reach peak plasma concentration (Tmax) were directly achieved from the plasma concentration vs. time data.

Area under the plasma concentration-time curve from time zero to last concentration time point (AUC_{0-t}) was determined by trapezoidal method. Area under the plasma concentration-time curve from time zero to infinity ($AUC_{0-\infty}$) was determined by the following equation:

$$AUC_{0-\infty} = AUC_{0-t} + \frac{C_t}{K_e}$$

where K_e, the elimination rate constant of single dose is estimated as a slope of the straight line by plotting the concentration (C_{max} to last concentration) against corresponding time on a microsoft excel sheet and C_t is last quantifiable concentration. The elimination half life ($t_{1/2}$) was calculated as $0.693/K_e$.

Evaluation of pharmacokinetic parameters

The plasma levels produced by the administration of the formulations in each volunteer were used to establish the pharmacokinetic profile. The plasma profile of the drug level was presented in tabular and graphical forms. The following pharmacokinetic parameters of the preparations C_{max} (Peak Plasma Concentration), t_{max} (Time to Maximum Plasma Concentration), $AUC_{(0-t)}$ (the area under plasma concentration time curve 0 to 24 h), $AUC_{(0-\infty)}$ (the area under plasma concentration time curve 0 to ∞), $t_{1/2}$ (elimination half-life), K_e (elimination rate constant) were calculated for each subject.

The AUC_{o-t} was determined by the trapezoidal method. Area under the plasma concentration-time curve from time zero to infinity (∞), $AUC_{0-\infty}$, was determined by the following equation:

$AUC_{o-\infty} = AUC_{o-t} + C(t)/K_e$

where K_e, is elimination rate constant.

In vivo data analysis

The drug concentration time data were evaluated by analysis of plasma sample by validate HPLC method. The measured plasma concentration was used to calculate the area under the plasma concentration point (AUC_{o-t}). The AUC_{o-t} was determined by the plasma concentration time profile from the zero to time t, $AUC_{0-\neg}$ by the following equation:

$$AUC_{0-\infty} = AUC_{0-t} + C(t)/K_e$$

where, k_e is the elimination rate constant.

The Wagner-nelson method was used to calculate the percentage of the drug absorbed.

$$F(t) = C(t) + K_e AUC_{0-t}$$

where, F (t) is the dose absorbed at any time t and % dose absorbed is calculated as:

$$\%\ \text{dose absorbed} = \left[\left\{C(t) + K_e AUC_{0-t}\right\}/K_e AUC_{0-\infty}\right] \times 100$$

Correlation development

The data which were produced from the bioavailability study were used to develop the IVIVC. The graphical correlation was developed by mean plasma concentration and mean release concentration of drug from various formulations (slow, moderate and fast) as shown in Figure 2A to D. The correlation models were developed using data from the following combinations of formulation (1) slow and fast (S/F), (2) moderate and fast (M/F), (3) slow and moderate(S/M) and (4) slow, moderate and fast (S/M/F). The percent of drug unabsorbed versus time was plotted on a semi log paper.

Internal validation of the correlation

An IVIVC should be validated to check whether the predictability of *in vivo* performance of a drug product from its *in vitro* dissolution characteristics is maintained over dissolution release rates and manufacturing changes or not. The internal validation was based on how well the defining four IVIVC models (that is, S/M, S/F, MF, S/M/F) predicted the *in vivo* performance of each formulations (that is, slow, moderate and fast). The procedure used for internal validation was as follows: the S/M, S/F, M/F and S/M/F-IVIVC models were used to predict the *in vivo* performance for slow, moderate and fast formulation, respectively. The IVIVC models predicted the plasma concentration was determined by the following procedure. The *in vitro* release data of each formulation was transformed in the *in vivo* release data by using the IVIVC model equation. The plasma concentration was calculated by numerical convolution of the *in vivo* release data and with the help of pharmacokinetic parameters generated from the reference immediate release formulation. The prediction of the plasma concentration was accomplished using the following first order one compartmental fitting equation:

$$y = \text{const.} \times (\text{Dose}) \times K_a/K_a - K_e\left(e^{-K_e t} - e^{-K_a t}\right)$$

where y=predicted plasma concentration (ng ml^{-1}); Const. = the constant representing F/V_d, where F = fraction absorbed, and V_d is the apparent volume of distribution; K_a = absorption rate constant; K_e = overall elimination rate constant. The de-convolution was accomplished on a spread sheet in Excel. The predicted plasma concentration was compared with the observed plasma data and the percentage prediction error (% PE) of the IVIVC model was regarding C_{max}, $AUC_{o-\infty}$. According to relevant FDA regulatory guidance, the permissible %PE values for C_{max} and AUC should be less than 15% for each product and less than 10% for the average, respectively.

$$\%PE_{Cmax} = \left[\left\{C_{max(obs)} - C_{max(pred)}\right\}/C_{max(obs)}\right] \times 100$$

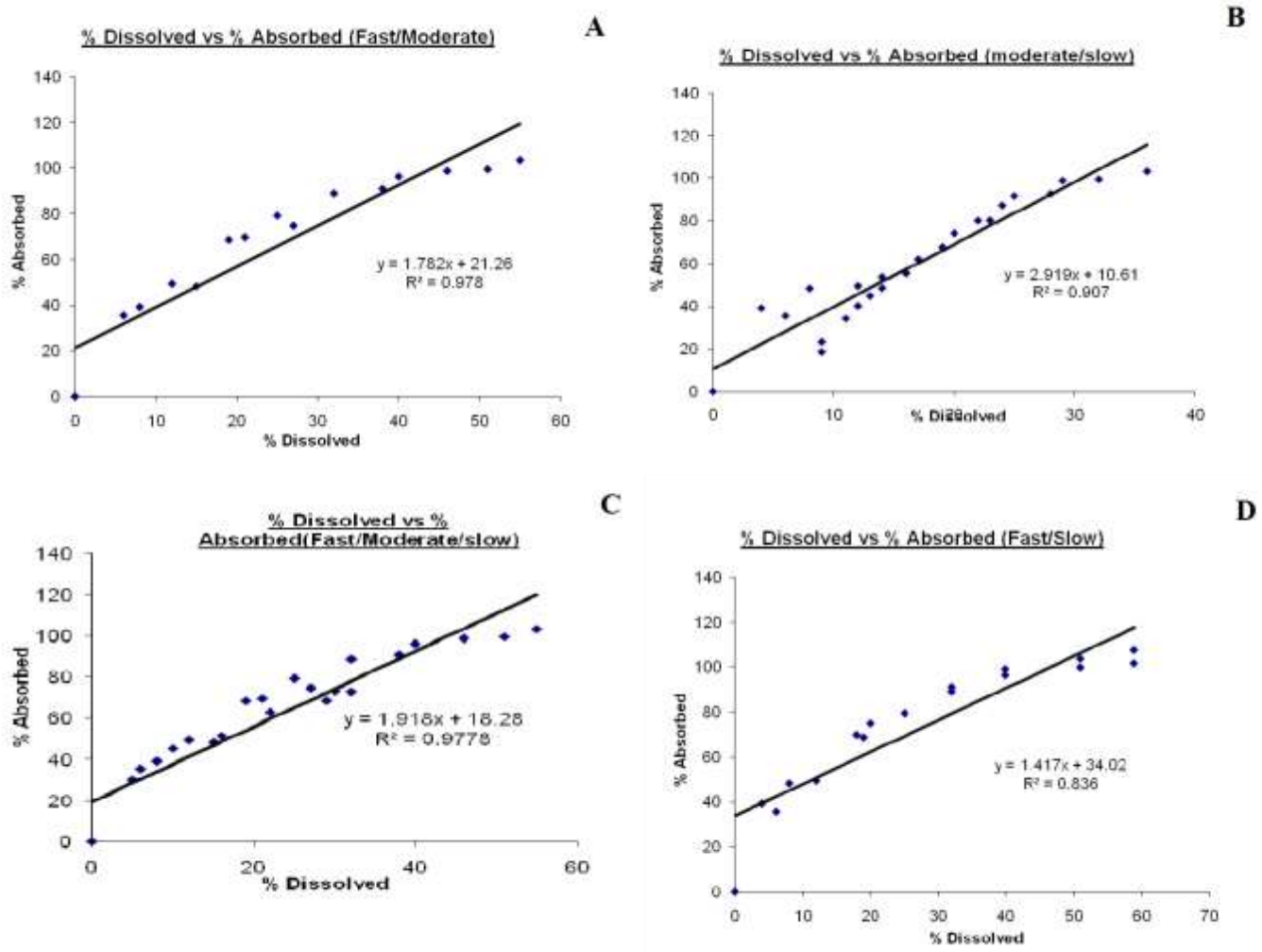

Figure 2. *IVIVC* model linear regression plots of '% Absorbed vs. % Dissolved' for (A) Fast and Moderate, (B) Moderate and Slow, (C) Fast, Moderate and Slow and (D) Fast and Slow.

$$\%PE_{AUC} = \left[\left\{AUC_{(obs)} - AUC_{(pred)}\right\} / AUC_{(obs)}\right] \times 100$$

where $C_{max(obs)}$ and $C_{max(pred)}$ are the observed and IVIVC-model-predicted maximum plasma concentration, respectively; and $AUC_{(obs)}$ and $AUC_{(pred)}$ are the observed and IVIVC-model-predicted $AUC_{0-\infty}$ for the plasma concentration profiles, respectively. The IVIVC was considered valid if the average absolute % prediction error is <10% for C_{max} and <15% for AUC in each formulation.

External validation of IVIVC

Evaluation of external predictability of the IVIVC should be performed as a final determination of the ability of the IVIVC to be used as a surrogate for bioequivalence. The external validation was accomplished by comparing the true *in vivo* data and predicted *in vivo* data of one of the optimized capsules filled with SR coated granules containing 100 mg metoprolol tartrate.

RESULTS AND DISCUSSION

In vitro dissolution studies

Mean profile of the percentage cumulative drug release from the slow, moderate and fast release formulations are illustrated in Figure 1. Similarity of the various formulations was tested by determination of f_2 values as shown in Table 2, where reference substance also was mentioned. f_2 values indicated the dissolution similarity between two profiles of formulations (reference and test sample). So, the aforementioned dissolution method was found suitable to establish *in vitro in vivo* correlation.

Validation of HPLC method for estimation of metoprolol in human plasma

A high-performance reversed-phase liquid

Table 2. f_2 test for SR Metoprolol tartrate formulations (Slow, moderate & fast release formulations).

Formulations	f_2 test between formulations	f_2 value
C1-F	Fast, Moderate	49.93
C1-M	Fast, Slow	40.65
C1-S	Moderate, Slow	54.3

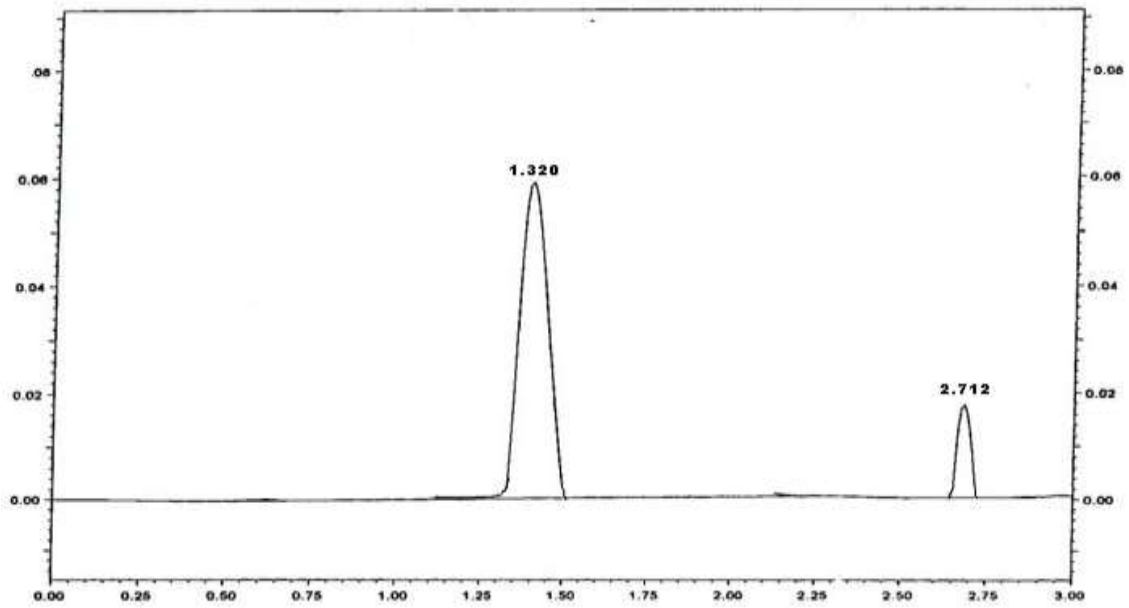

Figure 3. Representative Chromatogram obtained during quantification of metoprolol tartrate (t_R = 1.3 min) in human plasma with pinacidil monohydrate (t_R = 2.7 min).

Table 3. Mean pharmacokinetic parameters for Metoprolol tartrate from slow, moderate, fast and immediate release formulations.

Formulation	C_{max} (ng/ml)	T_{max} (h)	$AUC_{0-\infty}$
Immediate release	154.8 ± 3.1	2.0 ± 0.3	879.12 ± 34.76
Fast release (F)	123.09 ± 2.6	3.5 ± 0.2	1086.38 ± 44.32
Moderate release (M)	109.67 ± 1.8	3.6 ± 0.4	1164.07 ± 25.89
Slow release (S)	104.8 ± 3.5	4.5 ± 0.2	1214.81 ± 45.52

chromatographic method for quantification of metoprolol tartrate in human plasma is used according to method described in literature (Aqil et al., 2007). A C_{18} column was used with acetonitrile-water-triethylamine 18:81:1 (v/v) as mobile phase and pinacidil monohydrate as internal standard (IS). UV detection was at 275 nm and metoprolol tartrate was detected at retention times of 1.3 min. The method is sensitive with a limit of quantification of 20 ng mL^{-1} (Figure 3). The calibration plot for MT in plasma was linear in the concentration range 20 to 200 ng mL^{-1}. The method can be successfully used for analysis of MT in human plasma during pharmacokinetic studies.

In vivo bioavailability studies of different formulations

Mean pharmacokinetic parameters were summarized in Table 3. Mean plasma concentration versus time profile

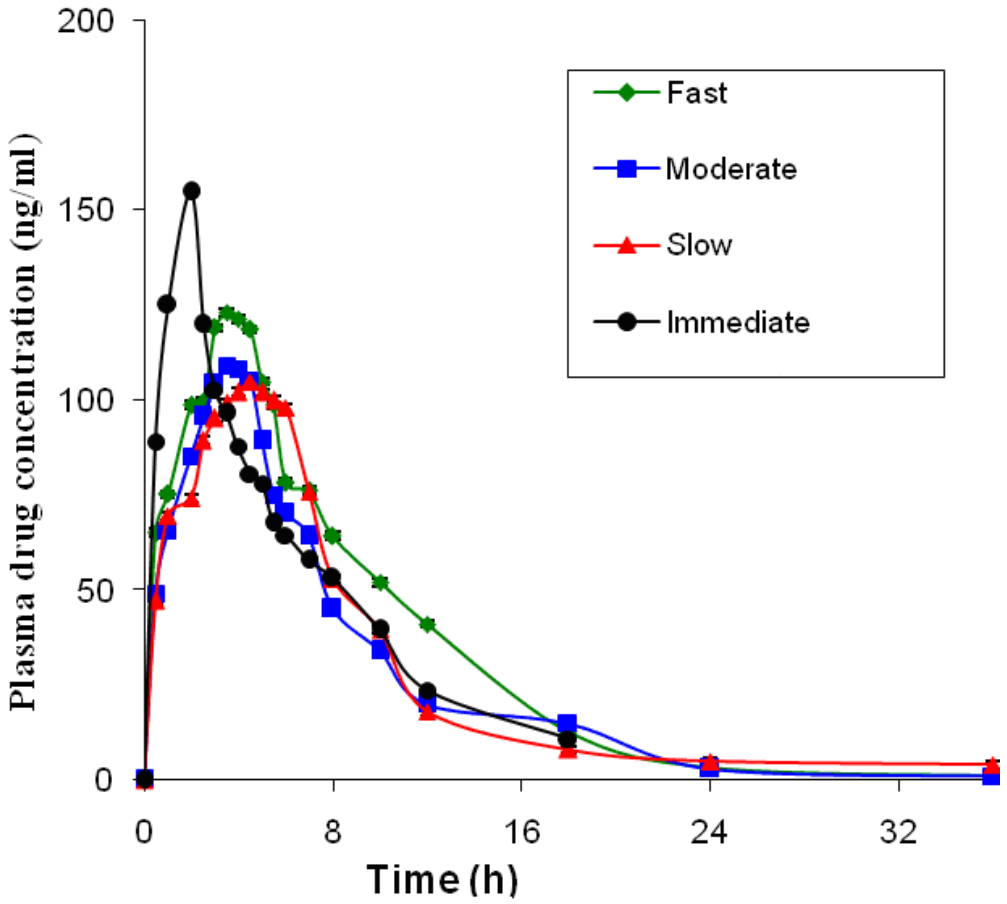

Figure 4. Mean Metoprolol tartrate plasma concentration versus Time profile for immediate, slow, moderate and fast release formulations.

after each formulation is presented in Figure 4. The rank order of release observed in the dissolution testing was also apparent in plasma drug concentration profile with a mean C_{max} 154.8, 123.09, 109.0, and 104.8 ng/ml for the immediate, fast, moderate and slow release formulations, respectively.

IVIVC correlation development

A 'level A' *IVIVC* was investigated using the percent absorbed data versus percent dissolved for the fast, moderate and slow formulation, using 0.1(N) HCl dissolution media and pH 6.8 phosphate buffer at 50 rpm as before. A good linear regression relation was observed between the percent dissolved in the dissolution test and percent absorbed data.

Internal validation

The internal validation was performed by convolution of the dissolution data that corresponded to each formulation (S/M/F). Each of the *IVIVC* model (S/M/F, S/M, M/F and S/F) as shown in Figure 2 predicted drug plasma concentration at various time and these were compared to the experimental data points using prediction error metrics. The validity of the correlation was also assessed by determining how well *IVIVC* model could predict the rate and extent of drug absorption as characterized by C_{max} and $AUC_{0-\alpha}$. Table 4 presents the error (%) estimated for the difference between the observed and predicted C_{max} and $AUC_{0-\alpha}$ for all the *IVIVC* models. None of the *IVIVC* model predicted parameters deviated from the experimental value by not more than 10%.

External validation

The external validation was accomplished by the optimized SR matrix formulation of drug containing Metoprolol tartrate and to predict the plasma concentration of the new formulation. All four *IVIVC* models (S/M/F, S/M, M/F and S/F) were used. The error estimated for the difference between the observed and predicted C_{max} and $AUC_{0-\alpha}$ value of the new formulation

Table 4. Prediction error (%) in C_{max} and $AUC_{0-\alpha}$ for Metoprolol tartrate *IVIVC*.

Formulation	*IVIVC* Models							
	S+M+F		S+M		S+F		M+F	
	C_{max}	$AUC_{0-\alpha}$	C_{max}	$AUC_{0-\alpha}$	C_{max}	$AUC_{0-\alpha}$	C_{max}	$AUC_{0-\alpha}$
Fast	-5.63	5.82	-6.28	-3.35	5.84	7.20	-6.00	-6.85
Moderate	4.86	-7.20	7.09	4.62	7.03	-5.34	7.15	3.35
Slow	6.05	4.26	-4.98	3. 78	6.15	5.62	5.72	7.21
C1	5.21	7.03	7.18	5.28	5.38	5.12	6.84	7.93

for the entire *IVIVC* model found less than 8% (Table 4).

Conclusions

The significant correlations between the *in vitro* and *in vivo* parameters reported here indicate that the novel approach of IVIVC was excellent for predicting different pharmacokinetic parameters. It was also observed that the prediction errors of $AUC_{0-\alpha}$ for Fast, Moderate and Slow formulations are in excellent agreement between the three dosage forms.

CONFLICT OF INTERESTS

The author has not declared any conflict of interests.

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