Evaluation of "External" Predictability of an *In Vitro–In Vivo* Correlation for an Extended-Release Formulation Containing Metoprolol Tartrate

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ABSTRACT: The purpose of this study was to examine the external predictability of an *in vitro–in vivo* correlation (IVIVC) for a metoprolol hydrophilic matrix extended-release formulation, with an acceptable internal predictability, in the presence of a range of formulation/manufacturing changes. In addition, this report evaluated the predictability of the IVIVC for another formulation of metoprolol tartrate differing in its release mechanism. Study 1 examined the scale up of a matrix extended-release tablet from a 3-kg small batch (**I**) to a 50-kg large batch (**II**). The second study examined the influence of scale and processing changes [3-kg small batch with fluid bed granulation and drying (**III**); 80-kg large batch with high shear granulation and microwave drying (**IV**), and a formulation with an alternate release mechanism formulated as a multiparticulate capsule (**V**)]. *In vitro* dissolution of all formulations (**I–V**) was conducted with a USP apparatus I at pH 6.8 and 150 rpm. Subjects received the metoprolol formulations, and serial blood samples were collected over 48 h and analyzed by a validated HPLC assay using fluorescence detection. A previously developed IVIVC was used to predict plasma profiles. Prediction errors (PE) were <10% for C_{max} and area under the curve (AUC) of concentration versus time for **I**, **II**, and **IV**. The C_{max} for **III** was slightly underestimated (11.7%); however, the PE of the AUC was <10%. Formulation **V** displayed a PE for C_{max} > 20% and an AUC within 5% of observed values. The low PEs for C_{max} and AUC observed for **I–IV** strongly suggest that the metoprolol IVIVC is externally valid, predictive of alternate processing methods (**IV**), scale-up (**II**, **III**), and allows the *in vitro* dissolution data to be used as a surrogate for validation studies. However, the lack of predictability for **V** supports the contention that IVIVCs are formulation specific.
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Keywords: metoprolol; *in vitro; in vivo;* correlation; extended-release; drug release; mechanism

INTRODUCTION

Use of *in vitro* drug release data to predict *in vivo* bioavailability parameters is desirable for rational development and evaluation of extended-release (ER) dosage forms. Development and applications of predictive mathematical relation-

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ships between *in vitro* drug release and *in vivo* drug absorption data, generally referred to as *in vitro–in vivo* correlation (IVIVC), plays a significant role in the regulatory decision-making process. Availability of an IVIVC with acceptable predictability reduces the need for *in vivo* bioequivalence tests to document unchanged quality and performance of ER products that undergo certain pre- and post-approval changes.[1,2]

General regulatory approaches for development and assessment of predictability of an IVIVC are described in a recent FDA guidance document.[2] The development of a correlation is based on the scientific principles associated with mathematical modeling, statistical evaluation, and numerical deconvolution. The development and validation of an IVIVC is based on the ability of the fraction of drug absorbed (FRA) versus fraction of drug dissolved (FRD) relationship of various formulations to be described through mathematical modeling. This modeling is performed by parameterizing the relationship between FRA versus FRD and subsequently, convolving the *in vivo* drug release with the pharmacokinetic parameters that describe the *in vivo* relationship. The IVIVC guidance document recommends that an IVIVC be evaluated to demonstrate that predictability of *in vivo* performance of a drug product is maintained over a range of *in vitro* release rates and manufacturing changes. The proposed evaluation approaches focus on the estimation of predictive performance or, conversely, prediction error (PE). Depending on the intended application of an IVIVC, as well as the therapeutic index of the drug, measures of PE internally and/or externally may be necessary. Application of one or more of these procedures to the IVIVC modeling process may be collectively defined as evaluation of predictability.

Evaluation of predictability with internal reference involves the use of the initial data used to define the IVIVC model. This step relates to evaluating how well the mathematical model describes the data used to define the IVIVC and is appropriate in all instances. One recommended approach involves the use of the IVIVC model to predict the plasma concentration profile using *in vitro* release data for each formulation being used to develop the IVIVC. The predicted bioavailability is then compared with the observed bioavailability for each formulation and a determination of PE is made. Acceptable predictability is established when (1) the average percent PE of 10% or less is observed for the bioavailability parameters (peak concentration, C_{max} and area under the curve, AUC), and (2) the %PE for each formulation does not exceed 15%. If these criteria are not met, or when a narrow therapeutic index drug is under consideration, an evaluation of external predictability of the IVIVC is needed

Evaluation of external predictability relates to how well the model predicts data when one or more additional test data sets are utilized that differ from those used to define the correlation. Percent PE of 10% or less, for both C_{max} and AUC, establishes the external predictability of an IVIVC. Percent PE between 10 and 20% indicates inconclusive predictability and suggests the need for further study using additional data sets. Results of estimation of PE from all such data sets may then be evaluated for consistency of predictability. Percent PE >20% generally indicates inadequate predictability.

The additional test data sets used for the external PE calculation may have several differing characteristics compared with the data sets used in IVIVC development. Although it is expected that formulations with different release rates may provide an optimal test of predictability, current regulatory practices does not require that such a formulation be specially prepared solely for this purpose.

The purpose of this study was to examine the external predictability of an IVIVC, with an acceptable internal predictability, in the presence of a range of formulation/manufacturing changes. The model ER formulation utilized in this study contained a hydrophilic polymer matrix for controlling release of the model drug metoprolol tartrate. Formulation development information, development of IVIVC, and evaluation of internal predictability have been previously reported elsewhere.[3–5] In addition, the predictability of the hydrophilic matrix formulation IVIVC for another formulation of metoprolol tartrate, differing in its drug release mechanism, was evaluated. A coated bead formulation, filled in hard gelatin capsule, was specifically developed to provide an *in vitro* drug release profile in the range and under the test conditions that allowed development of the IVIVC for the hydrophilic matrix ER formulation. Such an application of an IVIVC is not considered by the FDA to be acceptable.[2] This study was intended to provide data to support, or to question, this recommendation.

METHODS

Formulations for External Predictability Evaluation

Initial development and internal predictability assessment of an IVIVC was accomplished using three formulations with differing rates of drug release. These formulations were labeled as fast-, moderate-, and slow-release formulations.[3] In this evaluation, two separate *in vivo* studies were conducted for evaluation of external predictability. Information on these *in vivo* studies and the selected formulations are listed next.

Study #1

Larger batch size (50- compared with 3-kg batch size) of the moderate release formulation. In this report, the 3- and 50-kg batches are referred to as formulations **I** and **II,** respectively. Note that the 3-kg batch (**I**) was used in the initial IVIVC development study.[3]

Study #2

The 3-kg batch of moderate-release formulation was prepared using fluid-bed granulation and drying (referred to as formulation **III**, but is the same formulation and manufacturing procedure as **I** in Study # 1), and the 80-kg batch of moderate-release formulation was processed by high-shear granulation and microwave drying (formulation **IV**). In this study, the coated bead formulation (**V**) was also evaluated. Formulation **V** was manufactured by fluid bed technology using the Wurster process.[6]

The moderate-release hydrophilic matrix tablet and the coated-bead formulation each had a target drug weight of 100 mg. The composition of the hydrophilic polymer matrix tablet[5] was filler (lactose:dicalcium phosphate, 50:50), methocel K100LV (32.5%), and magnesium stearate (1.5%). The coated beads[6] were composed of sugar spheres 30/35 mesh (42.9%); drug layering ingredients methocel E5 (2.0%) as binder and talc (4%) as anti-adherent; seal-coating excipient, opadry (2.1%); and film-coating excipient, surelease (14.5%).

In Vitro Drug Release Tests

The *in vitro* drug release profiles of each ER formulation (**I–V**) were determined using the IVIVC dissolution test method.[4] Briefly, 12 units of each formulation were tested over a 12-h period in the USP Apparatus I (basket) at 150 rpm and in a pH 6.8 buffer medium. *In vitro* dissolution samples obtained for the tablet formulations (**I–IV**) were analyzed spectophotometrically at a wavelength of 275 nm, and *in vitro* dissolution samples for the capsule formulation (**V**) were analyzed by an ion-pairing high-performance liquid chromatography (HPLC) method at 245 nm due to interferences from the capsule shell.

In Vivo Studies

Both Study #1 and #2 were open-label, randomized, fasting, single-dose, and crossover studies. Formulations were administered with 240 mL of tap water. Each treatment was separated by a washout period of 7 days. Sixteen normal healthy subjects were randomly assigned to receive each of the metoprolol (100 mg) formulations in both studies. The health status of subjects in each study was based on physical examination, history, electrocardiogram, and clinical laboratory tests. In addition, the debrisoquin-type metabolizing capabilities of each subject were determined by dextromethorphan metabolism screening, and only extensive metabolizers were enrolled.[7] Six-milliliter samples of blood were collected pre-dose and at the following times post-dose: 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 16, 20, 24, 30, 36, and 48 h. Samples were centrifuged for 10 min at 25 °C. Blood pressure and heart rate were also determined prior to blood sample collections. The Institutional Review Boards of the University of Maryland and the Veteran's Administration Hospital in Baltimore approved the studies. Each subject provided a written informed consent prior to enrollment.

Assay Methodology

Two previously described fluorescence HPLC analytical methods were used to quantitate dextromethorphan and its metabolite, dextrophan, in urine as well as metoprolol in plasma.[8] The limit of quantitation for dextromethorphan was <0.05 μg/mL, and extraction recoveries were >90% for each analyte. The HPLC assay method for metroprolol levels in plasma was validated over a range of 1 to 400 ng/mL. Recovery was >92.9% at all concentrations, and intra- and interday precision ranges were 0.41–9.9% and 1.1–15.7%, respectively.

Data Analysis

In Vitro Release

The *in vitro* drug release profiles were compared using the similarity factor, f_2, presented in the following equation:[9]

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

where R_t and T_t are the percent dissolved at each time point for the reference product (formulation I or III) and test products (formulation II, IV, and V). In addition, the Hill equation listed below was used to parameterize the cumulative *in vitro* drug release data:

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

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

In Vivo Data Analysis

Metoprolol concentrations in plasma versus time data were evaluated using WINNONLIN Professional (SCI Software; Cary, NC). The highest measured metoprolol plasma concentration for a subject was identified as the peak concentration, $C_{\max}$. The time at which $C_{\max}$ occurred was identified as $T_{\max}$. The AUC from time 0 to the last concentration time point ($AUC_{0-C_{plast}}$) was determined by the trapezoidal method. The AUC_{inf} was determined by the following equation:

$$AUC_{inf} = AUC_{C\text{plast}} + \frac{C_{\text{plast}}}{\lambda_z} \quad (3)$$

The elimination rate constant (λ_z) was determined by linear regression of the linear portion of the ln(concentration) versus time profile. Typically, four to five points were used to determine the terminal elimination rate constant. Numerical deconvolution was employed to obtain values of fraction drug absorbed (FRA) as a function of time.

Evaluation of Predictability

Average data (metoprolol concentration in plasma) for each formulation obtained from the two studies was used to assess the external predictability of the IVIVC. The approach used was based on the recommendations in the FDA's IVIVC guidance.[2] The IVIVC model-predicted metoprolol plasma concentrations were determined as follows: First, *in vitro* release rates were calculated by taking the first derivative of the Hill equation already described. These were then converted to *in vivo* absorption rates using the IVIVC relationship (i.e., slope, and intercept). Predicted metoprolol concentrations in plasma were obtained by convoluting *in vivo* absorption rates and the pharmacokinetic model for oral solution administration of the drug. The pharmacokinetic parameters used were $\lambda_z = 0.29\ h^{-1}$ and $Vd = 5.9$ L/kg.[3] The convolution process was accomplished using a spreadsheet (Lotus 1-2-3, Lotus Development Corp., Cambridge, MA).

Predictability was evaluated by comparing the observed and IVIVC model-predicted $C_{\max}$ and AUC values. Prediction errors were determined as follows: Predictability was evaluated by comparing the observed and IVIVC model predicted $C_{\max}$ and AUC values. Prediction errors were determined as follows:

$$\%PE_{C\max} = \left[\frac{[C_{\max(\text{obs})} - C_{\max(\text{pred})}}{C_{\max(\text{obs})}}\right] \cdot 100 \quad (4)$$

$$\%PE_{AUC} = \left[\frac{[AUC(\text{obs}) - AUC(\text{pred})}{AUC(\text{obs})}\right] \cdot 100 \quad (5)$$

where $C_{\max}$(obs) and $C_{\max}$(pred) are the observed and IVIVC model-predicted maximum plasma concentrations, respectively; and AUC(obs) and AUC(pred) are the observed and IVIVC model-predicted AUC for the plasma concentration profiles, respectively.

RESULTS

In Vitro Studies

Profiles of the cumulative metoprolol fraction released from **I** (3-kg small batch) and **II** (50-kg large batch) evaluated in Study #1 are presented in Figure 1A. The two *in vitro* release profiles were essentially similar (f_2 = 75.8). The Hill equation parameters for the small and large batch were $D\text{max}_{\mathbf{I}} = 98.3$, $D50_{\mathbf{I}} = 1.76$, $\gamma_{\mathbf{I}} = 1.48$,

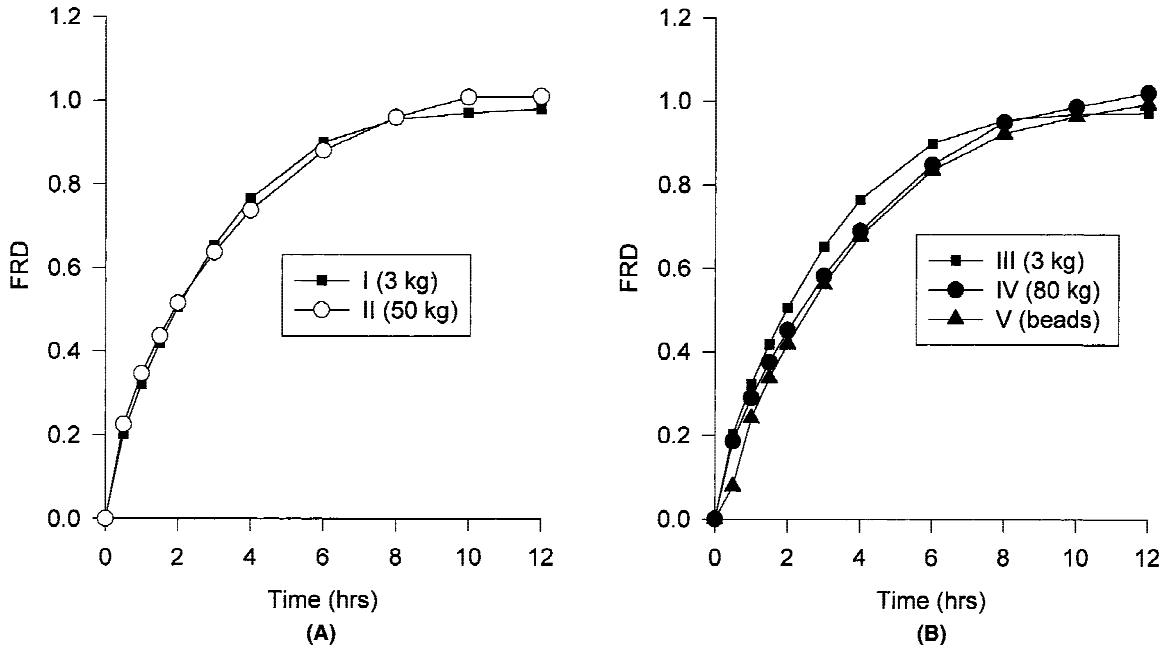

Figure 1. Mean metoprolol dissolution versus time profile for (A) **I** (small 3-kg batch) and **II** (large 50-kg batch) extended-release tablets and (B) **III** (3-kg fluid bed) (■), **IV** (80-kg high-shear and microwave drying) (●), and **V** (bead-capsule formulation) (▲) using Apparatus I at pH 6.8 and 150 rpm.

and $D\text{max}_{\mathbf{II}} = 99.5$, $D50_{\mathbf{II}} = 1.72$, $\gamma_{\mathbf{II}} = 1.38$, respectively. Figure 1B illustrates the *in vitro* drug release profiles from **III** (small batch fluid bed granulation), **IV** (80-kg high-shear granulation and microwave drying), and **V** (coated-bead formulation). The associated f_2 metric for comparison of **III** versus **IV** was 62.5 and for **III** versus **V** was 55.8. The f_2 results suggest that the release of **IV** and **V** was similar to that of **III**. The Hill equation parameters for **III**, **IV**, and **V** were, respectively, $D_{\text{max}_{\text{III}}} = 98.3$, $D_{50_{\text{III}}} = 1.76$, and $\gamma_{\mathbf{III}} = 1.48$; $D_{\text{max}_{\text{IV}}} = 99.8$, $D_{50_{\text{IV}}} = 1.70$, and $\gamma_{\mathbf{IV}} = 1.58$; and $D_{\text{max}_{\mathbf{V}}} = 98.3$, $D_{50_{\mathbf{V}}} = 1.76$, and $\gamma_{\mathbf{V}} = 1.48$.

In Vivo Studies

Thirteen subjects (10 males, 3 females) completed Study #1. Numerical values (mean ± SD) for age, height, and weight of the subjects in Study #1 were 35.9 ± 7.5 years, 69.3 ± 2.6 inches, and 164 ± 19 pounds, respectively. One subject was excluded from the analysis when on further evaluation it was determined that he was not an extensive metabolizer. Thirteen subjects completed Study #2 and the numerical values (mean ± SD) for age, height, and weight of these subjects were 37.3 ± 7.1 years, 69.3 ± 2.9 inches, and 164 ± 17 pounds, respectively. There were no serious adverse effects observed in either study.

Mean metoprolol plasma concentrations and mean pharmacokinetic parameters for formulations **I** and **II** are illustrated in Figure 2A and Table 1, respectively. Mean metoprolol plasma concentrations and mean pharmacokinetic parameters for formulations **III**, **IV**, and **V** are illustrated in Figure 2B and Table 1, respectively. The mean metoprolol pharmacokinetic profile and parameters for the fluid bed (**III**) and the high-shear (**IV**) formulations were relatively similar. However, the profile for the bead product (**V**) displayed a slower rate of absorption compared with **III** and **IV**.

Figures 3A and 3B illustrate the observed and IVIVC model-predicted metoprolol plasma concentrations for **I** and **II** in Study #1, respectively. The C_{max} prediction errors (Table 2) for the 3-kg (7.53%) and 50-kg (–3.17%) batch were both <10%. This same trend was observed for the predicted extent of drug absorption, AUC (Table 2), for the 3- and 50-kg batches.

Figures 4A–4C illustrates the observed and predicted metoprolol plasma profiles for **III**, **IV**, and **V**, respectively. The calculated prediction errors, associated with *C*max and AUC, for formulation **IV** (Table 2) were found to be within 10% of the observed mean values. Observed mean *C*max and AUC for the small-scale batch, **III**, were lower than the predicted values by 11.7 and 1.3%

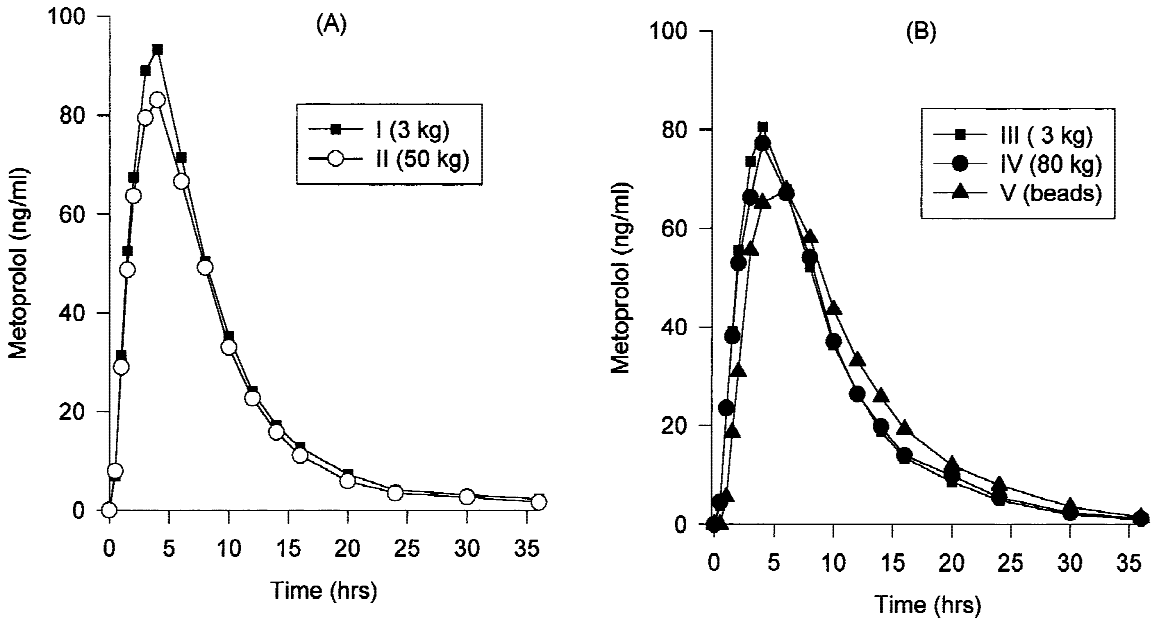

Figure 2. Mean metoprolol plasma concentrations versus time profile for (A) **I** (small 3-kg batch) and **II** (large 50-kg batch) extended-release tablets and (B) **III** (3-kg fluid bed) (■), **IV** (80-kg high- shear and microwave drying) (●), and **V** (bead-capsule formulation) (▲) using Apparatus I at pH 6.8 and 150 rpm.

for *C*max and AUC, respectively. In Study #1, observed mean *C*max and AUC for the small-scale batch, **I**, were higher than the predicted values by 7.53 and 6.13% for *C*max and AUC, respectively. These results suggests that the true prediction error for *C*max, may be ~10% for this formulation.

The second study also sought to examine the ability of the IVIVC to predict *in vivo* performance of a product with different drug release mechanism. As can be seen in Table 2, the IVIVC model-predicted values were higher for the capsule product (**V**) than the observed values, a –23% prediction error for *C*max. However, the extent of metoprolol absorbed from bead formulation was within 10% of the observed value.

Table 1. Mean (SD) Pharmacokinetic Parameters for Extended-Release Metoprolol Formulations

Formulation	C_{max} (ng/L)	T_{max} (h)	AUC_{inf} (ng·h/L)
Study I			
I (3 kg batch)	93.4	3.64	828
	(34.8)	(0.67)	(392)
II (50 kg batch)	83.1	3.73	760
	(35.6)	(0.90)	(371)
Study II			
III (3-kg batch)	80.5	3.76	778.8
	(25.1)	(0.60)	(419.2)
IV (80-kg high-shear)	77.2	3.58	798.2
	(19.5)	(0.72)	(325.2)
V (bead capsule)	70.3	5.4	845.5
	(26.4)	(0.83)	(421.2)

DISCUSSION

Manufacture of the selected ER formulations under different conditions (such as, changes in batch size and manufacturing processes) to yield products with similar *in vitro* drug release profiles, in an IVIVC test method with acceptable internal predictability, shall be considered to exhibit "similar *in vivo* performance." Under current regulatory practice,[2] this inference could have been reached simply on the knowledge of an acceptable internal predictability of the IVIVC. This report evaluated this practice by evaluating the external predictability of the IVIVC for selected manufacturing changes to the same formulation and also for a different formulation (different release mechanism). Results of this evaluation are in general agreement with current regulatory practice that (1) recommends the use of an IVIVC with acceptable internal predictability to justify certain manufacturing changes (except for drugs with narrow therapeutic index, for which a dem-

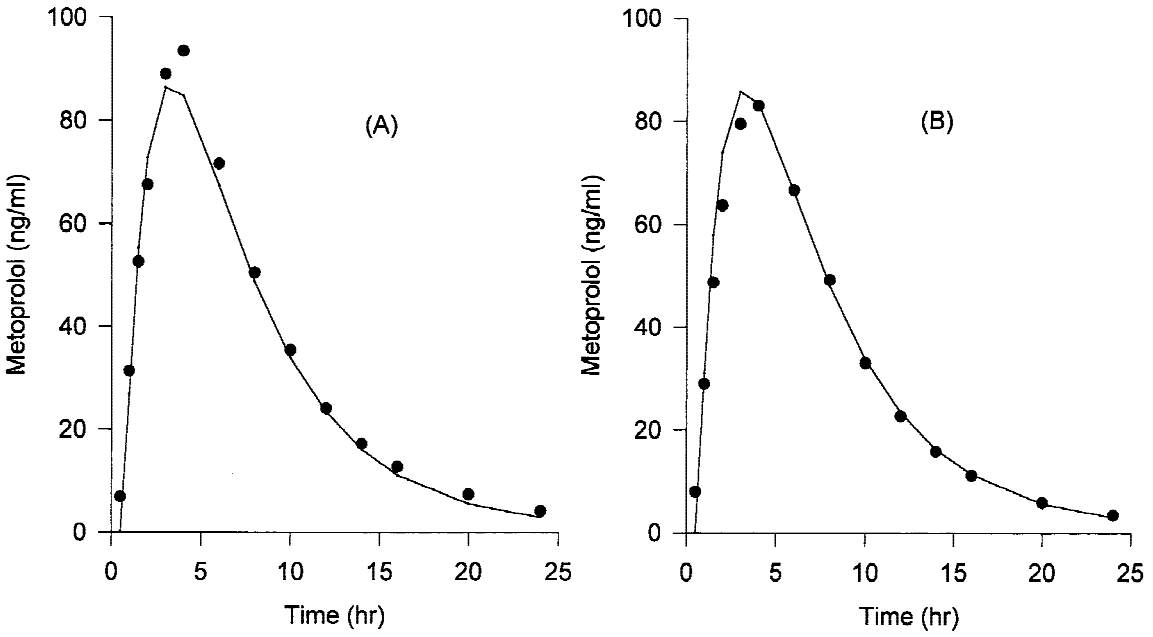

Figure 3. Observed (●) and predicted (solid line) metoprolol plasma concentration for the (A) **I** (small 3-kg batch) and (B) **II** (large 50-kg batch) extended-release tablets using the slow/moderate/fast IVIVC model.

onstration of acceptable external predictability is recommended), and (2) does not recommend the use of an IVIVC when a change in drug release mechanism is anticipated.

The IVIVC dissolution test conditions for the hydrophilic matrix ER tablet formulation were identified by evaluating dissolution media composition (pH), apparatus, and rates of agitation (Apparatus II, pH 1.2 and 6.8 at 50 rpm; and Apparatus I, pH 6.8 at 100 rpm).[3] Apparatus I (basket) at 150 rpm was found to yield acceptable IVIVC, suggesting that "polymer erosion" appears to be influencing *in vivo* drug release. Under these *in vitro* dissolution conditions, the coated-bead capsule formulation (**V**) appears to release drug at a rate that is faster than the *in vivo* rate of drug release (see figure 4C or PE of –23% for *C*max). Other factors that may contribute to the apparent failure of the IVIVC may relate to differential gastric emptying and/or intestinal transit of the matrix tablets and coated beads. Numerous studies have evaluated the gastrointestinal transit time of single-unit and/or multi-unit dosage forms.[10–12] Coupe et al.[10] reported a faster gastric transit for tablet dosage forms compared with pellets. These authors postulated that the differential emptying was due to (1) pellets becoming lodged in stomach folds and (2) contractions that preferentially force larger dosage forms out of the stomach. The slower absorption profile observed for the multiparticulate capsule dosage form may be explained by retention of the multi-unit system in the stomach. This retention may be less likely because drug release from the two systems appear to be insensitive to pH and the high permeability attributes of metoprolol. This study emphasizes that IVIVCs tend to be "formulation specific" and their utility should be restricted for justifying certain limited manufacturing changes that do not alter the drug release mechanism.

Table 2. Prediction Errors (%) Associated with C_{max} and AUC

Formulation	C_{max}	AUC
Study I		
I (3-kg batch)	7.53	6.13
II (50-kg batch)	–3.17	–2.20
Study II		
III (3-kg batch)	–11.7	–1.3
IV (80-kg high shear)	–8.03	1.3
V (bead capsule)	–23.0	2.5

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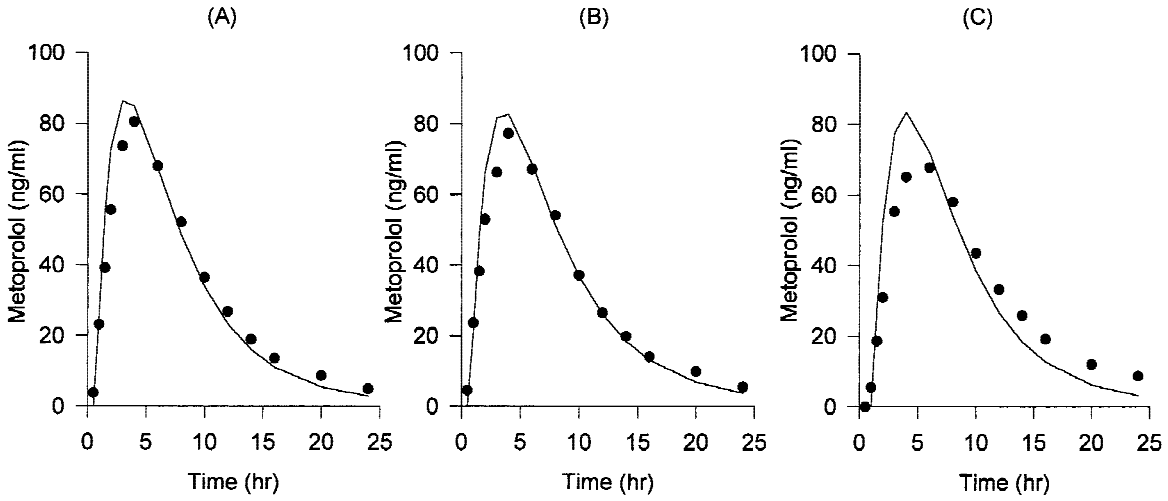

Figure 4. Observed (●) and predicted (solid line) metoprolol plasma concentration for (A) **III** (3-kg fluid bed), (B) **IV** (80-kg high-shear and microwave drying), and (C) **V** (bead capsule formulation) using the slow/moderate/fast IVIVC model.

technical suggestions and contributions to this work.

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