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In-vitro and in-vivo correlation for two gliclazide extended-release tablets

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Abstract

The aim of this study was to perform an in-vitro–in-vivo correlation (IVIVC) for two 60-mg gliclazide extended-release formulations (Fast and Slow release) given once a day and to compare their plasma concentrations over time. In-vitro release rate data were obtained for each formulation using the USP apparatus II, paddle stirrer at 50 and 100 rev min^{-1} in 0.1 M HCl and pH 7.4 phosphate buffer. The similarity factor (f_2) was used to analyse the dissolution data. Eighteen healthy subjects participated in the study, conducted according to a completely randomized, two-way crossover design. The formulations were compared using area under the plasma concentration–time curve, $AUC_{0-\infty}$, time to reach peak plasma concentration, T_{max}, and peak plasma concentration C_{max}, while correlation was determined between in-vitro release and in-vivo absorption. A linear correlation model was developed using percent absorbed data versus percent dissolved data from the two formulations. Predicted gliclazide concentrations were obtained by use of a curve fitting equation. Prediction errors were estimated for C_{max} and area under the curve $AUC_{0-\infty}$ to determine the validity of the correlation. 0.1 M HCl at 50 rev min^{-1} was found to be the most discriminating dissolution method. Linear regression analysis of the mean percentage of dose absorbed versus the mean percentage of in-vitro release resulted in a significant correlation ($r^2 > 0.98$) for the two formulations. An average percent prediction error for C_{max} was 4.15% for Fast release and 3.99% for Slow release formulation whereas for $AUC_{0-\infty}$ it was 6.36% and 4.66% for Fast release and Slow release formulation, respectively.

Introduction

In-vitro dissolution testing provides an easy and convenient means to evaluate the performance of pharmaceutical preparations during their developmental stage. However, satisfactory in-vitro release characteristics may not necessarily be a reliable index to predict the in-vivo performance accurately. To validate the in-vivo performance of preparations it is essential to test them in man. Studies using human subjects, however, are costly and tedious. Furthermore, it is not pragmatic or economical to conduct human studies on each and every batch of similar preparations. So the idea of in-vitro–in-vivo has evolved.

An in-vitro–in-vivo correlation (IVIVC) has been defined by United States Pharmacopoeia (USP 1995) and the Food and Drug Administration (FDA) as "a predictive mathematical model describing the relationship between an in-vitro property of a dosage form and in-vivo response" (FDA 1997). Developing an IVIVC for an extended-release tablet is an important object to facilitate product development and serves as a quality control procedure during product manufacture. Drug manufacturers typically use such tests to asses lot-to-lot variability, product shelf life, and to predict in-vivo performance (i.e. bioavailability) with reasonable assurance after conducting minor formulation and process changes (i.e. colour, size, shape, preservatives, flavour, coating procedure, amount and composition of materials, source of inactive and active ingredients and change in equipment or site of manufacture) (Skelley et al 1990). A meaningful IVIVC could lead to improved product quality and decreased regulatory burden (Rackley 1997; FDA 1997).

The in-vitro dissolution curve is usually determined by a suitable dissolution test and in-vivo absorption curve is frequently determined by deconvolution using model-dependent (e.g. Wagner-Nelson or Loo Regelman) or model-independent (e.g. DeMons) methods (Gibaldi et al 1982; USP Subcommittee on Biopharmaceutics 1988). Levels A, B and C and

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multiple Level C correlation has been described by the FDA for IVIVC. The most useful of these is Level A correlation, which is a point-to-point relationship between in-vitro dissolution and the in-vivo absorption rate of a drug from the dosage form. Generally this correlation is linear and considered most informative and very useful from a regulatory viewpoint. The FDA guidance describes the methods of evaluation of prediction error internally and externally. Internal validation determines how well the IVIVC model describes the data used to develop the correlation. External validation determines how well the IVIVC model describes data that was not used in the development of the model (FDA 1997).

Establishing a correlation between the in-vivo plasma concentration profile and in-vitro dissolution profile of an extended-release formulation has been of great interest for a number of years. Extended release of drugs in the gastrointestinal tract following oral administration is the intended rate-limiting factor in the absorption process. It is therefore desirable to use in-vitro data to predict in-vivo bioavailability parameters for the rational development and evaluation process for extended-release dosage forms (Hussein et al 1990; Sirisuth et al 2002).

Gliclazide (1-(3-azabicyclo [3.3.0] oct3-yl)-3-*p*-tolyl sulfonyl urea) is a hypoglycaemic agent of the sulfonyl urea group (Kobayashi et al 1984). Numerous IVIVC studies of sustained- or extended-release formulations have been previously reported (Eddington et al 1998; Mahayni et al 2000; Veng-Pedersen et al 2000; Balan et al 2001; Dalton et al 2001; Roshdy et al 2002), although there are none involving extended-release gliclazide formulations. Therefore, the purpose of this study was to develop an IVIVC for two novel hydrophilic matrix extended-release gliclazide 60-mg tablets. The validity of the correlation was established through the external predictability approach, by using the data from one study to predict the plasma concentration of a similar dosage form, with a different rate of release.

Materials and Methods

Materials

Gliclazide was provided by P. I. Pharmaceuticals. Hydroxypropyl methyl cellulose (HPMC K 4 M and 100 M) and Ethocel premium, manufactured by Dow Chemical Company (USA) were provided by A. N. Pharmacia (India). Lactose (grade 315 & 316), manufactured by Loba Chemie Pvt. Ltd (India), was supplied by Suppliers Syndicate (Kolkata). Magnesium stearate, talcum powder and silicone dioxide (Aerosil) were manufactured by Loba Chemie and purchased from Suppliers syndicate (Kolkata).

Formulations

Two extended-release matrix formulations of 60 mg gliclazide were developed by the aqueous wet granulation method using hydroxypropyl methylcellulose (HPMC K 4 M or HPMC K 100 M) as one of the release-rate-controlling excipients, and Ethocel premium as the other controlled-release polymer. Lactose (grade 315 & 316) was used as filler and magnesium stearate, talcum powder and Aerosil as lubricant. The formulations were designed to release gliclazide at two different rates, referred to as Fast (release up to 8 h) and Slow (release up to 12 h). The high-viscosity HPMC (K 100 M) and the low-viscosity HPMC (K 4 M) were used for slow and fast release, respectively. Final weight of the Fast formulation was 170 mg with average hardness of 5.0 kg cm^{-2}. The average weight of the Slow formulation was 200 mg with an average hardness of 6.0 kg cm^{-2}.

Dissolution testing

The dissolution behaviour of gliclazide extended-release matrix tablets (Fast and Slow) was continuously recorded using a semi-automatic dissolution apparatus (Electrolab, USP XXIII, TDT 06P). The release characteristics of the formulations were determined using USP Apparatus II at 50 and 100 rev min^{-1} in 0.1 M HCl or pH 7.4 phosphate buffer maintained at 37°C. Dissolution tests were performed on six tablets and the amount of drug released was analysed spectrophotometrically at a wavelength of 230 nm. Dissolution samples were collected at the following times: 0, 1, 2, 3, 4, 5, 6, 7, 8 and 12 h. The dissolution samples were cooled to room temperature before analysis for drug release from the tablets.

Bioavailability study

The bioavailability study was an open level, fasting, single dose and three-treatment crossover study using normal healthy subjects. Subjects provided informed consent to participate in the study. The study was approved by the Institution Ethical Committee of Jadavpur University, Kolkata. Eighteen male, non-smoking subjects were enrolled in the study and received two extended-release 60-mg gliclazide matrix tablets (Fast and Slow), once per day. Both the formulations were given in a randomized fashion. In addition to the extended-release formulations, an immediate-release 60-mg gliclazide tablet (CLAZOD, manufactured by Franco Indian, India) was also administered. The order of drug administration was randomized in three sequences (ABC, BCA and CAB) in blocks of three. Blood samples were obtained at thirteen time points from pre-dose (0 h) until 48 h post-dose (0, 1, 1.5, 2, 3, 3.5, 4, 6, 8, 10, 12, 24 and 48 h). Subjects fasted for 12 h before the morning drug administration when the extended release products were administered. A washout period of 1 week was allowed between dose administrations. The plasma samples were stored at −20°C until assayed.

Assay method for gliclazide

An analytical method for the determination of gliclazide and glipizide (as internal standard) in human plasma was developed and validated using high-performance liquid chromatography (HPLC; Model No. K 2501; Knauer, Germany, Eurochrom software). The method determined concentrations of gliclazide using a calibration range of 0.05–2.0 μg mL^{-1}. The accuracy of the assay for gliclazide (as determined from the calibration standards and control samples) was in the range 97.88–101% and 97.89–100.5%, respectively.

In-vitro dissolution data analysis

The dissolution profiles for each formulation were determined by plotting the cumulative percent of gliclazide dissolved at various time points. The in-vitro drug release profiles of the two extended-release dosage forms were compared using the similarity factor, f_2, presented in the following equation (US Department of Health, FDA 1997).

$$f_2 = 50\,\mathrm{LOG}\left\{\left(1+\frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right)^{-0.5}\times 100\right\} \quad (1)$$

Where LOG = logarithm base 10, n = number of sampling points and T_t and R_t = the cumulative percent dissolved at each of the selected time points of the test and the reference product, respectively. FDA has set a public standard of $50 < f_2 < 100$ to indicate similarity between two dissolution profiles.

In-vivo data analysis

The gliclazide concentration–time data were evaluated by analysis of plasma samples by validated HPLC method. The measured plasma concentrations were used to calculate the area under the plasma concentration–time profile from time zero to last concentration time point ($AUC_{0\text{-}t}$). The $AUC_{0\text{-}t}$ was determined by the trapezoidal method. Area under the plasma concentration–time curve from time zero to infinity (∞), $AUC_{0\text{-}\infty}$, was determined by the following equation:

$$AUC_{0\text{-}\infty} = AUC_{0\text{-}t} + C(t)/K_e \quad (2)$$

Where K_e, the elimination rate constant, was estimated by fitting the logarithm of the concentration versus time to a straight line over the observed exponential decline. The Wagner-Nelson method (Wagner 1971) was used to calculate the percentage of the gliclazide dose absorbed:

$$F(t) = C(t) + K_e\,AUC_{0\text{-}t} \quad (3)$$

Where F (t) is the amount absorbed. The percent of dose absorbed is determined by dividing the amount absorbed at any time by the plateau value, $K_e\,AUC_{(o\text{-}\infty)}$ and multiplying this ratio by 100:

$$\%\ \text{Dose absorbed} = [\{C(t) + K_e\,AUC_{0\text{-}t}\}/K_e\,AUC_{0\text{-}\infty}]\times 100 \quad (4)$$

In-vitro–in-vivo correlation

The data generated in the bioavailability study were used to develop the IVIVC. The percent of drug dissolved was determined using the aforementioned dissolution testing method and the fraction of drug absorbed was determined using the method of Wagner-Nelson (Wagner 1971). The deconvolution procedure was used to obtain in-vivo input profiles of gliclazide using immediate-release data as the reference treatment. Linear regression analysis was used to examine the relationship between percent of drug dissolved and percent of drug absorbed. The percent of drug unabsorbed was calculated from the percent absorbed. The percent of drug unabsorbed versus time was plotted on a semi log paper. The slope of the best-fit line for the semi-log treatment of this data was taken as the first order rate constant for absorption (K_a) where slope is equal to negative K_a divided by 2.303. The dissolution rate constant (K_{diss}) was determined from percent cumulative released versus the square root of time. Linear regression analysis was applied to the IVIVC plots and coefficient of determination (R^2), slope and intercept values were calculated.

Internal validation of the IVIVC

The internal predictability of the IVIVC was examined by using the mean in-vitro dissolution data and mean in-vivo pharmacokinetics of the extended release matrix tablets. Briefly, the correlation of the mean in-vitro dissolution rate constants was correlated to the mean absorption rate constants for the extended-release dosage forms. These two data points, along with the zero-zero intercept were used to calculate the expected absorption rate constants (i.e., where absorption rate constants = [slope] × dissolution rate constant + [intercept].

The prediction of the plasma gliclazide concentration was accomplished using the following curve fitting equation:

$$y = \mathrm{Const.}\times(\mathrm{Dose})\times K_a/K_a - K_e\,(e^{-Ket} - e^{-Kat}) \quad (5)$$

where y = predicted plasma concentration (ng mL^{-1}); Const. = the constant representing F/V_d, where F = fraction absorbed, and V_d is the volume of distribution; K_a = absorption rate constant; K_e = overall elimination rate constant. The de-convolution was accomplished on a spreadsheet in Excel.

To further assess the predictability and the validity of the correlations, we determined observed and IVIVC model-predicted C_{max} and $AUC_{0\text{-}\infty}$ values for each formulation. The percent prediction errors for C_{max} and $AUC_{0\text{-}\infty}$ were calculated as follows:

$$\%PE_{Cmax} = [\{C_{max\ (obs)} - C_{max\ (pred)}\}/C_{max\ (obs)}]\times 100 \quad (6)$$

$$\%PE_{AUC} = [\{AUC_{(obs)} - AUC_{(pred)}\}/AUC_{(obs)}]\times 100 \quad (7)$$

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-predected $AUC_{0\text{-}\infty}$ for the plasma concentration profiles, respectively.

External validation of the IVIVC

The external validation was accomplished by reformulating the extended-release dosage form to a release rate between the Fast and Slow rates, selected to provide a C_{max} of the reformulated product equivalent to the C_{max} obtained from the Fast and Slow tablets, and to re-test the re-formed product against the Fast and Slow tablets in another bioavailability study in human subjects.

Statistical analysis

All the results were expressed as mean ± standard deviation (s.d.). The values of C_{max}, T_{max} and $AUC_{0-\infty}$ obtained from three formulations were analysed using one-way analysis of variance with WinNonlin (version 4.1, Pharsight) software to determine statistically significant differences. The $AUC_{0-\infty}$ and C_{max} values were logarithmically transformed before statistical analysis. $P \leq 0.05$ denoted statistical significance.

Results and Discussion

In-vitro studies

For immediate-release tablets more than 90% gliclazide release (mean ± s.d., 94.37 ± 3.81%) occurred within 1 h, irrespective of dissolution medium and revs min^{-1}. Dissolution plots of the cumulative percent drug release from the Fast and Slow formulations are presented in Figures 1 and 2 using pH 7.4 phosphate buffer and 0.1 M HCl as dissolution medium, respectively. It was found that the high-molecular-weight (high viscosity) polymer had a slower dissolution rate than the dosage form with the lower-molecular-weight (lower viscosity) polymer in both pH media. The release of gliclazide from the Fast and Slow formulations was found to be almost indistinguishable from each other when the dissolution was measured in 0.1 M HCl and pH 7.4 phosphate buffer at 100 and 50 rev min^{-1}. The calculated similarity factors (f_2) between the Slow and Fast formulation at pH 7.4 phosphate buffer was found to be 47.39 and 42.95 at 100 rev min^{-1} and 50 rev min^{-1}, respectively. At 0.1 M HCl f_2 values were 46.77 and 39.99 at 100 rev min^{-1} and 50 rev min^{-1}, respectively. 0.1 M HCl dissolution media at 50 rev min^{-1} had the lowest f_2 value (39.99). Eddington et al (1998) reported that it is imperative to utilize a dissolution methodology that discriminates between formulations and mimics the in-vivo release profile in the process of developing an IVIVC. Accordingly, 0.1 M HCl at 50 rev min^{-1} was found to be the more discriminating dissolution media in our study and it was used in the IVIVC model development. Cumulative percent gliclazide release versus square root of time profile for Fast and Slow release tablets at different dissolution parameters (50 and 100 rev min^{-1}, pH 7.4 phosphate buffer; 50 and 100 rev min^{-1}, 0.1 M HCl) gave the straight line (slopes range from 35.07 to 49.31) and the slopes were used as dissolution rate constant (K_{diss}). The value of K_{diss} at 0.1 M HCl with 50 rev min^{-1} for Slow and Fast release formulation was found to be 35.20 ± 0.13 and 38.48 ± 0.27, respectively.

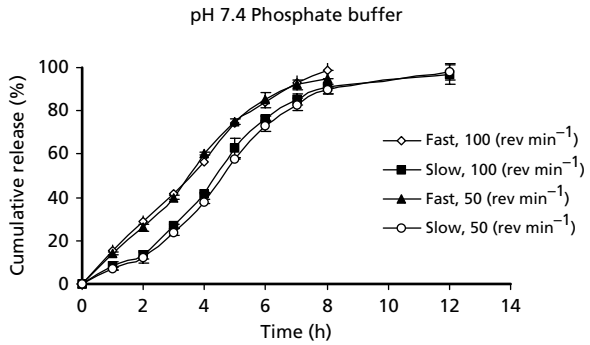

Figure 1 Cumulative gliclazide release versus time profile for fast- and slow-release formulation at 100 and 50 rev min^{-1} using pH 7.4 phosphate buffer. Each value represents the mean ± s.d., n = 6.

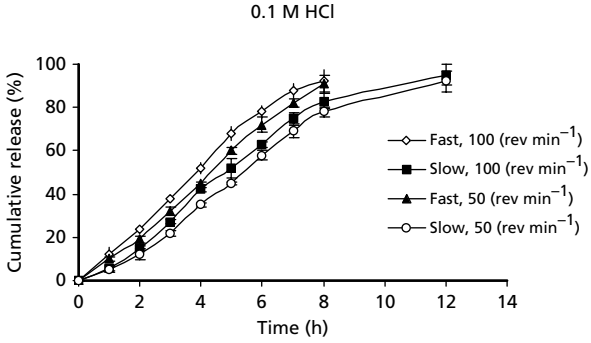

Figure 2 Cumulative gliclazide release versus time profile for fast- and slow-release formulation at 100 and 50 rev min^{-1} using 0.1 M HCl. Each value represents the mean ± s.d., n = 6.

In-vivo studies

The mean pharmacokinetic parameters are summarized in Table 1 and the mean plasma gliclazide concentration vs time profiles of Fast-, Slow- and Immediate-release formulations are presented in Figure 3. In our study, there were negligible differences in plasma concentration between the Fast and Slow formulations. It was also found that the rank order of release observed in the dissolution testing was followed in the plasma gliclazide concentration profiles, with a mean C_{max} of 1373.269 ± 92.056 ng mL^{-1} and 1064.215 ± 98.572 ng mL^{-1} for the Fast and Slow formulation, respectively (Table 1). Statistically significant differences ($P < 0.001$) were observed among treatments for C_{max} and T_{max} and the values were comparable with those reported in the literature (Glowka et al 1998; Hermann et al 2005). There was no significant difference between the $AUC_{0-\infty}$ from the Fast formulation and that from the Slow formulation, showing that the extent of absorption of gliclazide was the same despite the differences in release rates between the two dosage forms. The $AUC_{0-\infty}$ from immediate-release tablets (31158.5896 ± 3801.2500) was somewhat less than the $AUC_{0-\infty}$ from the extended-release formulations ($P < 0.05$), probably due to the shorter residence time of the immediate-release tablet than the extended-release tablets or drug–excipient interaction from the immediate-release tablet, which decreased the bioavailability of the immediate-release tablet.

IVIVC correlation development

A Level A IVIVC was investigated using the percent absorbed data versus percent dissolved for both the Fast and Slow formulations, using both 0.1 M HCl and pH 7.4 phosphate buffer dissolution media at both 50 and 100 rev min^{-1}.

Table 1 Pharmacokinetic parameters for gliclazide from slow-, fast- and immediate-release formulations

Formulation	C_{max} (ng mL^{-1})	T_{max} (h)	$AUC_{0-\infty}$ (ng h mL^{-1})
Immediate release	1500.173 ± 37.730	2.80 ± 1.10	31158.5896 ± 3801.2500
Fast	1373.269 ± 92.056**	8.00 ± 1.59**	41275.8934 ± 3510.1003*
Slow	1064.215 ± 98.572**	8.00 ± 1.21**	41454.8203 ± 5633.0637*

Values are presented as means ± s.d., n = 18. *$P < 0.01$; **$P < 0.001$ vs immediate-release.

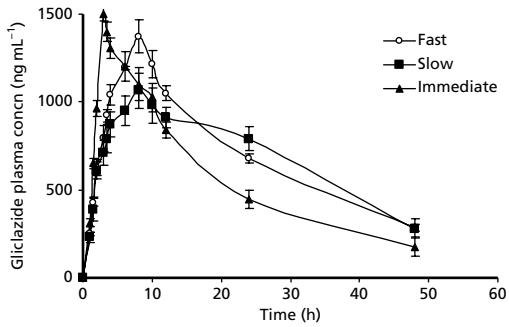

Figure 3 Mean gliclazide plasma concentration versus time profile of fast-, slow- and immediate-release formulations. Each value represents the mean ± s.d., n = 18.

A good linear regression relationship was observed between percent dissolved in the dissolution testing using 0.1 M HCl at 50 rev min^{-1} and the percent absorbed for the combined data of the two dosage (y = 1.2437x + 4.7565; correlation coefficient (R^2) = 0.9607). Another good linear regression relationship was observed between the percents dissolved in dissolution testing using pH 7.4 phosphate buffer as the dissolution media at 50 rev min^{-1}, and the percents absorbed for the combined data of the two dosage forms (y = 1.0631x + 3.45; correlation coefficient (R^2) = 0.9731).

It was also observed that the in-vivo absorption rate constants, K_a values for Slow (0.32 ± 0.02) and Fast (0.40 ± 0.03) formulations correlated well with the 0.1 M HCl in-vitro dissolution rate constants, K_{diss} for Slow (35.20 ± 0.13) and Fast (38.48 ± 0.27) formulations considering zero, zero point as theoretical, which exhibited a correlation coefficient (R^2) of 0.9874 (y = 0.0099x − 0.0021).

Internal validation

Dosage forms are designed to be the slow step in the absorption process; therefore, it should follow that the percent of the amount absorbed over time should mimic the in-vitro release of drug from the dosage form for a good IVIVC. The slopes of the in-vivo data (plotting of % cumulative $AUC_{0-\infty}$ vs square root of time) were determined to be 46.83 ± 0.58 and 39.55 ± 0.46 for the Fast and Slow dosage forms, corresponding to the in-vitro release rates of 38.48 ± 0.27 and 35.20 ± 0.13 for the Fast and Slow dosage forms, respectively. These are good indications that the mechanism and rates of absorption in-vivo mimic mechanism and rates of release in-vitro.

The predicted gliclazide plasma concentrations for the Fast and Slow formulations were calculated from the developed IVIVC. It was observed that there was a good correlation between the actual and the predicted plasma concentrations, where the correlation coefficient (R^2) values for Slow and Fast formulation were 0.9907 and 0.9867, respectively.

The validity of correlation was also assessed by determining how well the IVIVC models could predict the rate and extent of gliclazide absorption as characterized by C_{max} and $AUC_{0-\infty}$. Table 2 presents the percent errors estimated for the difference between the observed and predicted C_{max} and $AUC_{0-\infty}$ values for the IVIVC model. The C_{max} prediction errors for the Fast (4.15%) and Slow (3.99%) formulations were both found to be very close to the observed mean values. It was found that the prediction errors of the observed mean of $AUC_{0-\infty}$ values were 6.36% and 4.66% for Fast and Slow formulations, respectively.

The FDA guidance (FDA 1997) on IVIVC states that the average absolute percent prediction error of $\leq 10\%$ for C_{max} and $AUC_{0-\infty}$ establishes the predictability of the IVIVC. In addition, the percent prediction error for an individual formulation should not exceed 15%. In this study, the predicted $AUC_{0-\infty}$ value of Fast and Slow formulation was well below the FDA limit.

The significant correlation between Fast and Slow formulations indicate that the IVIVC was excellent for predicting C_{max} and $AUC_{0-\infty}$.

External validation

Gliclazide extended-release matrix tablets were reformulated with a release rate between the Fast and Slow formulations, and the IVIVC for the Fast and Slow formulation was used to predict the plasma concentrations of the new formulation. The actual (observed) maximum average plasma concentration of the new formulation at steady state was determined to be 1162.461 ± 73.956 ng mL^{-1}, and was very close to the maximum of the average predicted plasma concentration (1210.897 ± 87.137 ng mL^{-1}) for the same.

Conclusions

The significant correlations between the in-vitro and in-vivo parameters reported here indicate that the IVIVC was excellent for predicting C_{max} and $AUC_{0-\infty}$. It is also observed that the prediction errors of $AUC_{0-\infty}$ for Fast and Slow formulations (6.36% and 4.66%, respectively) are in excellent agreement between the two dosage forms.

Table 2 Prediction errors (%) associated with C_{max} and $AUC_{0-\infty}$

Formulation	C_{max} (ng mL^{-1})			$AUC_{0-\infty}$ (ng h mL^{-1})		
	Predicted	Observed	% Error	Predicted	Observed	% Error
Fast	1316.275	1373.269	4.15	38649.740	41275.893	6.36
Slow	1106.839	1064.269	3.99	39523.360	41454.820	4.66

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