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Research paper

The influence of first pass metabolism on the development and validation of an IVIVC for metoprolol extended release tablets

Nattee Sirisuth, Natalie D. Eddington*

Pharmacokinetics Biopharmaceutics Laboratory, Department of Pharmaceutical Sciences, School of Pharmacy, University of Maryland, Baltimore, MD, USA

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Abstract

To investigate the influence of α-hydroxymetoprolol (AHM) and 4-(2-hydroxy-3-isopropylaminopropoxy)-phenylacetic acid (ACMB), both derived from its first pass metabolism of metoprolol, an in vitro in vivo correlation incorporating first pass metabolite data for metoprolol extended release formulations was developed. Three different releasing formulations (slow (S), moderate (M) and fast (F), 100 mg) of metoprolol were evaluated in a previously reported clinical study. The non-first pass effect (Non-FPE) in vitro in vivo correlation (IVIVC) was developed using a fraction of metoprolol dissolved and a fraction of total drug (metoprolol + metabolites) as the absorption data for various combinations of formulations (S/M/F, M/F, S/M, and S/F). Direct convolution approaches predicting metoprolol concentrations and indirect convolution predicting total drug concentrations (metoprolol + metabolites) were used to determine in vivo behavior. The Non-FPE IVIVC using the S/M/F formulations displayed the strongest relationship ($r^2 > 0.92$). The IVIVC using the indirect approach was predictive of both the C_{max} (prediction errors (PE) 4.77, 3.94 and 6.14%) and AUC (10.7, 11.0 and 11.3%) for metoprolol, AHM and ACMB. Poor predictability (PE > 40% for C_{max} and AUC) was observed for metoprolol when using the direct methods. The predictability of the IVIVC using the indirect approach as compared to the direct method displays the influence of first pass metabolism on the development and evaluation of an IVIVC for a drug that displays a high extraction ratio. In addition, the indirect IVIVC allows for not only predicting the in vivo performance of the parent drug but also the metabolites formed via the first pass effect.

Keywords: Metoprolol; α-Hydroxymetoprolol; Correlation; In vitro in vivo correlation; Bioavailability

1. Introduction

In vitro in vivo correlation (IVIVC) as defined by the Food and Drug Administration (FDA) is "a predictive mathematical model describing the relationship between an in vitro property of a dosage form and an in vivo response" [1]. It is usually developed using parent drug data, even though in certain circumstances, the parent drug may undergo significant first pass metabolism prior to reaching the systemic circulation [2–5]. The development of an IVIVC is based on a mathematical model that relates the fraction of drug released (in vitro) to the fraction of total drug absorbed across the gastrointestinal mucosa (in vivo). A valid IVIVC empowers the in vitro dissolution data to predict the in vivo bioavailability profile assuming that in vivo drug absorption approximates in vitro release from the dosage form.

Previous studies have reported the importance of first pass metabolism in the accurate assessment of the bioequivalency [6,7]. The measurement of the rate and extent of a metabolite formed via first pass metabolism may indirectly reflect the in vivo characteristic of the formulation. In the presence of first pass metabolism, drug release in vivo is subject to biotransformation, hence, the amount of systemically available drug is less than the amount of drug actually released from the formulation. The use of absorption data of the parent drug for IVIVC development may not be appropriate, since it does not reflect the true in vivo drug release and hence, in vitro drug dissolution may not represent the in vivo drug absorption.

In our laboratory, we have developed and validated IVIVCs for agents which display extensive first pass metabolism such as metoprolol and diltiazem [2–5]. However, conceptual issues remain unresolved which are inherent in the assumptions associated with the development and subsequent validation of an IVIVC. As stated, an underlying issue in the development of IVIVCs for drugs with extensive first pass metabolism is resolving the fact that systemic drug levels are not reflective of the amount of drug released in

* Corresponding author. Pharmacokinetics Biopharmaceutics Laboratory, Department of Pharmaceutical Sciences, School of Pharmacy, University of Maryland, 100 Penn Street, AHB, Baltimore, MD 21201, USA. Tel.: +1-410-706-6710; fax: +1-410-706-6580.

E-mail address: neddingt@rx.umaryland.edu (N.D. Eddington).

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the gastrointestinal tract. Even though predictive IVIVCs have been developed using traditional approaches [2,4,5], the following questions remain: (1) is an IVIVC developed with total drug released (e.g. parent drug plus metabolites formed via first pass metabolism) a better predictor of in vivo bioavailability, as compared to (2) an IVIVC developed with the systemic parent drug levels only? The later issue ignores the fact that in vivo drug release is not reflective of in vitro drug release.

1.1. Objectives of the study

To examine the importance of incorporating first pas metabolism data into the development and validation of an IVIVC, we used a model drug, metoprolol. Metoprolol was selected since it undergoes extensive first pass elimination after oral administration [8]. The metabolism of metoprolol depends on genetic activity of the CYP2D6 isozyme [9,10], however two inactive first pass metabolites, α-hydroxymetoprolol (AHM) and 4-(2-hydroxy-3-isopropylaminopropoxy)-phenylacetic acid (ACMB), are formed [9]. As the recovery of metoprolol metabolites in plasma is very large, accounting for 75% of the dose [11], ignoring the metabolite data in the correlation development may result in a substantial loss of information concerning the 'true' in vivo drug release. The purpose of this study was to investigate the influence of first pass metabolism on the development and validation of an IVIVC. Incorporation of the metabolite data along with the parent drug data in the development of an IVIVC may provide more insight into the in vivo behavior of both parent and metabolite compounds as well as the release characteristic of the formulations.

2. Materials and methods

2.1. Formulations

Extended release formulations of metoprolol were manufactured at the Industrial Pharmacy Laboratory at the University of Maryland using hydroxypropyl methylcellulose (HPMC) as the release rate controlling excipient. The formulations were designed to release metoprolol (100 mg) at three different rates referred to as: slow (S), moderate (M) and fast (F) (~10, 15 and 24%/h, respectively). Metoprolol extended release formulation development and manufacturing have been previously reported elsewhere [2].

2.2. Dissolution

The release characteristics of the formulations were determine using USP Apparatus I, pH 6.8, 150 rev./min. Dissolution samples were collected at the following times: 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10 and 12 h. Dissolution tests were performed on six tablets and the amount of drug released was analyzed spectrophotometrically at a wavelength of 275 nm and using the assay methods reported below.

2.3. Bioavailability study

The bioavailability study has been previously reported [2]. Briefly, this was an open-label, fasting, single dose, four treatment crossover study using normal healthy volunteers. The debrisoquin-type metabolizing capabilities of each subject were determined by dextromethorphan screening and only extensive metabolizers were enrolled. Seven normal healthy, male and female, non-smoking volunteers were enrolled in the study and received three formulations (S, M, and F) 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. Blood samples (6 ml) were collected over a 24 h period after the administration of each treatment. Samples were centrifuged for 10 min at 25 °C and subsequently stored at −80 °C until assayed.

2.4. Assay method for metoprolol and metabolites

Plasma and dissolution samples were analyzed for metoprolol (MET) and AHM using valid high performance liquid chromatography (HPLC) with fluorescence detection [12]. Chromatography involved direct separation using a Chirobiotic T™ bonded phase column (250 × 4.6 mm) and a mobile phase consisting of ACN/MeOH/$MeCl_2$/glacial acetic acid/triethylamine (56/30/14/2/2 (v/v/v/v)). Solid phase extraction using silica bonded with ethyl group (C_2) was used to extract the compounds of interest from plasma and atenolol was used as the internal standard. The column effluent was monitored using fluorescence detection with excitation and emission wavelengths of 225 and 310 nm, respectively. The lowest level of quantitation for metoprolol was 0.5 ng/ml and for AHM 1.0 ng/ml.

A selective and specific HPLC method using fluorescent detection was developed to quantitate the acid metabolite (ACMB) of metoprolol in human plasma [13]. Precipitation of plasma proteins was accomplished with acetonitrile to separate interfering endogenous products from the compounds of interest. The organic layer was evaporated to dryness, reconstituted and extracted using a C_{18} solid phase column. The chromatography was performed with a Chirobiotic T™ analytical column and the mobile phase consisted of methanol/methylene chloride/glacial acetic acid/triethylamine (70/30/2/2 (v/v/v/v)) and was pumped at a flow rate of 2.2 ml/min. The lower limit of quantitation was 12.5 ng/ml.

2.5. In vitro dissolution data analysis

The dissolution profiles for each formulation (S, M, and F) were determined by plotting the cumulative fraction of the metoprolol dissolved (FRD) at various time points. The dissolution data were mathematically modeled by fitting the

mean profile of metoprolol to the following Hill equation:

$$\%\ \text{Dissolved} \frac{D_{\max} T^{\gamma}}{D_{50}^{\gamma} + T^{\gamma}} \quad (1)$$

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

The in vitro drug release profiles were compared using the similarity factor, f_2, presented in the following equation [14]:

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

where R_t and T_t are the percent dissolved at each time point for the reference and test products and n is the number of pooled points.

2.6. IVIVC development process

2.6.1. Determination of the fraction of 'total' drug absorbed

In order to assess the effect of first pass metabolism on the development of an IVIVC, it was necessary to determine the fraction of metoprolol absorbed prior to first pass metabolism. Hence, the amount of both AHM and ACMB would have to be determined and added to the amount of metoprolol. It should be noted that both AHM and ACMB are formed via first pass metabolism of metoprolol [9]. In order to determine the amount of AHM and ACMB, an approach involving mathematical modeling and computer simulation was used to estimate the volume of distribution for each metabolite. The following differential equations describe the mathematical model used to describe the disposition of metoprolol, AHM and ACMB.

$$\frac{dX_1}{dt} = -k_a \cdot X_1 \quad (3)$$

$$\frac{dX_2}{dt} = k_a \cdot X_1 - (k_{AHM} + k_{ACMB}) \cdot X_2 \quad (4)$$

$$\frac{dX_3}{dt} = k_{AHM} \cdot X_2 \quad (5)$$

$$\frac{dX_4}{dt} = k_{ACMB} \cdot X_2 \quad (6)$$

where X_1 and X_2 are the amount of metoprolol in the gastrointestinal tract and the body, respectively, X_3 and X_4 are the amount of AHM and ACMB in the body, respectively, and k_a, k_{AHM} and k_{ACMB} represent the absorption rate constant, the formation rate constant for AHM and the formation rate constant for ACMB, respectively. A model building procedure was used by simultaneously simulating the plasma concentrations of metoprolol as well as metabolites and subsequent estimation of their pharmacokinetic parameters using the Adapt II pharmacokinetic software [15].

The amount of each compound was calculated based on its volume of distribution derived from the aforementioned pharmacokinetic modeling process. The summation of metoprolol, AHM and the acid metabolite provided an estimate of the true 'total metoprolol' released from the formulation. The 'total metoprolol' concentration was defined as the in vivo metoprolol released prior to first pass metabolism and was used for estimating the fraction of drug absorbed (FRA) in the IVIVC.

2.6.2. Estimation of fraction of total drug absorbed (FRA) in vivo

The fraction of total drug (metoprolol + AHB + ACMB) absorbed for each formulation was determined using the Wagner–Nelson method (Eq. (7)).

$$\text{Fa}_t = \frac{\text{Cp}_t + \text{Kel}[\text{AUC}]_0^t}{\text{Kel}[\text{AUC}]_0^{\infty}} \quad (7)$$

where Fa_t is the fraction of drug absorbed at time t, Cp_t is the plasma drug concentration (metoprolol + AHB + ACMB) at time t, Kel is the elimination rate constant, $[\text{AUC}]_{0-t}$ is the area under the concentration time curve from time 0 to time t, and $[\text{AUC}]_{0-\infty}$ is the area under the concentration time curve from time 0 to infinity. The Kel used in this equation was obtained from the reference oral solution.

2.6.3. IVIVC development

A correlation between pooled FRD and pooled FRA was established for combinations of formulations (S/M/F, M/F, S/F, and S/M). A linear regression using an ordinary least squares method was applied to estimate the regression parameters. Determination coefficient (r^2) was evaluated and the F-statistic was estimated if the slope was significantly different form zero ($P < 0.05$). Since this correlation was established based on a fraction of the total amount (metoprolol + AHB + ACMB) released in vivo, assuming no first pass elimination this correlation is referred to as the Non-*f*irst *p*ass *e*ffect (Non-FPE) IVIVC.

2.6.4. IVIVC evaluation

The predictability of the Non-FPE IVIVC was based on its ability to estimate either metoprolol plasma concentrations or 'total' metoprolol (metoprolol + AHM + ACMB) concentrations. These approaches were defined as a direct and indirect method of evaluation, respectively. The direct method used the Non-FPE IVIVC to estimate the in vivo performance of metoprolol alone. The indirect method used the Non-FPE IVIVC to predict the total drug concentration. Using total drug concentration data generated from the indirect method, subsequent estimation of the metoprolol concentration was obtained by using AUC ratios of parent drug to metabolites to estimate metoprolol concentrations. The ratio of AHM/metoprolol and the acid metabolite/metoprolol ranged from 0.88 to 0.84 and 9.91 to 10.7, respectively. The direct and indirect methods were assessed to

examine the influence of first pass metabolism on the predictability of the developed IVIVC.

IVIVC model validation was performed using the convolution integral as defined in Eq. (8) [16].

$$c(t) = \int_0^t c_\delta(t-u) r_{abs}(u) \mathrm{d}u \quad (8)$$

where $c(t)$ is the in vivo plasma profile of the total compound, and c_δ represents the concentration time course that would result from the instantaneous absorption of a unit amount of drug and it is estimated from the solution data. For the direct approach, c_δ was obtained from metoprolol concentration data and for the indirect approach c_δ was obtained from the total concentration (metoprolol + AHM + ACMB).

Since the IVIVC is used as a surrogate of in vivo behavior, the predictability of C_{max} and AUC for metoprolol and total drug was determined. The in vivo plasma profile was estimated based on the convolution integral (Eq. (8)). Briefly, the in vitro dissolution rates were determined by taking the first derivative of the cumulative amount of drug dissolved. It then was converted to the in vivo dissolution rate by using the IVIVC regression parameters. The predicted plasma concentration corresponding to its in vivo dissolution rate was accomplished by convolution of the in vivo dissolution rate and the pharmacokinetic model for the oral solution. C_{max} and AUC prediction errors (PE) were obtained. The IVIVC was considered valid if the averaged absolute % PE was $\leq$10 for C_{max} and AUC and if the % PE for each formulation did not exceed 15%.

3. Results and discussion

3.1. In vitro dissolution and in vivo absorption

The profiles of the release of metoprolol from the slow, moderate and fast formulation using USP Apparatus I, pH 6.8, 150 rev./min (Fig. 1A) displayed differences in dissolution as indicated by a $f_2 < 50$ for each formulation pair. The mean plasma vs. time profiles of metoprolol, AHM, and ACMB for the tablets and oral solution are illustrated in Fig. 1B–D, respectively. Table 1 summarizes the pharmacokinetic parameters obtained after dosing for metoprolol, AHM and ACMB. No statistical differences were observed for the AUC of metoprolol across formulations. The extent of formation for AHM and ACMB also displayed no significant differences.

Fig. 2A–C presents the observed and pharmacokinetic model predicted plasma drug concentrations for metoprolol and the observed and model predictive cumulative concentrations of AHM and ACMB after the administration of the slow, moderate and fast formulation. The model was found to be predictive of metoprolol and the metabolites based on standard goodness of fit criteria. Table 2 summarizes the simulated pharmacokinetic parameters obtained from the modeling process for metoprolol, AHM and ACMB. The

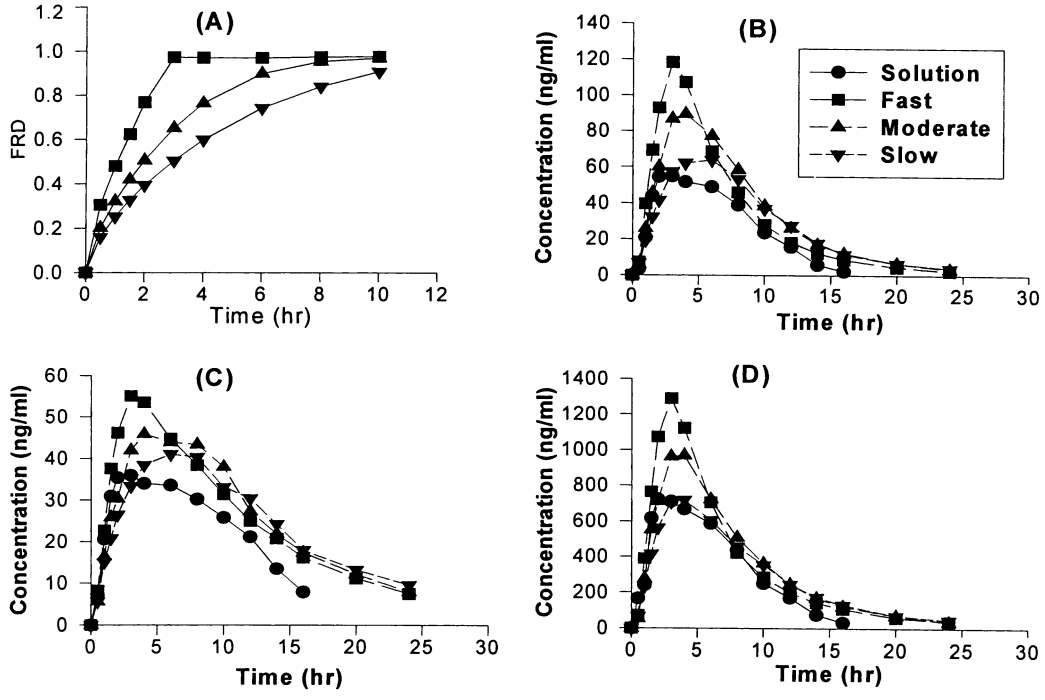

Fig. 1. Dissolution and plasma drug concentration vs. time profiles for the slow moderate and fast extended release formulations: (A) mean metoprolol fraction of drug dissolved (FRD) vs. time profile for the slow, moderate and fast formulations using USP Apparatus I, pH 6.8, 150 rev./min; (B) mean metoprolol plasma concentration vs. time profile for the slow, moderate and fast extended release formulations (100 mg) and the oral solution (50 mg); (C) mean AHM plasma concentration vs. time profile; and (D) mean acid metabolite plasma concentration vs. time profile.

Table 1
Mean (SD) bioavailability parameters for metoprolol, AHM and the acid metabolite after the administration of the slow, moderate and fast extended release formulation to normal healthy volunteers ($n = 7$)

Formulation[a]	Metoprolol		AHM		Acid metabolite	
	C_{max} (ng/ml)	AUC (ng h/ml)	C_{max} (ng/ml)	AUC (ng h/ml)	C_{max} (ng/ml)	AUC (ng h/ml)
Slow	63.7 (14.6)	696 (170)	41.4 (10.8)	589 (140)	741 (128)	6898 (1262)
Moderate	86.3 (29.3)	812 (281)	51.4 (18.9)	622 (192)	1003 (283)	8160 (1390)
Fast	108 (31.0)	791 (188)	55.7 (13.8)	633 (140)	1245 (149)	8444 (746)
P value	<0.05	NS[b]	<0.05	NS	NS	NS

[a] Formulation used for ANOVA test.
[b] NS, non-significant.

simulated model estimated a V_d of 400–-470 l for metoprolol. This was similar to a previous report in which the V_d for metoprolol was reported to be 392 l/70 kg [17].

3.2. IVIVC development

Non-FPE IVIVC models were developed using the dissolution and absorption data from various combinations of formulations. Fig. 3A–D presents the pooled FRD vs. FRA (total) for the following combinations of formulations: slow, moderate and fast formulations (Fig. 3A), moderate and fast (Fig. 3B), slow and fast (Fig. 3C) and slow and fast (Fig. 3D). All correlations were developed using USP Apparatus I, pH 6.8 at 150 rev./min, respectively. There was good linear correlation for these models, with r^2 values >0.9. Each correlation was found to be significant and the combination of the slow, moderate and fast formulations displayed the strongest relationship ($r^2 > 0.92$). In addition, the

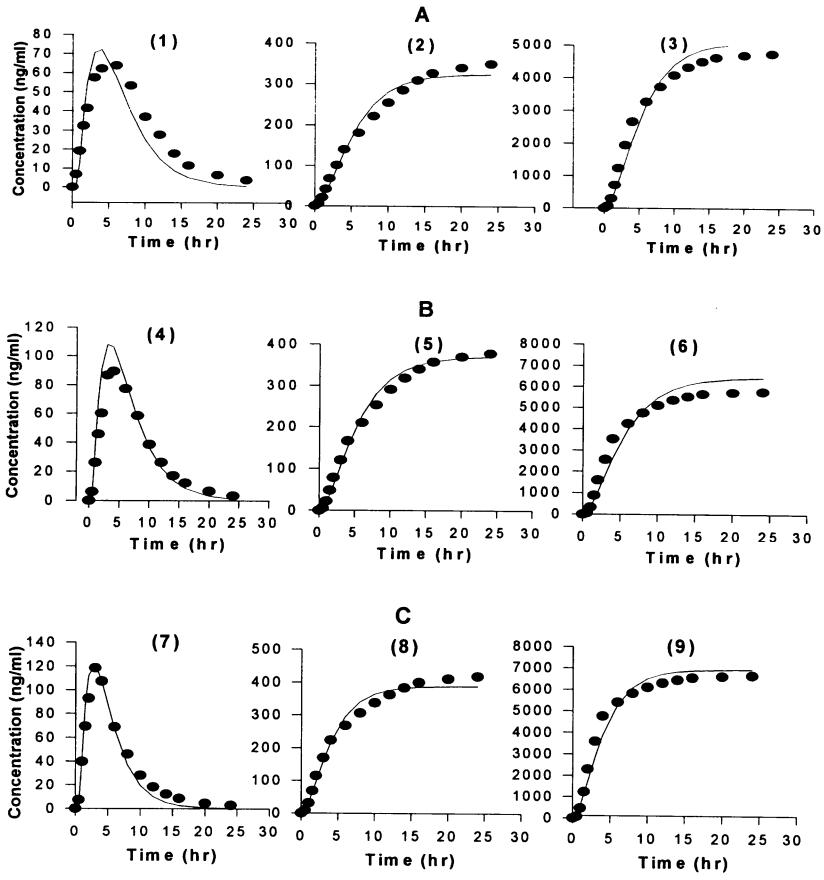

Fig. 2. The observed and pharmacokinetic model predicted plasma drug concentrations for metoprolol and metabolites: (A) slow formulation profiles for (1) metoprolol and the cumulative concentrations of (2) mean AHM and (3) mean acid metabolite; (B) moderate formulation profiles for (4) metoprolol and the cumulative concentrations of (5) mean AHM and (6) mean acid metabolite; and (C) fast formulation profiles for (7) metoprolol and the cumulative concentrations of (8) mean AHM and (9) mean acid metabolite.

Table 2
Compartment model simulated pharmacokinetic parameters for metoprolol, AHM and the acid metabolite after the administration of the slow, moderate and fast extended release formulations to normal healthy volunteers ($n = 7$)[a]

Formulation	V_d (l)	V_{AHM} (l)	V_{ACMB} (l)	k_a (h^{-1})	k_{AHM} (h^{-1})	k_{ACMB} (h^{-1})
F	400	34.6	12.7	0.66	0.05	0.30
M	450	32.3	15.1	0.49	0.03	0.23
S	470	40.6	17.1	0.33	0.05	0.33

[a] V_d, volume of distribution of metoprolol; V_{AHM}, V_d of AHM; V_{ACMB}, V_d of ACMB.

regression line obtained between FRA and FRD was significant ($P < 0.05$) and the slope was not significantly different from 1 ($P > 0.05$).

3.3. IVIVC evaluation

The direct method to evaluate the predictability of the Non-FPE IVIVC used the correlation to estimate the in vivo performance of metoprolol alone. Table 3 presents the C_{max} and AUC metoprolol PEs for the slow, moderate and fast formulations using the Non-FPE IVIVC. The average absolute PE (% PE) for C_{max} and AUC was 72.2 and 43.5%, respectively. Based on these PEs, the Non-FPE IVIVC model was unable to accurately predict the rate and extent of absorption for metoprolol. The Non-FPE IVIVC correlates the metoprolol FRD with the FRA obtained from the summation of metoprolol and metabolites (AHM and ACMB). The failure of the Non-FPE IVIVC model, which considers the role of first pass metabolism, indicates that this process has a significant impact in the IVIVC development for metoprolol.

The indirect approach uses the Non-FPE IVIVC to estimate the total (metoprolol, AHM, ACMB) drug concentration prior to first pass metabolism after the administration of the slow, moderate and fast formulations. The AUC ratios of parent drug to metabolite were used to estimate metoprolol concentrations. The Non-FPE IVIVC model was able to accurately predict the in vivo behavior of metoprolol. Table 3 also includes the C_{max} and AUC PEs for total metoprolol concentration. Both the rate as well as the extent of

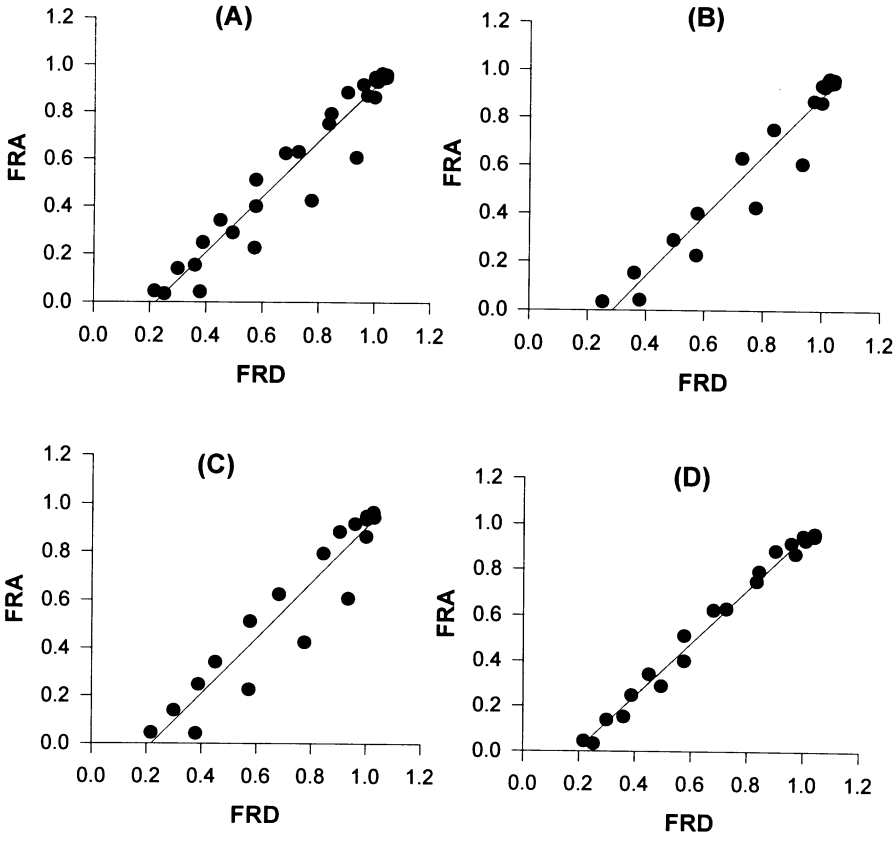

Fig. 3. Non-FPE IVIVC linear regression plots using USP Apparatus I, pH 6.8, 150 rev./min for various combinations of formulations: (A) model using slow, moderate and fast formulations; (B) model using moderate and fast formulations; (C) model using slow and fast formulations; and (D) model using slow and moderate formulations.

Table 3
C_{max} and AUC % PE for metoprolol, AHM and the acid metabolite for the slow, moderate and fast formulations using the Non-FPE model and the direct and indirect convolution approaches

Parameters	Direct approach				Indirect approach			
	Slow	Moderate	Fast	Average	Slow	Moderate	Fast	Average
Metoprolol								
C_{max}	− 83.6	− 65.0	− 67.8	72.2	− 9.26	1.94	3.10	4.77
AUC	− 46.6	− 43.0	− 41.0	43.5	9.27	11.5	11.4	10.77
AHM								
C_{max}	–	–	–	–	− 7.96	0.65	3.20	3.94
AUC	–	–	–	–	12.7	10.3	10.1	11.0
Acid metabolite								
C_{max}	–	–	–	–	− 13.1	− 1.81	3.54	6.14
AUC	–	–	–	–	9.69	11.5	12.7	11.3

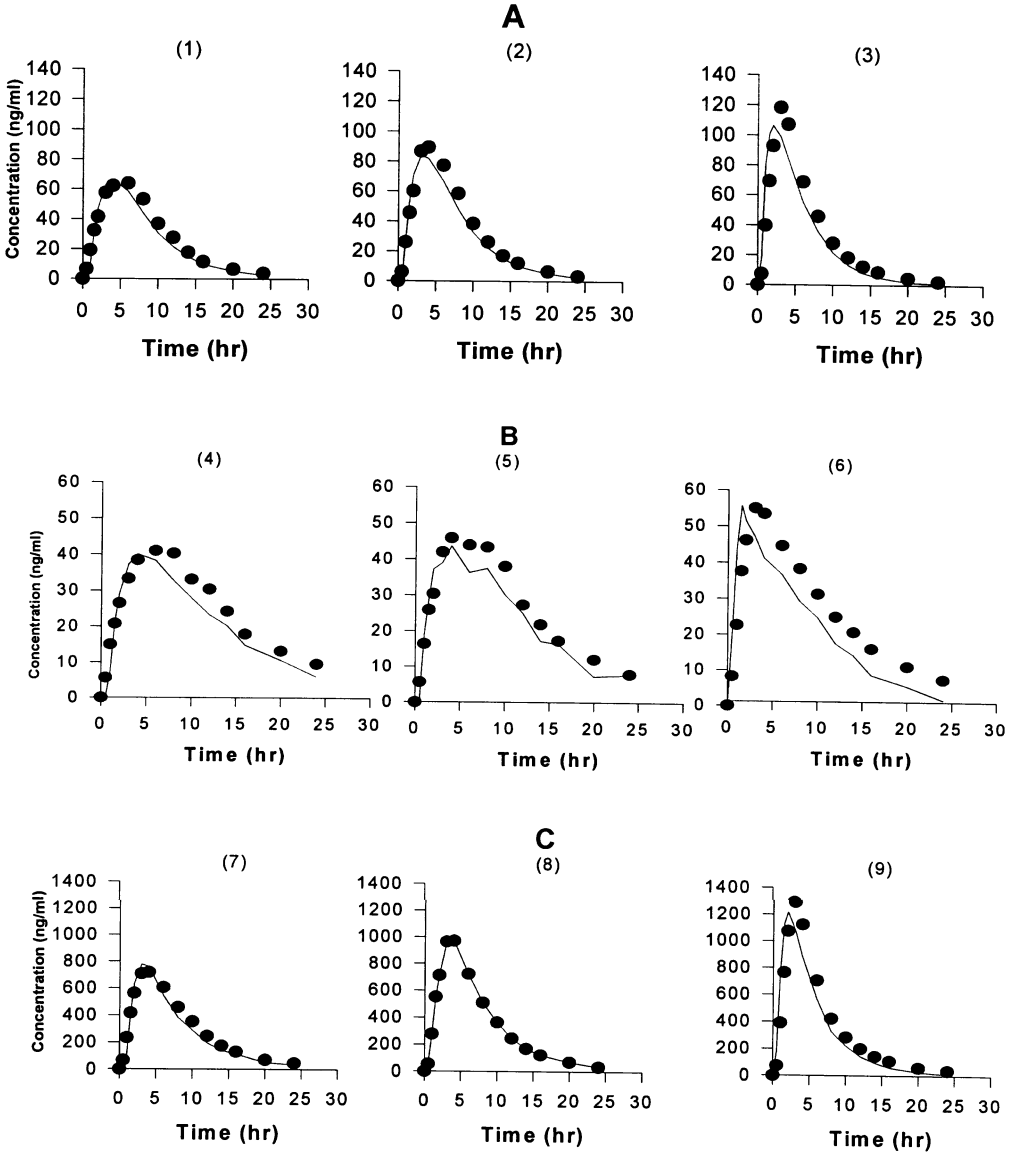

Fig. 4. Observed and predicted Non-FPE F/M/S-IVIVC plasma metoprolol concentrations for fast, moderate, and slow formulations. Observed and predicted Non-FPE F/M/S-IVIVC plasma (A) metoprolol, (B) AHM and (C) ACMB concentrations for fast, moderate, and slow formulations.

metoprolol absorption prior to first pass metabolism were well predicted. The PEs for C_{max} ranged from −9.26 to 3.1% and for AUC from 9.27 to 11.5%. The ability of the Non-FPE IVIVC model in predicting metoprolol in vivo was more reliable compared to the results obtained from the direct approach. Fig. 4A illustrates the observed and Non-FPE IVIVC (indirect approach) predicted metoprolol plasma profiles for the slow (Fig. 4A1), moderate (Fig. 4A2) and fast (Fig. 4A3) formulations. The observed and model predicted profiles were in general agreement.

The Non-FPE IVIVC model using the indirect approach was also used to estimate the in vivo performance of the first pass metabolites, AHM and ACMB. The averaged absolute C_{max} and AUC PEs (Table 3) for AHM were 3.94 and 11.0%, respectively. This metabolite was well predicted by the Non-FPE IVIVC as illustrated by the observed vs. predicted profiles for AHM (Fig. 4B) after the administration of the slow (Fig. 4B4), moderate (Fig. 4B5) and fast (Fig. 4B6) formulations. Table 3 also presents the C_{max} (6.14%) and AUC (11.3%) PEs for the acid metabolite using the indirect method. The model predicted plasma concentration profiles of the acid metabolite are presented in Fig. 4C. As was observed for both metoprolol and AHM, the ACMB observed and predicted profiles were in good agreement.

4. Summary

The results of this study highlight the influence of first pass metabolism on the development and evaluation of an IVIVC for a drug that displays a high extraction ratio. In general, an IVIVC relates the fraction of drug released using in vitro dissolution techniques to the fraction of drug absorbed in vivo. The predictability process involves the conversion of the in vitro dissolution rate into an in vivo dissolution rate. The latter rate in effect is determining the rate of drug released in vivo. For drugs undergoing first pass metabolism, the data obtained to determine the 'rate of drug release in vivo' are minus less the biotransformed fraction. The Non-FPE IVIVC models (Table 3) failed to accurately predict the in vivo metoprolol performance when using the direct approach. This is in view of the fact that the in vitro FRD data represent the total dose, the in vivo FRA represents the total dose, however the metoprolol plasma concentration vs. time data represents the fraction of drug reaching the systemic circulation.

Metoprolol predictability was valid when the indirect approach was used. In this approach the Non-FPE IVIVC model predicts total drug concentration with subsequent determination of the parent drug and metabolites using ratios. It should be noted that this laboratory has validated an IVIVC for metoprolol using typical correlation methods, which did not account for first pass metabolism [2]. Nonetheless, the development of the Non-FPE IVIVC accurately determines the in vivo metoprolol release prior to and after the first pass effect as well as the in vivo metabolite performances. This is especially appealing if an IVIVC is required to predict the performance of a high extraction drug which forms active metabolites (e.g. prodrugs, enalaprilat). The ability to predict the in vivo metoprolol release prior to the first pass effect provided the 'true' release characteristic of the formulation in the absence of physiological changes associated with gut or liver metabolism. This approach may provide an accurate prediction of in vivo performance for other drugs with similar characteristics as metoprolol, such as first pass metabolism. It should also be noted that the development of the Non-FPE IVIVC may not be valid for a drug where hepatic metabolism is not the main elimination process as the sum of parent drug and first pass metabolite may not represent the true drug release in vivo.

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