Predictive Ability of Level A *in Vitro–in Vivo* Correlation for RingCap Controlled-Release Acetaminophen Tablets

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Purpose. The goal of this study was to establish and validate an *in vitro–in vivo* correlation (IVIVC) for two sustained-release formulations (i.e., a matrix tablet and a RingCap banded matrix tablet) containing 750 mg of acetaminophen.

Methods. The *in vitro* dissolution and *in vivo* disposition of these formulations were examined by using a USP type III dissolution apparatus and a single-dose, three-way, crossover study that included an immediate-release acetaminophen dosage form, respectively. An IVIVC was established by using the mean fraction dissolved (FD) and mean fraction absorbed (FA) and used to simulate the plasma concentation-time profile of acetaminophen after administration of the matrix tablet (*i.e.,* internal validation) and RingCap banded matrix tablet (*i.e.,* external validation).

Results. A statistically significant relationship ($r^2 = 0.997$, $P < 0.001$) existed between the FD and FA for matrix tablets and was best described by the equation (FA) = 0.984 × (FD) + 0.0133. The percent predictions errors in CMAX and AUCL were <10% when predicting the plasma concentration-time profiles for the two formulations, validating the internal and external predictability of the IVIVC.

Conclusions. The data (i) show that *in vitro* dissolution data are a good predictor of *in vivo* fraction absorbed for acetaminophen, (ii) support the general use of *in vitro* dissolution data for readily soluble and readily absorbed drugs, (iii) suggest that acetaminophen may serve as a model drug for evaluating novel sustained-release delivery systems, and (iv) provide a tangible example of the limitations of current methods for predicting and validating IVIVC.

KEY WORDS: *in vitro, in vivo,* correlation, pharmacokinetics, controlled release, acetaminophen.

INTRODUCTION

The ability to use the *in vitro* characteristics of a controlled-release dosage form to predict its *in vivo* bioavailability can greatly simplify dosage form development. An *in vitro–in vivo* correlation (IVIVC) is most commonly established by developing formulations with different release rates, collecting data on the *in vitro* dissolution rates and *in vivo* plasma concentration-time profiles for these formulations, and using appropriate deconvolution and statistical techniques to verify the link between dissolution rate and fraction absorbed. However, it is important to note that establishing the IVIVC is only the first step in the process. For the IVIVC to be practically useful, it must be validated by investigating the predictability of the model for formulations with different release rates. Only then can the IVIVC be used prospectively to estimate the *in vivo* plasma concentration-time profile of an experimental formulation from its *in vitro* dissolution data. IVIVCs have been reported for a number of formulations, incorporating carbamazepine, diltiazem, metoprolol, and other drugs (1–3). The concepts and methods used in establishing valid IVIVC are reviewed elsewhere (4,5).

RingCap is a patented oral controlled-release delivery system. The dosage form is a capsule-shaped matrix tablet to which bands of insoluble polymer are applied circumferentially to the surface of the tablet. These bands modify the release rate of drug from the tablet through the control of surface area and erosion (6,7). Parameters affecting the release rate include the number, width, and placement of the bands on the tablet. The goal of these studies was to establish and validate an IVIVC relationship for drug release from this delivery system by using a model drug meeting the criteria as a class I drug according to the Biopharmaceutics Classification System, as originally proposed by Amidon *et al.* (8). The absorption of class I drugs should be dependent on their *in vivo* dissolution. Acetaminophen is generally classified as a drug with high solubility that shows high permeability throughout the intestinal tract (9–11). The approach was to develop the IVIVC for the matrix tablet and then validate the external predictability of the IVIVC by examining its ability to predict the *in vivo* concentration-time profile of a RingCap banded matrix tablet from its *in vitro* dissolution data. The results of these *in vitro* and *in vivo* studies with the acetaminophen and the RingCap delivery system are reported herein.

MATERIALS AND METHODS

Dosage Forms

Two controlled-release formulations containing 750 mg of acetaminophen were used for these studies. The first controlled-release formulation was a matrix tablet comprised of (w/w) acetaminophen 72%, Polyox Coagulant 13%, mannitol 13%, and stearic acid 2%. The formulation, hereafter referred to as the matrix tablet, was prepared by using a low-shear alcohol wet granulation method. The granulation was wet screened and tray dried at ambient temperature. The dry granulation was then milled and blended with lubricant to produce the final blend. Tablets were compressed manually by using 2000-lb compression force and film coated with hydroxypropylmethylcellulose. The second controlled-release formulation, hereafter referred to as RingCap banded matrix tablets, was a matrix tablet to which two 4-mm bands had been applied. The band material was Eudragit NE 30 D with 5% triacetin as a plasticizer. The 2 × 4-mm band configuration was chosen after evaluation of the *in vitro* dissolution profiles of 12 different band configurations. The 2 × 4-mm band configuration provided the greatest difference in *in vitro* release rate compared with the matrix tablet. Thus, we selected this band configuration with the expectation that it would show the greatest differences in clinical performance and provide proof of principle for the establishment of the IVIVC. A

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commercially available immediate release formulation of acetaminophen (Tylenol, two 325-mg tablets) was also used in the clinical bioavailability study.

Dissolution Testing

In vitro dissolution studies were performed by using a USP type III dissolution apparatus (VanKel BioDis, Cary, NC) and USP simulated intestinal fluid without enzymes. Nine tablets from each formulation were used for these studies. Individual tablets were dipped (20 dips/min) in 250 mL of buffer held at 37°C. The entire buffer solution was removed and replaced with fresh buffer at 1-h intervals for up to 36 h (*i.e.,* 1, 2, 3, . . . 36 h). The concentration of acetaminophen in each sample was determined by UV absorbance at 244 nm (model 8452A diode array spectrophotometer; Hewlett Packard, Wilmington, DE). A standard curve for acetaminophen was constructed over the linear range of 0.024–0.0024 mg/mL. Control samples containing no acetaminophen (*i.e.,* SIF alone) or 0.0096 mg/mL acetaminophen were analyzed with the samples from the dissolution experiments. The fraction of acetaminophen dissolved at each interval (FD) was calculated as (the cumulative amount released) divided by (750 mg). The mean FD (n = 9) for each formulation was used to establish the IVIVC and complete the internal and external validation, described below. The dissolution profiles were compared by using the similarity factor (f2) as described by Moore and Flanner (12) and recently adopted by the FDA (13), where an f2 value <50 indicates that the two profiles are different.

Clinical Study

A single-dose, three-way, crossover study was conducted in 12 healthy volunteers (8 males and 4 females) to compare the pharmacokinetics of the immediate release dosage form of acetaminophen (Tylenol, two 325-mg tablets) to the pharmacokinetics of the two 750-mg sustained release dosage forms of acetaminophen. The study was reviewed and approved by the University of Tennessee Institutional Review Board. Before entry into the study, subjects received a complete blood and urine analysis, an electrocardiogram, a physical examination, and provided written informed consent. The study was conducted in three phases, separated by an interval of 1 week. Subjects were divided into three groups (n = 4 per group), with formulations administered in a crossover design to minimize sequence-related effects. Doses were administered under fasting conditions, and blood samples (7 mL each) were obtained from each subject before the dose and at 0.33, 0.67, 1.0, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 15, and 25 h after each dose. Blood samples were centrifuged, and the plasma fraction was stored at –20°C until analysis.

Acetaminophen Analysis

A reversed-phase high-pressure liquid chromatographic (HPLC) method was developed to quantitate acetaminophen in human plasma. Briefly, an aliquot of plasma (0.25 mL) was extracted with ethyl acetate (4 mL) after addition of internal standard (0.25 mL of 150 μg/mL aqueous solution of theophylline). Each sample was centrifuged at approximately 500 g for 10 min at 4°C. The organic layer was transferred to a clean 15-mL nonsilanized conical tube and evaporated under a stream of nitrogen. Samples were reconstituted with 0.15 mL of 20% methanol and transferred to an autosampler vial for HPLC injection. The isocratic mobile phase contained 14% (v/v) methanol in 0.05 M sodium phosphate buffer (pH 4.4) and was pumped at a flow rate of 1 mL/min. The stationary phase was a C18 reversed-phase column (NovaPak, 3.9 × 150 mm, Waters Corp., Milford, MA), and the analytes were monitored with UV detection at 248 nm. The retention times of acetaminophen and theophylline were 3.5 and 6.0 min, respectively. The HPLC system consisted of an isocratic pump (model 501, Waters Corp.), automated injector (model 717, Waters Corp.), and variable wavelength UV detector (model 481, Waters Corp.). Chromatographic data were collected and analyzed by using Atlas software (Thermo Labsystems Chromserver, Beverly, MA). All standard curves were fit with a weight of 1/y and exhibited a correlation coefficient (r^2) ≥ 0.995 over the standard curve range of 0.153–30.6 μg/mL. The coefficients of variation for the standards ranged from 9.4% for the lowest concentration (0.153 μg/ml) to 2.0% for the highest concentration (30.6 μg/mL). The coefficients of variation for all controls were <6.6%.

Pharmacokinetic and Statistical Analyses

Mean plasma concentration-time profiles were constructed for each formulation. The maximal plasma concentration (CMAX) was determined by direct inspection of the mean plasma concentration-time profile. The rate constant (K) describing the terminal slope of mean plasma concentration-time profile was determined by linear least squares fitting of the natural logarithm (Ln) transformed terminal plasma concentrations vs. time to the equation for a straight line. Plasma concentrations observed between 2 and 15 h after dose administration were used for this calculation. The terminal slope of the mean plasma concentration-time profile observed after administration of the immediate release formulation was used for calculation of the half-life ($T_{1/2}$), extrapolation of the plasma concentration-time curve to time infinity, and calculation of the area under the curve from time zero to time infinity (AUCI) and fraction of the dose absorbed (FA) in all phases of the study. This was necessary due to the prolonged absorption of acetaminophen after administration of the sustained release dosage forms [*i.e.,* the terminal slope of the plasma concentration-time profile after administration of these formulations was not representative of the terminal elimination rate constant (K) of acetaminophen]. The area under the plasma concentration-time profile from time zero to 25 h (AUCL) was calculated by using the linear trapezoidal rule. The area under the plasma concentration-time profile from time zero to infinity (AUCI) was calculated as the sum of (AUCL) and (CpL/K), where CpL was the last measurable plasma concentration of acetaminophen and K was determined as described above. The FA for each formulation was calculated by using the mean (n = 12) plasma concentration-time profile for each formulation and the Wagner-Nelson method (14). Oral clearance (CL) was calculated as (dose) divided by (AUCI). All other comparisons were performed by using ANOVA.

Development of the Correlation

The IVIVC was developed by using the mean *in vitro* dissolution data and mean *in vivo* plasma concentration-time

profile of the matrix tablet. At each time point, the mean FD (n = 9 from *in vitro* dissolution studies) was plotted vs. the FA calculated from the mean plasma concentration-time profile observed for matrix tablets, as suggested by the FDA guidance on IVIVC (15). The slope, intercept, and correlation coefficient describing the relationship between mean FD and FA were determined by using linear regression.

Internal Validation of the IVIVC

The internal predictability of the IVIVC was examined by using the mean *in vitro* dissolution data and mean *in vivo* pharmacokinetics of matrix tablets. Briefly, the mean *in vitro* dissolution data from matrix tablets were used to calculate the expected FA after the dose. This calculation was performed by using the IVIVC established for matrix tablets (*i.e.,* where FA = [slope] × FD + [intercept]). The [intercept] value represents the value of FA at FD equal to zero and should approximate zero for a "perfect" IVIVC (*i.e.,* when FA varies in direct proportion to FD). The first derivative of the predicted FA for matrix tablets was then used as the input rate for a one-compartment pharmacokinetic model with first-order elimination to simulate the expected plasma acetaminophen concentration-time profile after an oral dose of matrix tablets. Stella II software (version 3.0.7; High Performance Systems, Hanover, NH) was used for all pharmacokinetic simulations. The volume of distribution and the elimination rate constant (K) used for this simulation were fixed at 97 L and 0.24 h^{-1}, respectively, representing the values of these parameters as determined from the mean plasma concentration-time profile of acetaminophen after administration of immediate release tablets. The CMAX and AUCL for the simulated plasma acetaminophen concentration-time profile were determined as described above and compared with that observed during the clinical study with matrix tablets. The FDA guidance (15) on IVIVC states that an average absolute percent prediction error of ≤10% for CMAX and AUC establishes the predictability of the IVIVC. In addition, the percent prediction error for each formulation should not exceed 15%.

External Validation of the IVIVC

The external predictability of the IVIVC established with matrix tablets was then used with the mean *in vitro* dissolution data of RingCap banded matrix tablets to predict the *in vivo* pharmacokinetics of RingCap banded matrix tablets. In this case, the mean *in vitro* dissolution data (FD) from RingCap banded matrix tablets was used to calculate the expected fraction of the dose absorbed (FA) after an oral dose of RingCap banded matrix tablets. The calculation of FA was performed as described above for internal validation. The first derivative of the predicted FA for RingCap banded matrix tablets was then used as the input rate to simulate the expected plasma acetaminophen concentration-time profile after an oral dose of RingCap banded matrix tablets. All other pharmacokinetic and simulation parameters were identical to those used for internal validation.

RESULTS AND DISCUSSION

The mean *in vitro* dissolution profiles for the matrix tablets and RingCap banded matrix tablets are shown in Fig. 1. Matrix tablets released 98% of their drug content within 17 h, whereas only 84% of the drug was released by 24 h with RingCap banded matrix tablets. RingCap banded matrix tablets required 30 h for complete dissolution. The release rates of the two formulations were different with an f2 value of 30.1, suggesting that the acetaminophen release rates from these two formulations would result in differences in their *in vivo* pharmacokinetics (12,13).

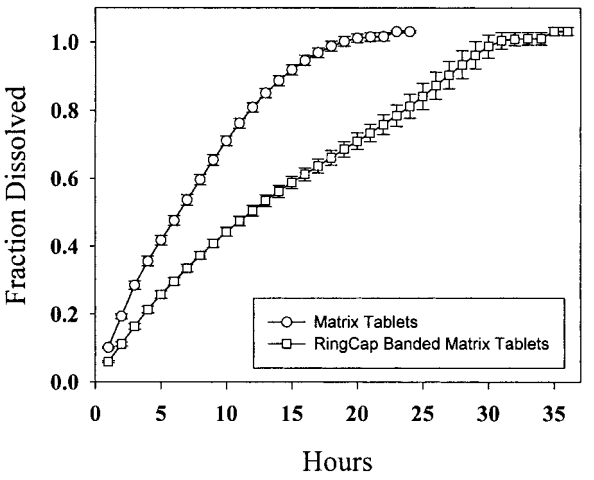

Fig. 1. *In vitro* dissolution profiles. The mean fraction of acetaminophen dissolved from the matrix tablet (open circles) and RingCap banded matrix tablet (open squares) were determined by using USP type III apparatus for *in vitro* dissolution. Each time point represents the mean fraction dissolved of nine tablets. Error bars represent means ± SD.

The mean plasma concentration-time profiles after oral administration of the immediate-release and two sustained-release acetaminophen formulations are shown in Fig. 2. Mean values of TMAX, AUCI, oral CL, and MRT for each formulation are shown in Table I. The results of this study indicated that both formulations significantly slowed and prolonged the absorption of acetaminophen, relative to the immediate release formulation. The mean terminal $T_{1/2}$ (%CV)

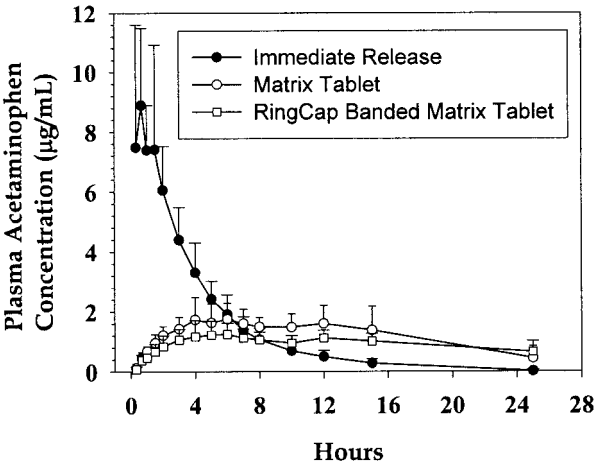

Fig. 2. *In vivo* plasma concentration-time profiles. Profiles represent the mean (n = 12) plasma concentration of acetaminophen observed in these subjects after administration of the immediate-release formulation (solid circles), matrix tablet (open circles), and RingCap banded matrix tablet (open squares). Error bars represent means ± SD for each observation.

Table I. Pharmacokinetics of Acetaminophen after Oral Administration[a]

Formulation	TMAX (h)	AUCI (μg × h/mL)	Oral CL (L/h)	MRT (h)
Immediate-release				
Mean	0.8	36.4	18.7	1.46
%CV	70	23	21	50
Matrix tablet				
Mean	8.4	32.5	26.8	11.7
%CV	54	39	42	20
RingCap banded matrix tablet				
Mean	7.4	26.4	30.3	13.9
%CV	56	26	27	13

[a] Plasma concentration-time profiles after oral administration of the immediate-release and two sustained-release acetaminophen formulations were determined by using a validated HPLC method. Pharmacokinetic parameters for individual profiles (n = 12 for each formulation) were calculated by using noncompartmental methods. ANOVA showed highly significant differences ($P < 0.001$) among the formulations for each of the measures listed.

and oral CL of acetaminophen in these subjects after administration of immediate-release tablets were 3.54 (22%) h and 18.7 (21%) L/h, respectively. These values closely resemble literature values for the terminal $T_{1/2}$ and oral CL of acetaminophen (16). The CMAX values (Table II), of the mean plasma concentration-time curve for the sustained-release formulations (750-mg dose) were 1.75 μg/mL and 1.25 μg/mL for matrix tablets and RingCap banded matrix tablets, respectively. The AUCL of the mean plasma concentration-time curve for RingCap banded matrix tablets was lower than that observed for matrix tablets (Table II). The lower AUCL for RingCap banded matrix tablets was at least in part due to the prolonged dissolution required for this formulation and the fact that no blood samples were collected after 25 h. That is, the AUCL of RingCap banded matrix tablets was likely lower due to the fact that absorption was still occurring at the conclusion of the 25-h study period. Evidence supporting this hypothesis lies in the observations (i) that only 87% of the dose was released over 25 h during *in vitro* dissolution experiments and (ii) that plasma concentration-time profiles in all subjects after administration of RingCap banded matrix tablets had not reached the terminal elimination phase at 25 h.

The IVIVC was established by using the *in vitro* dissolution data and *in vivo* plasma concentration-time profile observed for matrix tablets (Fig. 3). Linear regression analysis showed that a statistically significant relationship ($r^2 = 0.997$, $P < 0.001$) existed between the FD and FA for matrix tablets and was best described by the equation (FA) = 0.984 × (FD) + 0.0133. The CMAX, AUCL, and pharmacokinetic parameters determined from the simulated plasma concentration-time profile (Fig. 4) using the IVIVC (*i.e.,* FA calculated by using the equation above) are presented in Table II. The percent prediction errors for CMAX and AUCL were <10%, validating the internal predictability of the IVIVC.

It should be noted that the trends in the actual and predicted plasma concentration-time profile in Fig. 4 differ. For example, the predicted plasma concentration-time profile increases more rapidly in the 0–6-h time interval, does not include a second peak in plasma drug concentration at approximately 12 h, and has an increasing tendency in the 20–25-h

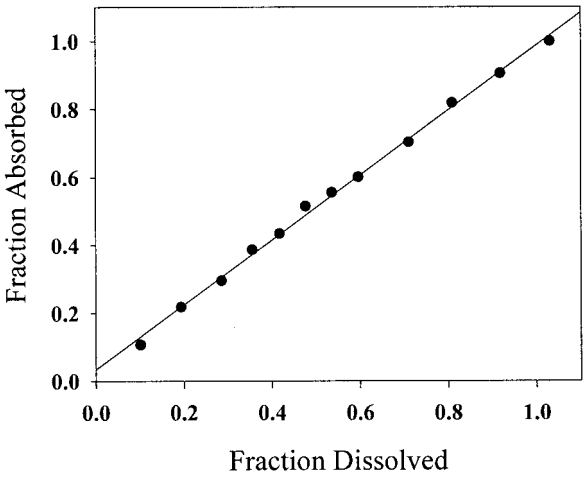

Fig. 3. Relationship between the mean fraction absorbed *in vivo* and the mean fraction dissolved *in vitro* for matrix tablets. Mean FD and mean FA were determined for matrix tablets and used to establish the IVIVC. The line represents the linear regression of the data, where (Fraction Absorbed) = 0.984 × (Fraction Dissolved) + 0.0133 and $r^2 = 0.997$.

time interval, compared with the actual data observed during the clinical study. These observations call attention to the inherent limitations of the FDA methods for development of IVIVC, namely, that CMAX and AUCI provide incomplete data about the time course of drug concentrations in the plasma. These deviations between the actual and predicted concentration-time profile were also seen during external validation of the IVIVC (Fig. 5).

The external predictability of the IVIVC was examined by using the *in vitro* dissolution profile of RingCap banded matrix tablets to predict the plasma concentration-time pro-

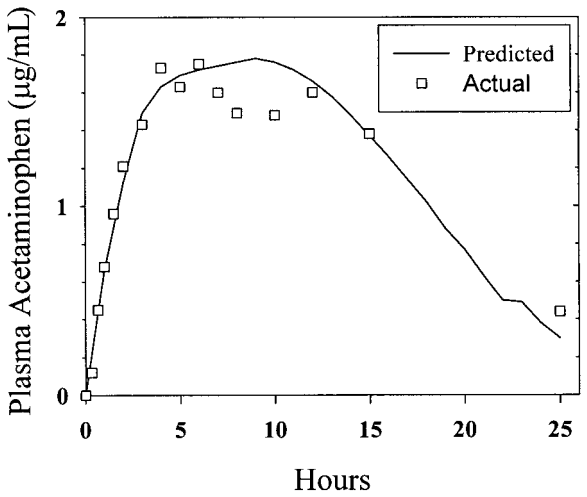

Fig. 4. Internal validation. The first derivative of the predicted FA for matrix tablets was used as the input rate for simulation of the expected plasma acetaminophen concentration-time profile after an oral dose of matrix tablets using a one-compartment pharmacokinetic model with first-order elimination and Stella II software (version 3.0.7; High Performance Systems). The line represents the plasma concentration-time profile predicted by using the established IVIVC (*i.e.,* FA = 0.984 × FD + 0.0133), and the open squares circles represent the actual plasma concentrations of acetaminophen observed during the clinical study.

Table II. Validation and Prediction of IVIVC[a]

	Actual values	Predicted with FA = 0.984 × FD + 0.0133 (%)
Prediction of plasma concentration-time profile for matrix tablets		
Cmax (μg/mL)	1.75	1.83 (4.6)
AUCL (μg × h/mL)	30.3	31.3 (3.3)
Prediction of plasma concentration-time profile for RingCap banded matrix tablets		
Cmax (μg/mL)	1.25	1.16 (7.2)
AUCL (μg × h/mL)	23.2	23.1 (0.4)

[a] The IVIVC was validated internally by examining its ability to predict the concentration-time profile of the matrix tablet. The predictive ability of the IVIVC was examined by using the IVIVC developed with use of matrix tablets to predict the plasma concentration-time of the RingCap banded matrix tablet. Actual values are those observed during completion of the clinical study for each formulation. Numbers in parentheses represent the percent error between actual and predicted values. It is important to note that the actual values of CMAX and AUCL represents the pharmacokinetics of the mean concentration-time profile for each formulation and cannot be directly compared with the mean values of these measures calculated by using individual concentration-time profiles as presented in Table I.

file after administration of an oral dose of RingCap banded matrix tablets. The predicted and observed plasma concentration-time profiles for acetaminophen after an oral dose of RingCap banded matrix tablets are shown in Fig. 5. The percent prediction error in CMAX and AUCL were <10% when using the IVIVC. The plasma concentration-time profiles for the two sustained-release formulations were also predicted by using a perfect IVIVC (*i.e.,* FA = FD). Percent prediction errors for CMAX and AUCL were <10% for both formulations, indicating that the slope and intercept of the IVIVC were indistinguishable from one and zero, respectively.

CONCLUSIONS

This study established and validated the internal and external predictability of an IVIVC relationship for sustained-release acetaminophen formulations. The *in vivo* CMAX and AUCL were predicted by calculating FA from the IVIVC. In both instances, the simulated plasma concentration-time profile for acetaminophen closely predicted (<10% error) the CMAX and AUCL of the formulation after oral administration. The ability of the IVIVC to accurately predict the observed plasma concentration-time profile of these sustained-release formulations supports the assertion that the *in vitro* dissolution of acetaminophen in this dosage form is closely related to the *in vivo* fraction absorbed. Acetaminophen meets the criteria for classification as a class I drug according to the Biopharmaceutics Classification System (8–11). These studies support the idea that an IVIVC for high-solubility, high-permeability drugs will be observed when dissolution is the rate-limiting step in absorption (8,9).

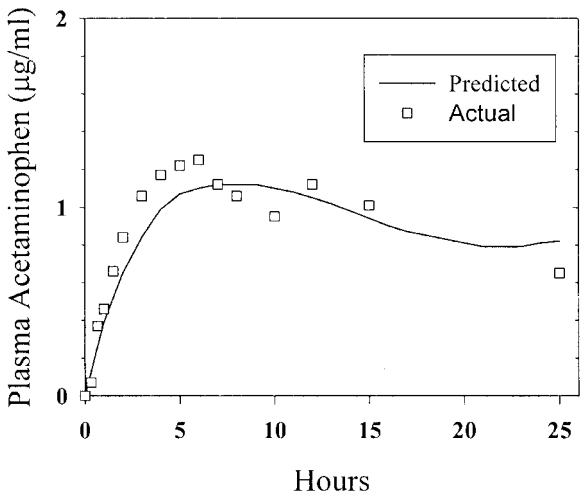

Fig. 5. External validation. The first derivative of the predicted FA for RingCap banded matrix tablets was used as the input rate for simulation of the expected plasma acetaminophen concentration-time profile after an oral dose of RingCap banded matrix tablets using a one-compartment pharmacokinetic model with first-order elimination and Stella II software (version 3.0.7; High Performance Systems). The line represents the plasma concentration-time profile predicted by using the established IVIVC (*i.e.,* FA = 0.984 × FD + 0.0133), and the open squares circles represent the actual plasma concentrations of acetaminophen observed during the clinical study.

Although the IVIVC established in this research clearly meets the criteria for a valid IVIVC, notable differences between the shape of the actual and predicted plasma concentration-time profiles were observed. The fact that these differences were observed under such ideal conditions (*i.e.,* when using a drug that shows a near perfect linear relationship between FA and FD and optimal solubility and permeability characteristics) highlights the limitations of current FDA standards for establishing IVIVC. Clearly, improved methods to predict *in vivo* plasma concentration-time data from *in vitro* dissolution data are needed. Frequency domain and/or proportional odds and hazards modeling may provide new and reasonable approaches to this problem and are currently under development (17,18).

Thus, these data (i) provide a tangible example of the limitations of current methods for predicting and validating IVIVC, (ii) show that *in vitro* dissolution data are a good predictor of *in vivo* fraction absorbed for acetaminophen, (iii) support the general use of *in vitro* dissolution data to predict *in vivo* disposition for readily soluble and readily absorbed drugs, and (iv) suggest that acetaminophen may serve as a model drug for evaluating novel sustained-release delivery systems.

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