Development and Internal Validation of an *In Vitro–In Vivo* Correlation for a Hydrophilic Metoprolol Tartrate Extended Release Tablet Formulation

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Purpose. To develop and validate internally an *in vitro-in vivo* correlation (IVIVC) for a hydrophilic matrix extended release metoprolol tablet.

Methods. *In vitro* dissolution of the metoprolol tablets was examined using the following methods: Apparatus II, pH 1.2 & 6.8 at 50 rpm and Apparatus I, pH 6.8, at 100 and 150 rpm. Seven healthy subjects received three metoprolol formulations (100 mg): slow, moderate, fast releasing and an oral solution (50 mg). Serial blood samples were collected over 48 hours and analyzed by a validated HPLC assay using fluorescence detection. The f_2 metric (similarity factor) was used to analyze the dissolution data. Correlation models were developed using pooled fraction dissolved (FRD) and fraction absorbed (FRA) data from various combinations of the formulations. Predicted metoprolol concentrations were obtained by convolution of the *in vivo* dissolution rates. Prediction errors were estimated for C_{max} and AUC to determine the validity of the correlation.

Results. Apparatus I operated at 150 rpm, and pH of 6.8 was found to be the most discriminating dissolution method. There was a significant linear relationship between FRD and FRA when using either two or three of the formulations. An average percent prediction error for C_{max} and AUC for all formulations of less than 10% was found for all IVIVC models.

Conclusions. The relatively low prediction errors for C_{max} and AUC observed strongly suggest that the metoprolol IVIVC models are valid. The average percent prediction error of less than 10% indicates that the correlation is predictive and allows the associated dissolution data to be used as a surrogate for bioavailability studies.

KEY WORDS: convolution; metoprolol; validation; dissolution; prediction errors.

INTRODUCTION

The development and subsequent validation of an in vitro-in vivo correlation (IVIVC) is an increasingly important component of extended release dosage form optimization. An IVIVC is a relationship (preferably linear) between a biological parameter (Cmax, Tmax or AUC) produced by a dosage form and an in vitro characteristic (e.g. in vitro dissolution) (1). The highest level of correlation, Level A, is usually linear and is a direct relationship between the amount of drug dissolved and the amount of drug absorbed (1–3). The recent In Vitro/In Vivo Correlation Guidance developed by the FDA states that the main objective of developing and evaluating an IVIVC is to enable the dissolution test to serve as a surrogate for in vivo bioavailability studies. This may reduce the number of bioequivalence studies required for approval as well as during scale-up and post approval change (3). There are numerous examples of Level A correlations in the literature, however many fall short in assessing the predictability of the correlation. The process for the development and validation of an IVIVC has been outlined in the FDA-IVIVC guidance (3). The development of the correlation usually involves the following three steps:

(1) develop formulations with different release rates, e.g. 3 release rates, slow, medium and fast,

(2) obtain in vitro dissolution profiles and in vivo plasma concentration profiles for these formulations, and

(3) estimate the in vivo absorption or in vitro dissolution time course using an appropriate deconvolution technique for each formulation.

The internal validation (3) of the correlation focuses on using prediction error metrics to determine how well the IVIVC model predicts the plasma concentration profile of those formulations used to develop the correlation.

Numerous sustained or extended release metoprolol formulations have been previously developed (4–6), however there are limited examples of validated IVIVCs for metoprolol. According to the Biopharmaceutics Classification System, metoprolol is a "Class I" drug, i.e. high solubility and permeability (7). In addition, its relatively short half-life suggests that it is a suitable candidate for an extended release formulation. In previous work, we have examined the in vitro dissolution behavior and in vivo bioavailability of immediate release (8) and extended release (9) formulations of metoprolol tartrate. The availability of a meaningful IVIVC of high quality and predictability for an extended release metoprolol formulation should provide a sound foundation for product optimization. An established IVIVC allows for certain post-approval changes as described in the Scale-up and Post Approval Changes for Modified Release (SUPAC-MR) FDA Guidance (10). The purpose of this investigation was to develop an IVIVC for an experimental hydrophilic matrix extended release metoprolol tablet. The validity of the correlation was assessed through internal predictability approaches.

METHODS

Formulations

Numerous metoprolol extended release formulations were manufactured at the Industrial Pharmacy Laboratory at the University of Maryland using hydroxypropyl methylcellulose (HPMC) as the release rate controlling excipient (9). These

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formulations were manufactured in a batch size of 3 kg to examine the influence of formulation or processing changes on drug release (9). Of these formulations, three prototypes (9) were selected to examine the influence of formulation or processing changes on *in vitro* dissolution as well as *in vivo* bioavailability. The formulations were designed to release metoprolol at three different rates referred to as: slow, moderate and fast (~24, 15 and 10%/hr, respectively).

Dissolution

The release characteristics of the formulations were examined using the following dissolution testing methodologies:

(1) USP Apparatus II, pH 6.8, at 50 rpm;
(2) USP Appratus II, pH 1.2 at 50 rpm; and
(3) USP Apparatus I, pH 6.8 at 100 and 150 rpm.

Dissolution tests were performed on six tablets and the amount of drug released was analyzed spectophotometrically at a wavelength of 275 nm (9). Dissolution samples were collected at the following times: 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10 and 12 hours.

Bioavailability Study

This was an open, fasting, single dose, four treatment crossover study. The health status of each subject was based on physical examination, history, ECG and clinical laboratory tests. In addition, the debrisoquin-type metabolizing capabilities of each subject was determined by dextromethorphan screening and only extensive metabolizers were enrolled (11). For the dextromethorphan screening, subjects consumed a 30 mg dose of dextromethorphan, urine samples were collected over an eight hour period, stored at -80°C and subsequently analyzed by a validated HPLC method (12). Nine normal healthy, male and female, non-smoking volunteers were enrolled in the study and received three formulations of metoprolol (100 mg) in a randomized fashion. In addition, to the extended release formulations, an oral solution (50 mg) of metoprolol tartrate was also administered. In the first phase, subjects received 50 mg of metoprolol tartrate oral solution (50 ml; 1mg/ml) after an overnight fast. Blood samples (6 ml) were collected at the following times: 0 (pre-dose) and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18, and 24 hours post-dosing. After a one week washout period, subjects were randomly assigned to receive each of the three extended release metoprolol formulations. Tablets were administered with 240 mL of tap water. Six ml of blood were collected pre-dose and at the following times post dosing: 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 16, 20, 24, 30, 36 and 48 hours. Samples were centrifuged for 10 minutes at 25°C and subsequently stored at-80°C until assayed. Each metoprolol administration was separated by a washout period of seven days. Pulse rate and blood pressure were monitored in each subject at least three minutes prior to each blood sample collection. The study was approved by the University of Maryland and the Baltimore Veteran's Administration Institutional Review Boards and each subject provided informed consent prior to enrollment.

Assay Methodology

Two analytical methods were used in this study to quantitate dextromethorphan and its metabolite, dextrophan in urine as well as metoprolol in plasma (12). Extraction of both agents was accomplished with a C_2 (ethyl) solid phase extraction column. Sample analysis was performed using HPLC with fluorescence detection. The limit of quantitation was less than 0.05 μg/ml and extraction recoveries were greater than 90 percent for each analyte. A simple, sensitive and specific reverse-phase high performance liquid chromatographic method was used to determine metoprolol concentration in plasma. An efficient and reproducible extraction method from plasma was used employing C_2 (ethyl) solid phase extraction columns. A C_4 butyl analytical column with fluorescence detection was used to separate metoprolol from endogenous compounds. Fluorescence detection provided high sensitivity and specificity with a limit of quantitation of 1 ng/ml for metoprolol. The plasma HPLC assay method was validated over a range of 1 to 400 ng/ml. Recovery was greater that 92.9% at all concentrations and intra-day and inter-day precision ranged from 0.41 % and 9.9 % and 1.1–15.7 %, respectively.

Dissolution Data Analysis

The *in vitro* dissolution data was analyzed by estimation of a similarity factor, the f_2 metric (13) and parameterized by the sigmoid Emax model. The dissolution profiles were compared using the similarity factor, f_2, presented in the following equation:

$$f_2 = 50 \log\{[1+1/n \Sigma_t^n = 1 (R_t - T_t)^2]^{-0.5} \times 100\} \quad (1)$$

where R_t and T_t are the percent dissolved at each time point for the reference product and the test product, respectively. Using the f_2 values, dissolution profiles were considered dissimilar if these values were less than 50 with the average difference between any dissolution samples not being greater than fifteen percent.

The following Hill equation (14) was used to parameterize the cumulative *in vitro* dissolution data:

$$\% \text{ Dissolved} = \frac{D_{max} * T^{\gamma}}{D_{50}^{\gamma} + T^{\gamma}} \quad (2)$$

where % dissolved is the amount of drug dissolved at time t, D_{max} = the maximum (cumulative) amount of drug dissolved, D_{50} is the time required for 50% of the drug to dissolve, T = time and γ is the sigmoidicity factor.

In Vivo Data Analysis

The metoprolol concentration-time data were evaluated using the Phast® program (Phoenix Scientific Software, Version 2.2, Montreal, Canada) and WINNONLI® Professional (SCI Software; Cary, North Carolina). The highest metoprolol plasma concentration measured for a subject was the $C_{max.}$ The time at which C_{max} occurred was the $T_{max.}$ The AUC from time 0 to the last concentration time point (AUC_{Cplast}) was determined by the trapezoidal method. The AUC_{inf} was determined by the following equation:

$$AUC_{inf} = AUC_{Cplast} + \frac{Cp_{last}}{\lambda_z} \quad (3)$$

The elimination rate constant (λ_z) was determined by linear regression of the linear portion of the ln(concentration) versus

time profile. Typically 4 to 5 points were used to determine the terminal elimination rate constant.

The percent of drug absorbed versus time was determined using numerical deconvolution, where the pharmacokinetic parameters of the oral solution were used as the impulse function. The numerical deconvolution program, PCDCON, (W.R. Gillespie, Austin, Texas) was used to perform the analysis.

Correlation Development

The data generated in the bioavailability study were used to develop the IVIVC. The correlation was developed using mean metoprolol plasma concentration vs. time data following the slow, moderate and fast releasing formulation. Prior to the development of the IVIVC, the fraction of drug dissolved (FRD) was determined using the aforementioned dissolution testing methods; and the fraction of drug absorbed (FRA) was determined using numerical deconvolution. Correlation models were developed using pooled mean FRD and pooled mean FRA data from various combinations of formulations including:

(1) slow, moderate and fast (S/M/F),
(2) slow and fast (S/F),
(3) moderate and fast (M/F), and
(4) slow and moderate (S/M) formulations.

Linear regression analysis was used to examine the relationship between FRD and FRA.

Internal Validation

The internal validation or predictability is defined as how well the four IVIVC models described the data used to develop the model. The internal validation was based on how well the defining four IVIVC models (i.e., S/M, S/F, M/F and S/M/F) predicted the *in vivo* performance of each formulation (i.e., slow, moderate and fast). The procedure used for the 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 of the slow, moderate and fast formulations, respectively. Cross validation was also used to evaluate predictability and it occurred when the IVIVC model did not contain the formulation being predicted. One formulation (i.e. F, S or M) was left out and the in vivo plasma metoprolol concentration vs. time profile was determined from the IVIVC correlation obtained from the remaining two formulations (i.e. S/M, M/F or S/F, respectively).

The IVIVC model predicted metoprolol plasma concentration was determined by the following procedure. First, in vitro dissolution rates were obtained from the dissolution data by taking the first derivative of the fit for the cummulative amount of drug dissolved (Hill equation described above). The in vitro dissolution rates were then converted to in vivo dissolution rates by using the IVIVC models (i.e, slope, intercept). The prediction of the plasma metoprolol concentrations from the corresponding in vivo dissolution profiles was accomplished by convolution of the in vivo dissolution rates and the pharmacokinetic model for the oral solution administration of the drug. The pharmacokinetic parameters used were $\lambda z = 0.29\ hr^{-1}$ and Vd = 5.9 l/kg. The convolution was accomplished on a spreadsheet in Lotus 1-2-3 (Lotus Development Corp.).

Methods of Evaluating the Predictability of IVIVC

To assess the predictive performance of the IVIVC models, a naive pooled model was used. For this work, the naive pooled model was defined as the mean metoprolol concentrations from the formulations used to develop the IVIVC. The naive pooled model assumes that there is no correlation between the fraction of drug dissolved and the fraction of drug absorbed. Four sets of mean metoprolol concentrations were derived from the IVIVC models (i.e., S/M, S/F, M/F and S/M/F to generate four naive pooled models. The naive pooled model is described as follows:

$$P_{naive}(t) = \frac{1}{N}\sum_{k=1}^{N} O_k(t) \tag{4}$$

where $P_{naive}(t)$ = naive model prediction of *in vivo* response at time *t*, N = number of formulations, and $O_k(t)$ = observed *in vivo* responses to the k^{th} formulation at time *t*. Prediction errors (described below) from the naive pooled models were compared to the errors from the internal validation.

Metrics to Evaluate Predictability of IVIVC

Mean absolute prediction error (PE_{abs}) and root mean square error (PE_{rms}) metrics were used to describe the predictability of the IVIVC models (15) as described below:

$$PE_{abs} = \frac{1}{\sum_{i=1}^{N} nk}\sum_{i=1}^{nk} |O(tki) - P(tki)| \tag{5}$$

$$PE_{rms} = \sqrt{\frac{1}{\sum_{i=1}^{N} nk}\sum_{i=1}^{nk} [O(tki) - P(tki)]^2} \tag{6}$$

The PE_{abs} and PE_{rms} from the IVIVC models were compared to the metrics from the corresponding Naive Pooled Model prediction errors.

To further assess the predictability and the validity of the correlations, we determined the observed and IVIVC model predicted C_{max} and AUC for each formulation from the bioavailability study. Prediction errors for the observed and predicted C_{max} and AUC were calculated for each formulation to determine the accuracy of the IVIVC and Naive Pooled models in characterizing the rate and extent of metoprolol absorption. The percent prediction errors for C_{max} and AUC were calculated as follows:

$$\%PE_{Cmax} = \left[\frac{[C_{max}(obs) - C_{max}(pred)}{C_{max}(obs)}\right] * 100 \tag{7}$$

$$\%PE_{AUC} = \left[\frac{[\,AUC(obs) - AUC(pred)}{AUC(obs)}\right] * 100 \tag{8}$$

Where C_{max}(obs) and C_{max}(pred) = the observed and IVIVC model predicted maximum plasma concentration profiles, respectively; and AUC(obs) and AUC(pred) = the observed and IVIVC model predicted AUC for the plasma concentration profiles, respectively. The IVIVC was considered valid if the

average absolute % prediction error is < 10 for Cmax and AUC and if the % prediction error for each formulation does not exceed 15%.

RESULTS

In Vitro Studies

Mean profiles of the cumulative metoprolol fraction dissolved from the slow, moderate, and fast formulations are illustrated in Figure 1. The CV% associated with the dissolution data for each formulation was < 5 percent. The dissolution testing methods were Apparatus II, pH 1.2 at 50 rpm (Figure 1a), Apparatus II, pH 6.8 at 50 rpm (Figure 1b), Apparatus I, pH 6.8 at 100 rpm (Fig. 1c) and Apparatus I, pH 6.8 at 150 rpm (Fig. 1d). The associated f_2 metrics, which determines the similarity of the various formulations are shown in Table 1. An f_2 value between 50 and 100 suggests that two profiles are similar. Accordingly, Apparatus I, pH 6.8 at 50 and 150 rpm were found to be the most discriminating dissolution methods. However, as illustrated in Figure 1, Apparatus I, pH 6.8 at 150 rpm more accurately described the in vivo absorption profile and was subsequently used in the IVIVC model development.

In Vivo Studies

Seven subjects (4 males, 3 females) completed the study, two subjects withdrew voluntarily. The mean ± SD age, height and weight of the subjects were 40.4 ± 6.8 years, 65.8 + 2.5 inches and 159 + 14 pounds, respectively. There were no serious adverse reactions reported in the study. Mean pharmacokinetic parameters are summarized in Table 2 and mean metoprolol concentration versus time profiles after each formulation and the oral solution are presented in Figure 2. The rank order of release observed in the dissolution testing was also apparent in the plasma metoprolol concentration profiles with a mean C_{max} of 66.2, 91.0 and 120 ng/ml for the slow, moderate and fast releasing formulations. In addition, a rank order was also apparent in the AUC_{inf} (Table 2).

Table 1. f_2 Metric for Various Dissolution Testing Systems for Extended Release Metoprolol Formulations

pH	Conditions	Formulations		f_2
1.2	Paddle, 50 rpm	moderate	fast	39.95
		moderate	slow	70.59
		fast	slow	30.28
6.8	Paddle, 50 rpm	moderate	fast	42.35
		moderate	slow	42.04
		fast	slow	28.05
6.8	Basket, 100 rpm	moderate	fast	33.41
		moderate	slow	77.05
		fast	slow	31.51
6.8	Basket, 150 rpm	moderate	fast	45.99
		moderate	slow	39.26
		fast	slow	30.88

IVIVC Correlation Development

Figures 3a–3b presents the pooled FRD vs. FRA for the slow, moderate and fast formulations using Apparatus II, pH

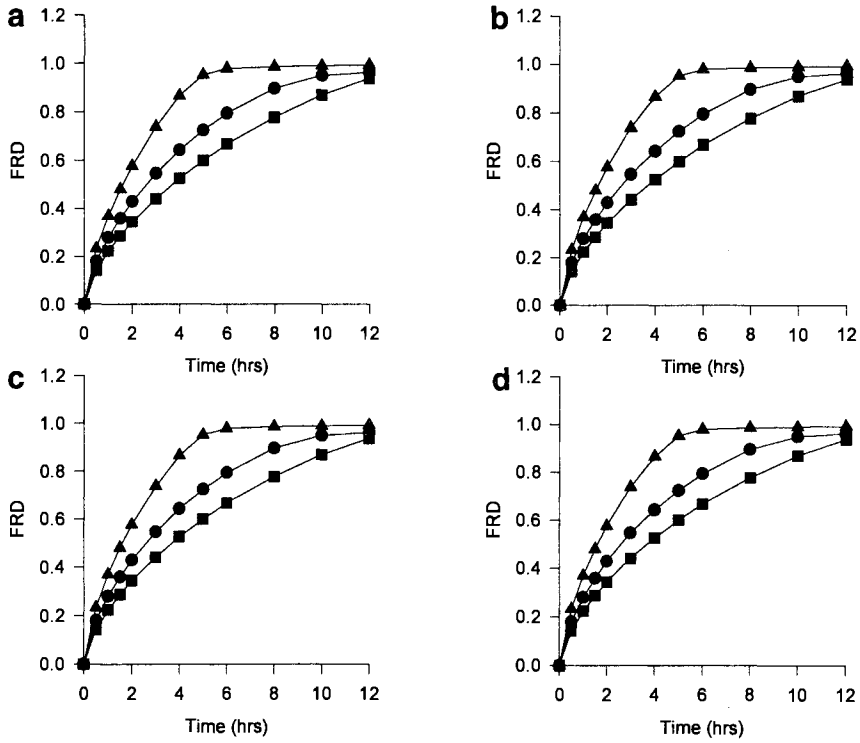

Fig. 1. Mean metoprolol dissolution versus time profile for slow (▪), moderate (●) and fast (▲) extended release tablets using: (a) Apparatus II, pH 1.2, 50 rpm, (b) Apparatus II, pH 6.8, 50 rpm, (c) Apparatus I, pH 6.8, 100 rpm and (d) Apparatus I, pH 6.8, 150 rpm.

Table 2. Mean Pharmacokinetic Parameters after Extended Release Metoprolol Formulations

Formulation	C_{max} (ng/L)	T_{max} (hrs)	AUC_{inf} (μg·hr/L)
Solution	58.6	2.07	346
	(13.8)	(0.53)	(40.6)
Slow	66.2	4.86	718
	(15.4)	(1.06)	(192)
Moderate	91.0	3.57	810
	(32.5)	(0.53)	(287)
Fast	120	3.14	821
	(31.5)	(0.38)	(197)

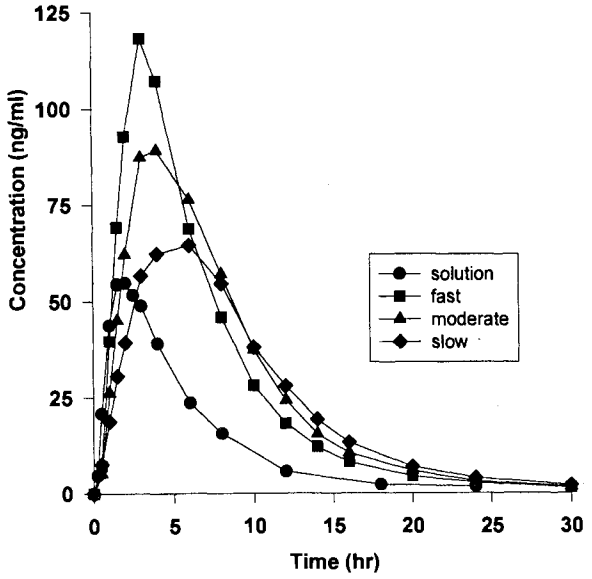

Fig. 2. Mean metoprolol plasma concetration versus time profile after oral solution, slow, moderate and fast release formulations.

6.8 at 50 rpm and Apparatus I, pH 6.8 at 150, respectively. Linear correlations between the fraction of metoprolol dissolved (FRD) and the fraction of metoprolol absorbed (FRA) could not be developed for the dissolution systems using Apparatus II, pH 1.2 or 6.8 at 50 rpm as seen in Figure 3a. Dissolution testing using Apparatus I, pH 6.8 at 150 rpm was more representative of the *in vivo* absorption profiles and linear regression relationships were developed. There was good linear correlation for these models, with r^2 values > 0.9 for the IVIVC models. Each correlation was found to be significant and the combination of the slow and moderate formulation displayed the strongest relationship (r^2 = 0.991). Conversely, the correlation for the slow and fast formulations was less descriptive as compared to the other correlation models (r^2 =0.946). The regression lines obtained between FRA and FRD for all IVIVC models were significant ($p < 0.05$) and the slopes were not significantly different from 1 ($p > 0.05$).

Internal Validation

The internal validation was performed by convolution of the dissolution data (i.e. Apparatus I, pH 6.8, 150 rpm) that corresponded to each formulation (S/M/F). Each of the IVIVC model predicted metoprolol plasma concentration versus time profiles were compared to the experimental data points using prediction error metrics. Figure 4 illustrates the observed and IVIVC model metoprolol plasma concentrations for the slow (Figure 4a), moderate (Figure 4b) and fast (Figure 4c) formulations using the S/M/F IVIVC model, respectively. The absolute and root mean squared prediction errors for each IVIVC models are presented in Table 3. The validity of the correlations was also assessed by determining how well the IVIVC models could predict the rate and extent of metoprolol absorption as characterized by C_{max} and AUC. Tables 4 and 5 present the percent errors estimated for the difference between the observed and predicted C_{max} and AUC values for the IVIVC and naive pooled models, respectively. None of the IVIVC model predicted parameters deviated from the experimental values by more than twenty percent. In general, the IVIVC models had lower

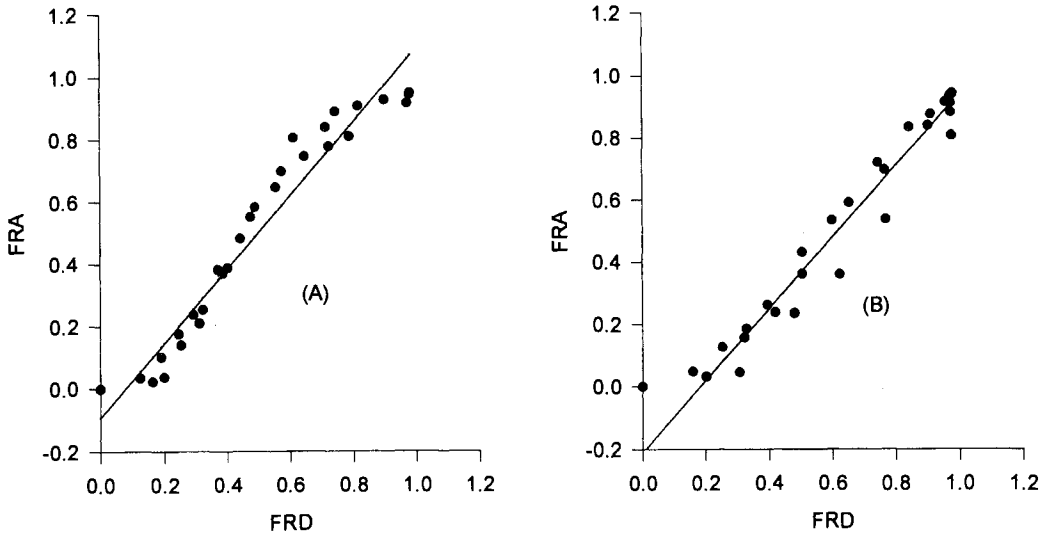

Fig. 3. IVIVC model linear regression plots of FRA vs FRD for the slow, moderate and fast tablets: (A) Apparatus II, pH 6.8, 50 rpm and (B) Apparatus I, pH 6.8, 150 rpm.

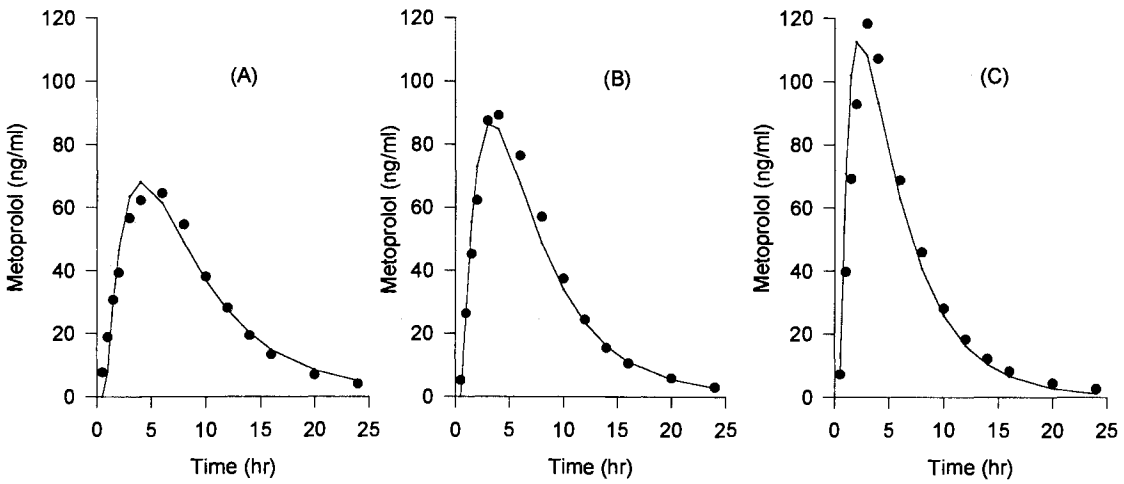

Fig. 4. Observed (●) and predicted (—) metoprolol plasma concentration for the (A) slow, (B) moderate and (C) fast releasing formulation using apparatus I, pH 6.8 150 rpm and the S/M/F IVIVC model.

Table 3. PE_{abs} and PE_{rms} for Metoprolol IVIVC Models

	PE_{abs}			
Formulation	S/M/F	S/M	M/F	S/F
Slow	3.85	4.45	3.83	3.83
Moderate	3.94	4.42	3.93	4.18
Fast	9.28	10.2	9.01	9.35
	PE_{rms}			
Formulation	S/M/F	S/M	M/F	S/F
Slow	5.06	6.03	4.94	4.94
Moderate	5.52	6.49	5.14	5.66
Fast	14.1	17.1	13.3	13.7

prediction error estimates as compared to the naive pooled models for both C_{max} and AUC.

DISCUSSION

The FDA-IVIVC Guidance and the USP/AAPS/FDA-Workshop II, which examined the scale-up of oral extended release dosage forms, stated that the objective of an IVIVC was the use of dissolution as a surrogate for bioequivalency testing and as an aid in setting dissolution specifications (3, 16). In the process of developing an IVIVC, it is imperative to utilize dissolution methodology that discriminates between formulations and mimics the *in vivo* release profile. We examined various dissolution testing methods to characterize the release of the three formulations of metoprolol tartrate. This is in accordance with specifications on dissolution data presented in the SUPAC-MR (10) and IVIVC (3) guidances. The initial IVIVC development began with using the USP defined dissolution methodology for metoprolol (i.e. Apparatus II, pH 1.2 or 6.8 at 50 rpm). These dissolution methods produced a curvilinear relationship (Figure 3a) between FRD and FRA and the dissolution results were not representative of the *in vivo* metoprolol absorption profile. The release profile generated lagged behind the absorption profile. An increase in the shear force or velocity of the testing system was required to approximate the absorption profile. Dissolution testing with Apparatus I, pH 6.8 at 150 rpm provided FRD data that was predictive of the FRA. It appears that the increase in agitation generated from this in vitro dissolution system appropriately simulated the erosion that occurs in vivo with this formulation. Once identified, the

Table 4. C_{max} Prediction Errors (%) for Metoprolol IVIVC and Naive Pooled Models

	IVIVC Models			
Formulation	S/M/F	S/M	M/F	S/F
Slow	−5.67	−11.38	−3.75	−3.75
Moderate	−0.85	−1.55	5.18	4.25
Fast	3.97	−1.83	3.55	5.74
	Naive Pooled Models			
Formulation	S/M/F	S/M	M/F	S/F
Slow	−35.57	−17.39	−59.2	−35.51
Moderate	−1.93	15.01	−15.26	1.89
Fast	26.06	35.93	13.1	26.03

Table 5. AUC Prediction Errors (%) for Metoprolol IVIVC and Naive Pooled Models

	IVIVC Models			
Formulation	S/M/F	S/M	M/F	S/F
Slow	−0.76	−5.77	1.05	1.05
Moderate	5.22	1.52	7.07	6.94
Fast	4.52	−0.97	3.71	6.25
	Naive Pooled Models			
Formulation	S/M/F	S/M	M/F	S/F
Slow	−9.76	−6.85	−14.64	−7.73
Moderate	−3.51	−6.07	−0.77	5.30
Fast	5.01	−7.54	0.79	6.77

dissolution methodology should be used in any further evaluation of the correlation, such as external validation.

Correlations were developed with the slow, moderate and fast formulations as well as combinations of two formulations (e.g. slow and moderate, moderate and fast, slow and fast). The evaluation of the correlation displayed a significant linear relationship between FRD vs. FRA when using either two (S/M, M/F or S/F) or three (S/M/F) formulations. The IVIVC relationship was demonstrated consistently with a minimum of two formulations as well as all three formulations.

The predictability of the correlations developed were tested by internal validation which consisted of calculating prediction errors (PE_{abs}, PE_{rms}, $\%PE_{Cmax}$, and $\%PE_{AUC}$). These errors were then compared to the errors generated by the naive pooled model. In general, (1) the prediction errors for the internal validation were relatively low, (2) in most instances the IVIVC model prediction errors were less than the naive pooled model, and (3) the S/M/F- IVIVC model produced the lowest prediction errors. Through the process of assessing the internal validity, the utility of the prediction errors, PE_{abs} and PE_{rms}, was also examined. As they relate to IVIVC validation, these metrics appear to be relative in nature and do not provide an indication of the true predictive performance of the model as it relates to experimental values.

A realistic measurement of the validation is the ability of the IVIVC models to estimate the observed rate and extent of absorption. All IVIVC models predicted the observed C_{max} and AUC within 12 percent of the experimental values (Tables 4 and 5). The lowest prediction error for C_{max} (0.38 %) was found for the moderate formulation using the S/M IVIVC model. The M/F IVIVC model provided the best estimate of AUC for the slow formulation (-0.70%). Also, the IVIVC models in general displayed lower prediction errors as compared to the naive pooled models. The relatively low prediction errors (PE_{rms} and PE_{abs}) and percent prediction errors (C_{max} and AUC) found strongly suggest that the metoprolol IVIVC models are valid. The average percent prediction error of less than 10% indicates that the correlation is predictive and is acceptable according to the FDA-IVIVC guidance (13). Based on the results of the internal prediction error calculation, evaluation of this IVIVC externally is not required.

In conclusion, the best IVIVC model developed herein, demonstrates that dissolution data can be used to accurately and precisely determine the *in vivo* performance of this metoprolol extended release formulation. *In vivo* bioavailability/bioequivalency waivers as well as meaningful dissolution specifications can be set for formulations falling within the release rate ranges of the established correlations. These alternative formulations may be the result of changes in the release and non-release controlling excipients within a specified range, changes in site of manufacture, changes in batch size, and manufacturing equipment or processing changes as outlined in the SUPAC-MR guidance (10). This IVIVC is now being externally validated to predict the influence of site changes, processing changes, scale-up as well as predicting the absorption profile of a metoprolol extended release product with a different release mechanism.

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