Vitro-In-Vivo

U. of Maryland & IAGIM

IVIVC Series Part I

Correlations

In Vitro In Vivo Correlation with Metoprolol Extended Release Tablets Using Two Different Releasing Formulations: An Internal Validation Evaluation

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Summary/Abstract

The objective of this analysis was develop and validate internally an in-vitro in-vivo correlation (IVIVC) for a hydrophilic matrix extended release metoprolol tablet using a combination of two formulations with different release rates. Three formulations of a hydrophilic matrix extended release tablet were manufactured to release metoprolol at a slow, moderate and fast rate. The in vitro dissolution methods utilized USP Apparatus II, pH 6.8 at 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 two formulations (slow/moderate; moderate/fast and slow/fast).

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.

An average percent prediction error for C_{max} and AUC for all formulations of less than 12% was found for all IVIVC models. The relatively low prediction errors for C_{max} and AUC observed strongly suggest that the metoprolol IVIVC models with two formulations used in development are valid.

Previous IVIVC with all three formulations was also found to be valid. The relatively low prediction error indicates that the correlations are predictive when using two or three formulations, and allows the associated dissolution data to be used as a surrogate for bioavailability studies.

Introduction

The process of developing and validating an in vitro in vivo correlation (IVIVC) is playing an exceedingly prominent role in the formulation of extended release products.

The development and validation of IVIVCs has been discussed extensively over the past 10 years. The focus of the debates center on the processes of developing an IVIVC and methods to assess its validity.

Even though there are numerous examples of IVIVCs in the literature, many of the correlations have not been rigorously tested through a systematic evaluation of their predictability.

A validated IVIVC allows for the prediction of the in vivo behavior of alternative formulations, provided that

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the "new" formulation is within a predefined range determined by the formulations used to develop the correlation.

In addition, the identification of an appropriate dissolution testing system is critical in IVIVC development and subsequent validation, since it provides the link between dosage form optimization and the oral absorption profile.

The recent FDA-IVIVC guidance, outlines methods of internally and externally validating an IVIVC along with the predictive criteria to assess its validity.[1]

Internal validation refers to how well the IVIVC model predicts the in vivo behavior of the formulations used to develop the correlation.

External validation focuses on how well the IVIVC model predicts the bioavailability of alternative formulations, which differ from those, used in the initial correlation.

The alternative formulations may represent changes in release and non-release controlling excipients, manufacturing site changes, and manufacturing process changes or scale-up of a formulation.

Previous work in our laboratory has focused on the influence of processing changes, excipient changes and scale-up on in vitro dissolution and in vivo bioavailability.[2,3]

Further extension of this work examined the development and internal validation of a matrix metoprolol extended release dosage form.[4]

Numerous sustained or extended release metoprolol formulations have been previously developed, however there are limited examples of validated IVIVCs for metoprolol.

Previously, an IVIVC was developed and validated for a hydrophilic matrix extended release metoprolol formulation.

The IVIVC was developed using three formulations of metoprolol tartrate as well as various combinations of the three formulations.

According to the Biopharmaceutics Classification System, metoprolol is a "Class I" drug, i.e. high solubility and permeability.[5]

In addition, its relatively short half-life suggests that it is a suitable candidate for an extended release formulation. In previous work, we have developed and validated a correlation for extended release metoprolol tablets using three different releasing formulations.

The IVIVC guidance suggests that a correlation can be developed with two or three formulations. The purpose of this work is to assess the ability of developing a correlation with metoprolol extended release formulations using various combinations of two formulations.

METHODS

Formulations. Metoprolol formulations evaluated in this analysis have been previously described.[4]

Three formulations were designed to release metoprolol at a slow, moderate and fast rate. The formulations 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 at three different rates referred to as: **slow, moderate** and **fast**.

Dissolution.

The release characteristics of the slow, moderate and fast formulations were examined using the following dissolution testing methodologies: USP Apparatus I, pH 6.8 at 150 rpm.

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Dissolution tests were performed on six tablets and the amount of drug released was analyzed spectophotometrically at a wavelength of 275nm. Dissolution samples were collected over a 12 hour period.

Bioavailability Study:

The Bioavailability Study has been previously reported.[4] 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.

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.

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. Samples were centrifuged for 10 minutes at 25oC. 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.

Metoprolol plasma sample analysis was performed with a previouly validated HPLC fluorescence detection method.[6]

Dissolution Data Analysis.

The in vitro dissolution data was analyzed by estimation of a similarity factor, the f_2 metric[7] and parameterized by the sigmoid Emax model.

The dissolution profiles were compared using the similarity factor, f_2, presented in the following equation (1):

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

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.

In Vivo Data Analysis.

Metoprolol concentration-time data was evaluated using the Phast program*. The bioavailability parameters, C_{max}, T_{max} and AUC_{inf} were estimated for each subject. (*Phoenix Scientific Software, Version 2.2, Montreal, Canada) and WINNOLIN Professional (SCI Software; Cary, North Carolina)

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.

Correlation Development and Internal Validation.

The data generated in the bioavailability study was 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.

The correlation models was developed using pooled mean FRD and pooled mean FRA data from the following combinations of two formulations: (1) slow and moderate (S/F), (2) moderate and fast (M/F) and (3) slow and fast (S/F). Linear regression analysis was used to examine the relationship between FRD and FRA.

The internal validation was based on how well each IVIVC model (S/M, M/F and S/F) predicted the in vivo performance of each formulation (i.e., slow, moderate and fast).

The in IVIVC model predicted metoprolol plasma concentration was determined by convoluting the in vivo dissolution rate with the pharmacokinetic parameters from the oral solution administration.

The validity of the three correlation models (S/M, M/F or S/F) was determined by calculating the prediction errors for the observed and predicted C_{max} and AUC for each formulation to determine the accuracy of the IVIVC models in characterizing the rate and extent of metoprolol absorption.

The percent prediction errors for C_{max} and AUC were calculated as follows:

(2) - $\%PE_{Cmax}$

$$= \left[\frac{[C\max(obs) - C\max(pred)}{C\max(obs)}\right] * 100$$

(3) - $\%PE_{AUC}$

$$= \left[\frac{[AUC(obs) - AUC(pred)}{AUC(obs)}\right] * 100$$

KEY

Where C_{max}(obs.) and C_{max}(pred.) = The observed and IVIVC model predicted maximum plasma concentration profiles, respectively;

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 C_{max} and AUC prediction errors were $\leq$ 10 percent.[1]

RESULTS

In vitro and in vivo studies.

Profiles of the cumulative metoprolol fraction dissolved from the slow and moderate (S/M), moderate and fast (M/F) and slow and fast (S/F) formulations using USP Apparatus I, pH 6.8, 150 rpm are illustrated in **Figure 1A, 2A and 3A**, respectively.

The associated f_2 metrics for the S/M, M/F and S/F were found to be 39.26, 45.99 and 30.9 respectively, which suggested that the two profiles were not similar.

Mean pharmacokinetic parameters are summarized in **Table 1.**

Table 1. Mean Pharmacokinetic Parameters after Extended Release Metoprolol Formulations.

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

Figures 1B – 3B:-

Present the fraction of drug absorbed for the slow and moderate (S/M), moderate and fast (M/F) and slow and fast (S/F) formulation vs time.

IVIVC Correlation, Development and Validation.

Figures 4A - 4C present the pooled FRD vs. FRA for the S/M, M/F and S/F formulations using USP Apparatus I, pH 6.8 at 150 rpm.

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 ($p < 0.05$).

The internal validation was performed by convolution of the (S/M, M/F and S/F) dissolution data that corresponded to each formulation (S/M/F). Each of the IVIVC models predicted metoprolol plasma concentration versus time profiles was compared to the experimental data points using prediction error metrics.

Figure 5, 6 and 7 illustrate the observed and IVIVC model metoprolol plasma concentrations for each formulation using the S/M, M/F and S/F IVIVC models, respectively.

The validity of the correlations was assessed by determining how well the IVIVC models could predict the rate and extent of metoprolol absorption as characterized by C_{max} and AUC.

Table 2 presents the percent errors estimated for the difference between the observed and predicted C_{max} and AUC values for the S/M, M/F and S/F IVIVC models.

Table 2. Regression Parameters for IVIVC Models of Metoprolol

IVIVC Models

Formula Types	Slope	Intercept	r	P value
S/M	1.171	-0.191	0.991	p <0.001
M/F	1.207	-0.276	0.966	p <0.001
S/F	1.131	-0.203	0.946	p <0.001

None of the model predicted parameters deviated from the experimental values by more than twelve percent (12%).

DISCUSSION

The availability of a meaningful IVIVC of high quality and predictability for an extended release 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.[8]
Further, a valid IVIVC allows for the use of dissolution data in place of additional bioavailability studies.

The objective of this analysis was to assess the development and validation of an IVIVC for metoprolol tartrate tablets using two formulations. Previously, we have internally validated a correlation using a total of three formulations designed to release the drug at a slow, moderate and fast rate.[4]

An average percent prediction error for C_{max} and AUC of less than 10% was found for the IVIVC model developed with all three formulations.

The average percent prediction error of less than 10% indicates that the three-formulation correlation was predictive and allows the associated dissolution data to be used as a surrogate for bioavailability studies.

Our current analysis examined how well two formulations were able to accurately predict the in vivo bioavailability profile of various extended release formulations of metoprolol.

IVIVC models developed with combinations of the slow and moderate, moderate and fast and slow and fast formulations were able to accurately predict the rate of metoprolol absorption from the extended release formulations.

Prediction errors for Cmax were all less than **6%**, except for the slow and moderate IVIVC that displayed an error

of 11.38 % (Table #3). AUC prediction errors were all less than **10%** irrespective of the formulations used to develop the IVIVC suggesting that the IVIVC models also predicted the extent of drug absorption.

According to the IVIVC guidance, the average prediction error across formulations cannot be greater than **10%** and a formulation cannot have a prediction error greater than **15%.** Based on these criteria, each of the IVIVC models is **valid** in terms of the **rate and extent** of drug absorption.

In summary, correlations were developed with combinations of two formulations (e.g. slow and moderate, moderate and fast, slow and fast). The evaluation of the correlation of FRD vs. FRA displayed a significant linear relationship for each of the combinations.

As observed with correlation developed with three formulations, each correlation here was able to accurately estimate the rate as well as the extent of absorption. These results indicate that a predictive correlation can be developed with two or three formulations with this Class I agent and this suggests that similar results may be observed with other agents in this classification.

Table 3.

C_{max} and AUC Prediction Errors (%) for Metoprolol IVIVC

Formulation	Cmax S/M	M/F	S/F
Slow	-11.38	-3.75	-3.75
Moderate	-1.55	5.18	4.25
Fast	-1.83	3.55	5.74
AUC			
Formulation	S/M	M/F	S/F
Slow	-5.77	1.05	1.05
Moderate	1.52	7.07	6.94
Fast	-0.97	3.71	6.25

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EIGHT IVIVC STUDIES in 2000

This article represents the first in the series of **eight** IVIVC reviews by the author in a joint collaboration project with the International Drug Development Association – **IAGIM** Full details of the 12 month joint venture with the **University of Maryland** VA USA and IAGIM can be viewed at: http://www.locum.co.il/future

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Figure 1.
Mean dissolution and absorption profiles for the **SLOW** and **MODERATE** Formulation:
(A) Fraction of drug dissolved (FRD) and (B) Fraction of drug absorbed (FRA).

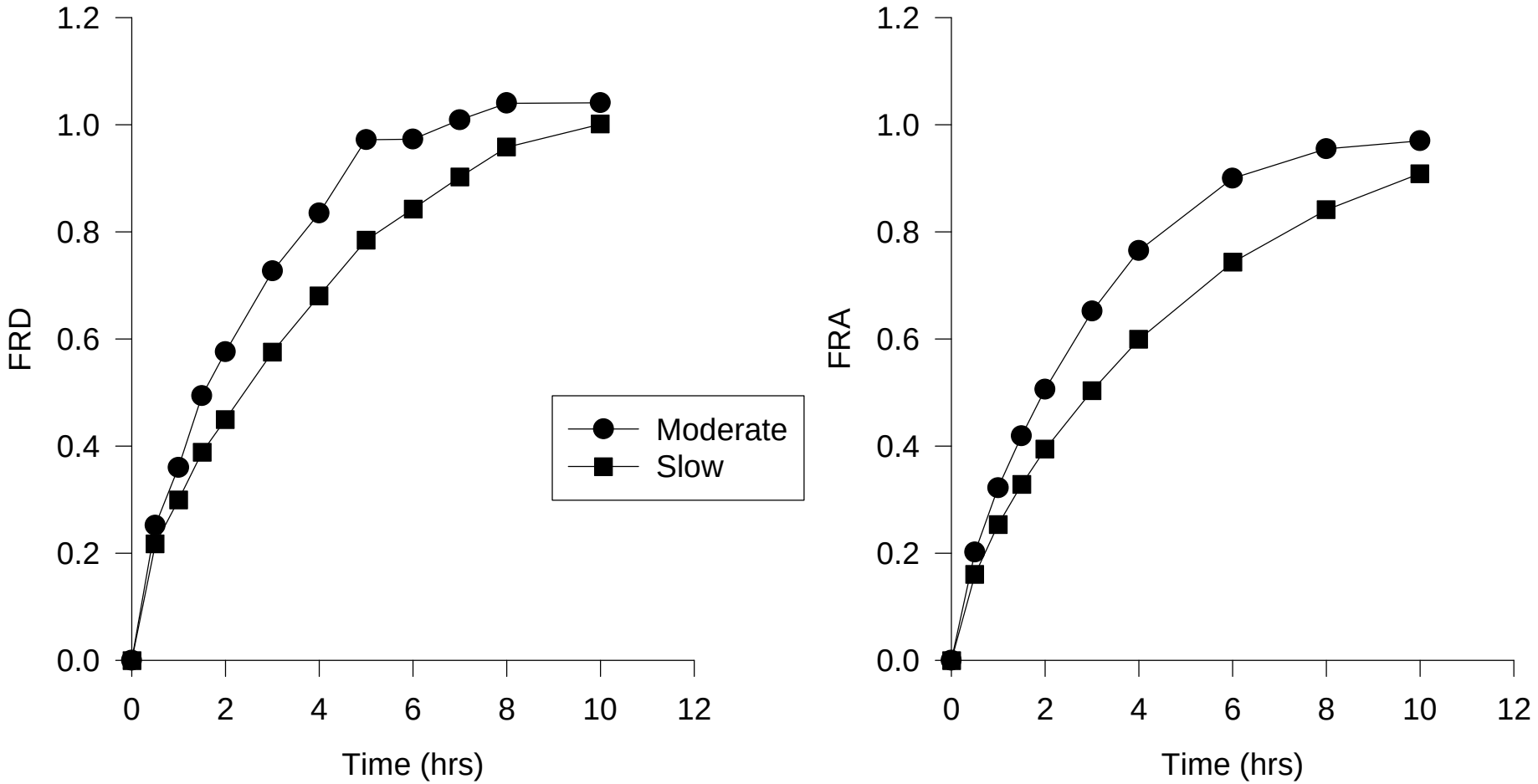

Figure 2. Mean dissolution and absorption profiles for the **MODERATE** and **FAST** Formulation:
(A) Fraction of drug dissolved (FRD) and (B) Fraction of drug absorbed (FRA).

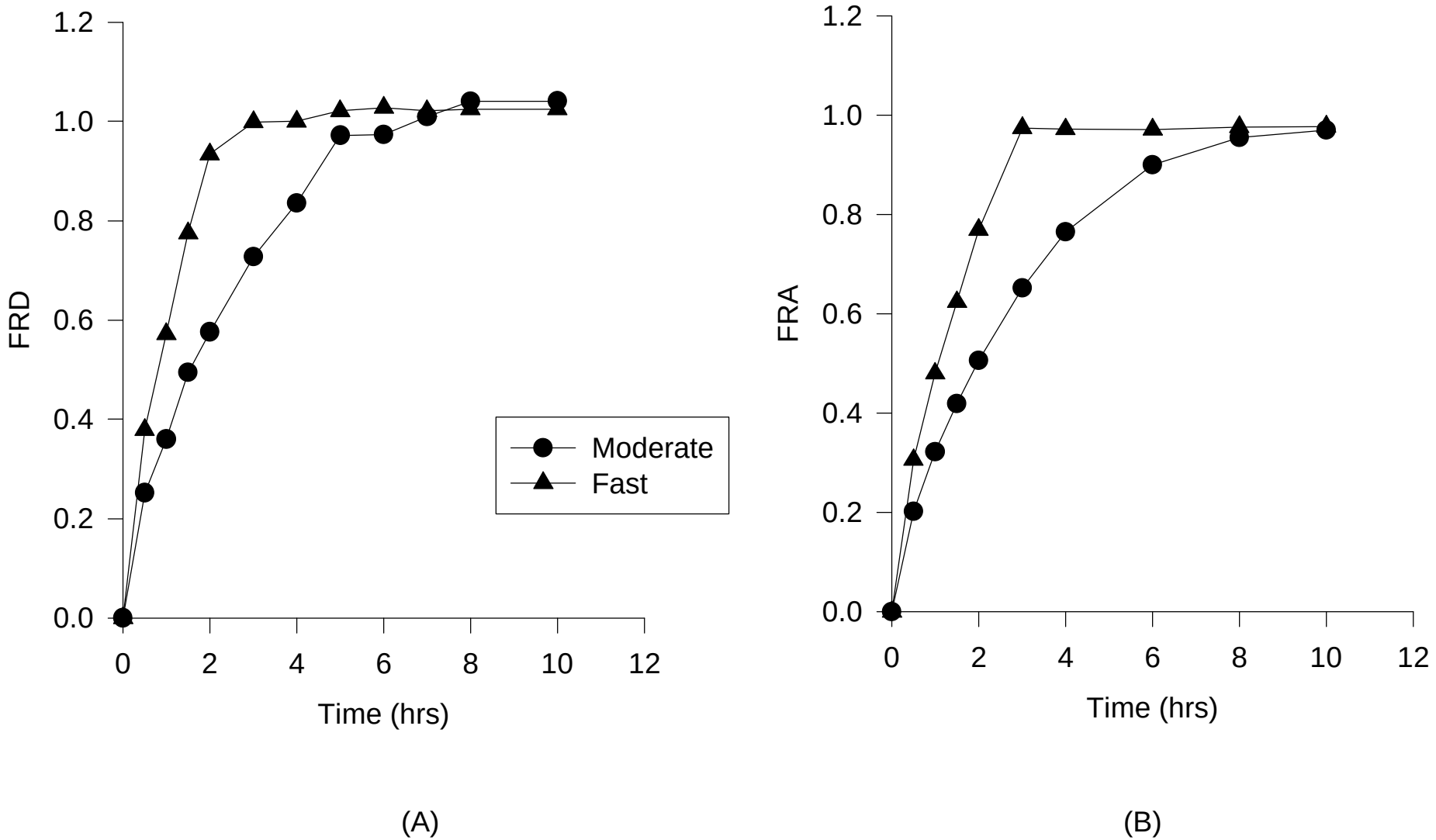

Figure 3.
Mean dissolution and absorption profiles for the **SLOW** and **FAST** formulation:
(A) Fraction of drug dissolved (FRD) and (B) Fraction of drug absorbed (FRA).

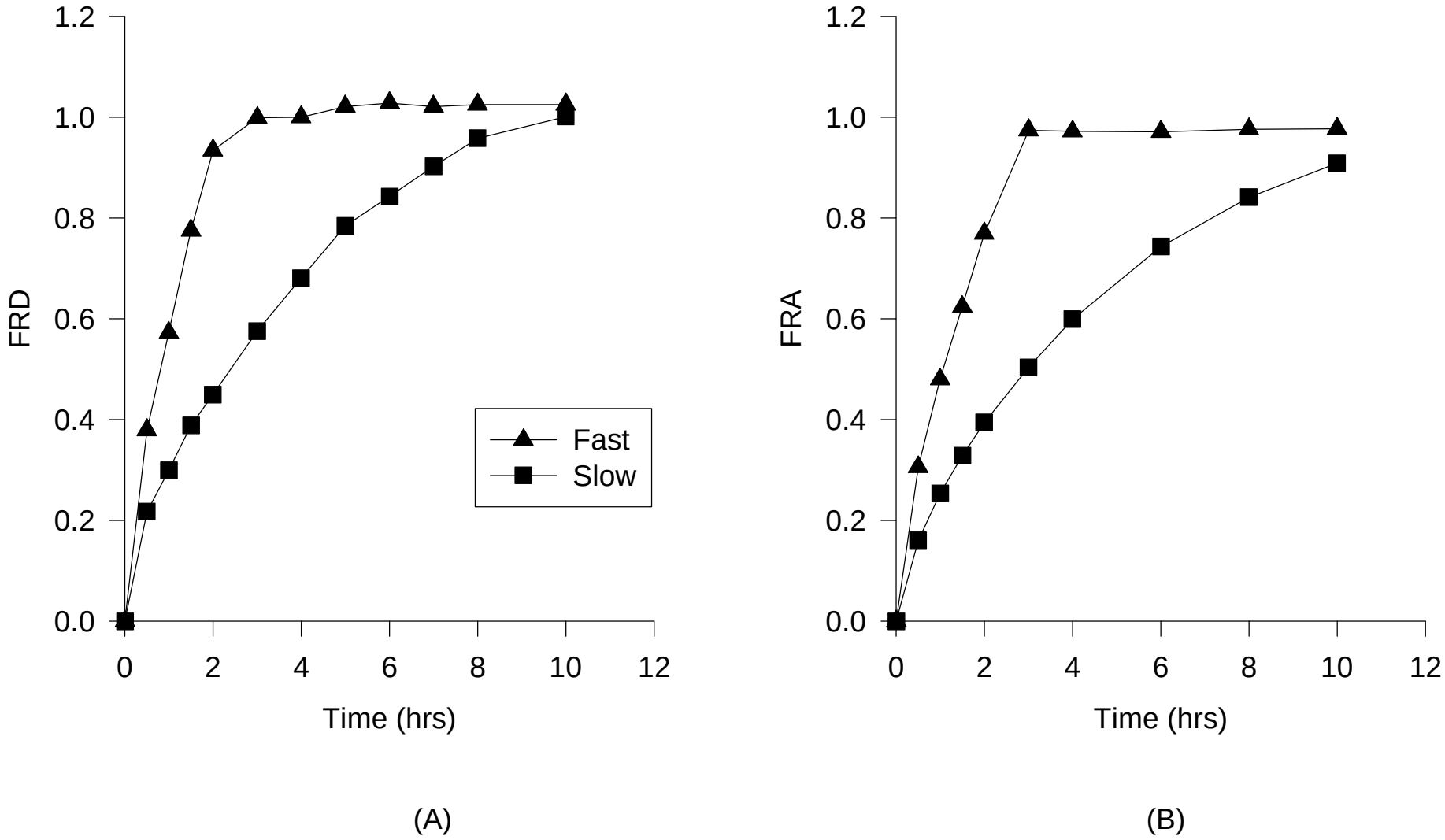

Figure 4.
IVIVC model linear regression plots of FRA vs FRD:
(A) SLOW and MODERATE Formulations, (B) MODERATE and FAST Formulations and (C) **SLOW** and **FAST** Formulations.

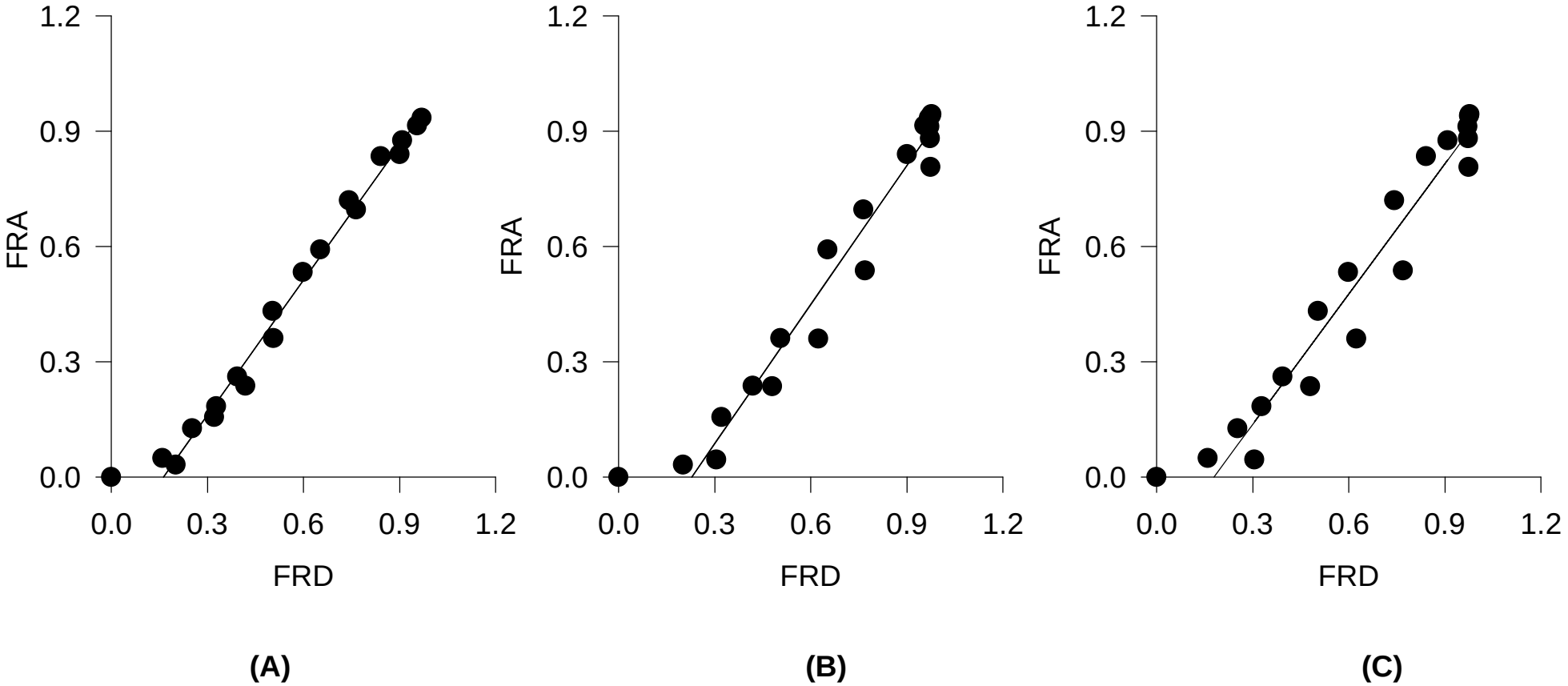

Figure 5.
Observed and predicted metoprolol plasma concentration for the **SLOW** and **MODERATE** IVIVC:
(A) **SLOW** Formulation, (B) **MODERATE** Formulation and (C) **FAST** Formulation.

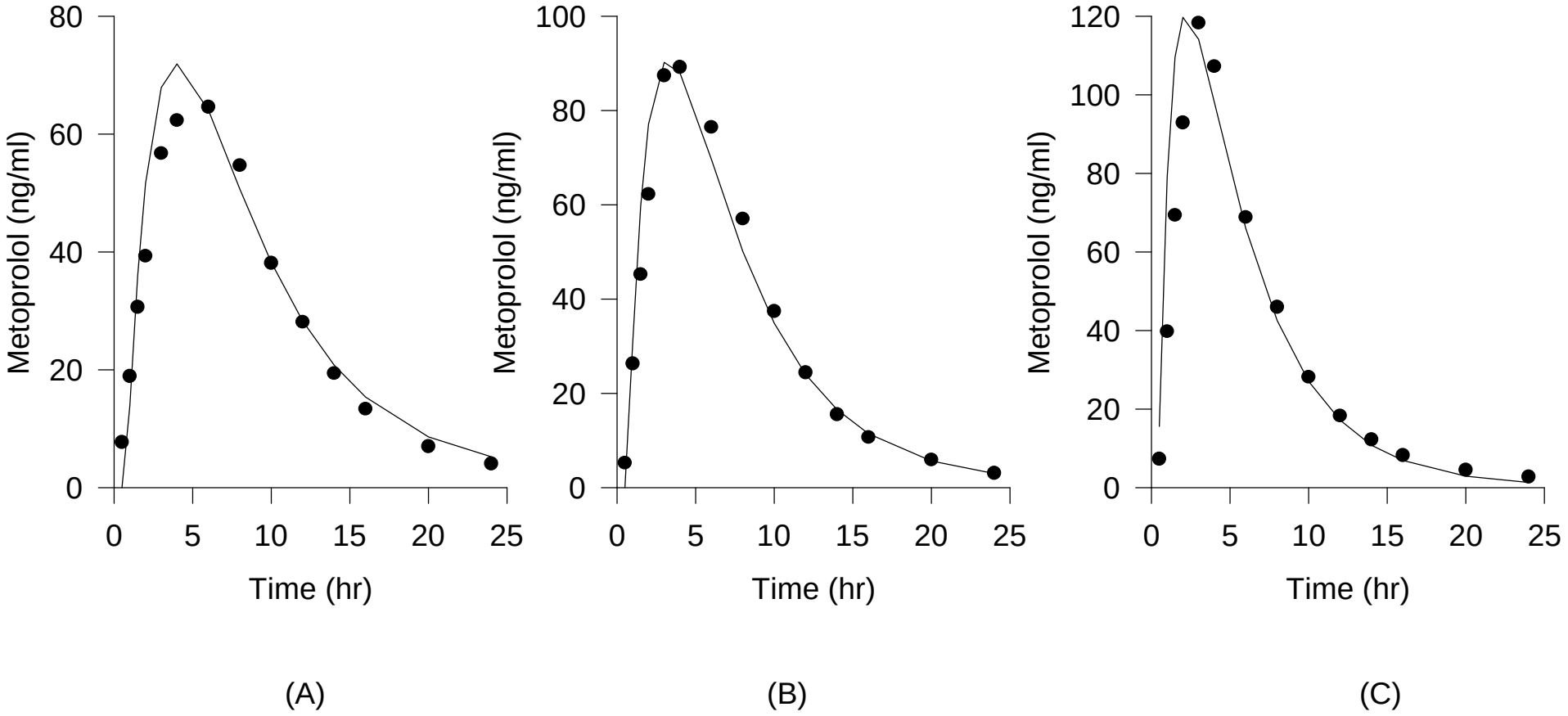

Figure 6.
Observed and predicted metoprolol plasma concentration for the **MODERATE** and **FAST** IVIVC:
(A) **SLOW** Formulation, (B) **MODERATE** Formulation and (C) **FAST** Formulation.

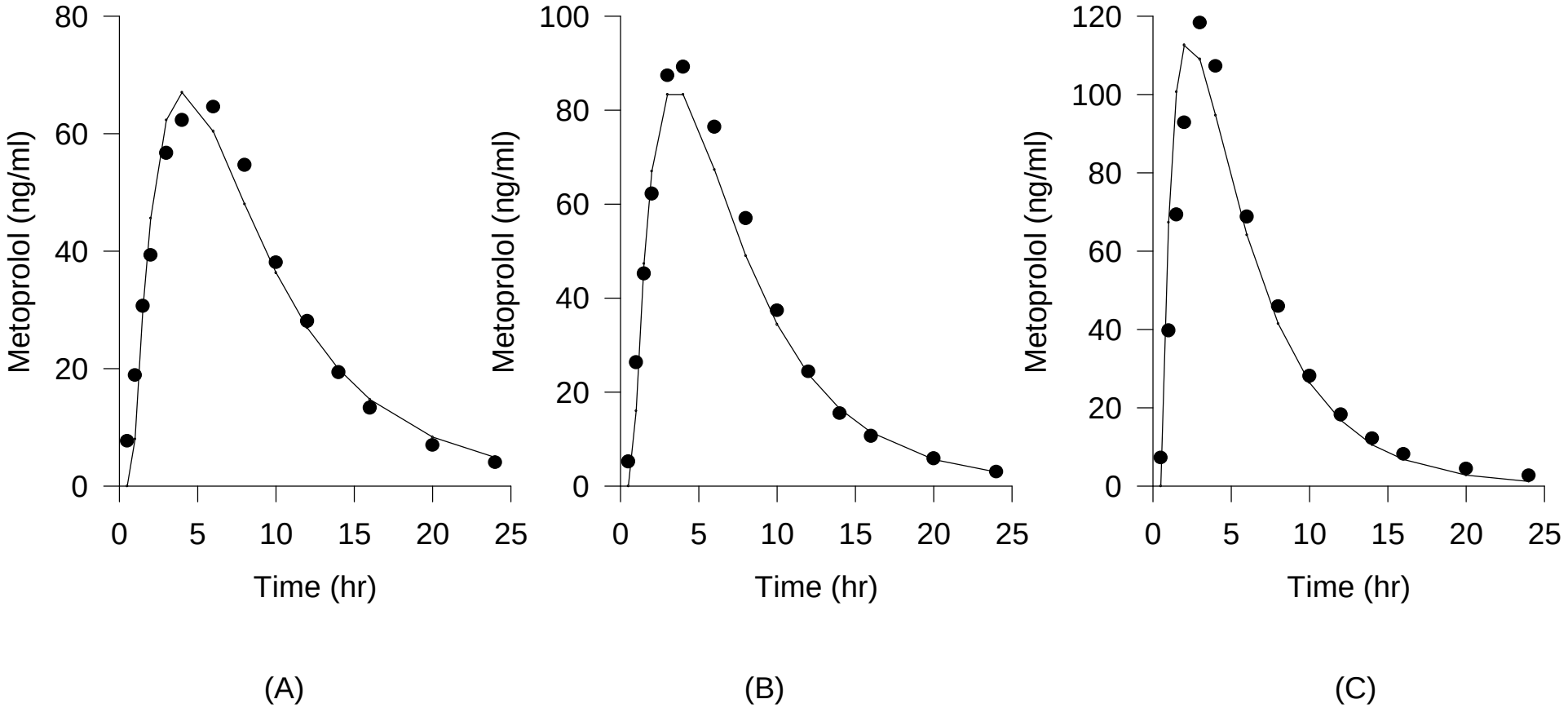

Figure 7.
Observed and predicted metoprolol plasma concentration for the **SLOW** and **FAST** IVIVC:
(A) SLOW Formulation, (B) MODE**R**ATE Formulation and (C) **FAST** Formulation.