Extended Release Dosage Form of Glipizide: Development and Validation of a Level A in Vitro–in Vivo Correlation

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Defining a quantitative and reliable relationship between in vitro drug release and in vivo absorption is highly desired for rational development, optimization, and evaluation of controlled-release dosage forms and manufacturing process. During the development of once daily extended-release (ER) tablet of glipizide, a predictive in vitro drug release method was designed and statistically evaluated using three formulations with varying release rates. In order to establish internally and externally validated level A in vitro–in vivo correlation (IVIVC), a total of three different ER formulations of glipizide were used to evaluate a linear IVIVC model based on the in vitro test method. For internal validation, a single-dose four-way cross over study (n=6) was performed using fast-, moderate-, and slow-releasing ER formulations and an immediate-release (IR) of glipizide as reference. In vitro release rate data were obtained for each formulation using the United States Pharmacopeia (USP) apparatus II, paddle stirrer at 50 and 100 rev. min⁻¹ in 0.1 M hydrochloric acid (HCl) and pH 6.8 phosphate buffer. The $f_2$ metric (similarity factor) was used to analyze the dissolution data. The formulations were compared using area under the plasma concentration–time curve, AUC₀⁻∞, time to reach peak plasma concentration, Tₚₚ, and peak plasma concentration, Cₚₚ, while correlation was determined between in vitro release and in vivo absorption. A linear correlation model was developed using percent absorbed data versus percent dissolved from the three formulations. Predicted glipizide concentrations were obtained by convolution of the in vivo absorption rates. Prediction errors were estimated for Cₚₚ, and AUC₀⁻∞, to determine the validity of the correlation. Apparatus II, pH 6.8 at 100 rev. min⁻¹ was found to be the most discriminating dissolution method. Linear regression analysis of the mean percentage of dose absorbed versus the mean percentage of in vitro release resulted in a significant correlation ($r²≥0.9$) for the three formulations.

Keywords controlled release; in vitro–in vivo correlation; bioavailability; dissolution; in vitro model

The development and subsequent validation of an in vitro–in vivo correlation (IVIVC) is an increasingly important component of extended release dosage form optimization. An IVIVC is a relationship (preferable linear) between a biological parameters ($C_{ₚₚ}$, $T_{ₚₚ}$, or AUC) produced by a dosage form and an in vitro characteristics (e.g., in vitro dissolution). The in vitro dissolution curve is usually determined by a suitable dissolution test and in vivo absorption curve is frequently determined by deconvolution using model dependent (e.g., Wagner–Nelson or Loo–Regelman) or model independent (e.g., DeMons) methods. Level A, B, C and multiple Level C correlation has been described by the Food and Drug Administration (FDA) for IVIVC. The highest level correlation, Level A, is usually linear and is a direct relationship between the amounts of drug dissolved and the amount of drug absorbed. The recent in vitro–in vivo correlation guidance developed by the FDA, states that the main objective of developing and evaluating an IVIVC is to enable the dissolution test to serve as a surrogate for in vivo bioavailability studies. This may reduce the numbers of bioequivalence studies required for approval as well as during scale-up and post approval change. There are numerous examples of Level A correlations in the literature, however many fall short in assessing the predictability of the correlation. The process for the development and validation of an IVIVC has been outlined in the FDA IVIVC guidance. The development of the correlation usually involves the following three steps:

1. develop formulation with different release rates, e.g. slow, moderate and fast,
2. obtain in vitro dissolution profiles and in vivo plasma concentration profiles for these formulations, and
3. estimate the in vivo absorption or in vitro dissolution time course using an appropriate deconvolution technique for each formulation.

The internal validation of the correlation focuses on using prediction error metrics to determine how well the IVIVC model predict the plasma concentration profile of those formulations used to develop the correlation. Establishing a correlation between the in vivo plasma concentration profile and in vitro dissolution profile of an extended release formulation has been great interest for a number of years. Extended release of drugs in the gastrointestinal tract following oral administration is the intended rate-limiting factor in the absorption process. It is therefore desirable to use in vitro data to predict in vivo bioavailability parameters for the rational development and evaluation process for extended-release dosage forms.

Glipizide (N-[2-[4-(cyclohexylcarbamoylsulfamoyl)phenyl]-ethyl]-5-methyl-pyridine-2-carboxamide) is a hypoglycemic agent of the sulfonylurea group. Numerous IVIVC studies of extended release formulation have been previously reported, although there are none involving extended release glipizide formulations. Therefore, the purpose of this study was to develop an IVIVC for three novel hydrophilic matrix extended release glipizide 5 mg tablets. The validity of the correlation was established through the external predictability approach, by using the data from one study to predict the plasma concentration of a similar dosage form, with different rate of release.

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MATERIALS AND METHODS

**Materials** Glipizide was provided by Stadmed Pharmaceuticals, hydroxypropyle methylcellulose (HPMC K 4M, 15M and 100M) was manufactured by Dow Chemical Company (U.S.A.) provided by Stadmed Pharmaceuticals (India). Lactose (grade 315, 316), manufactured by Loba Chemicals Pvt. Ltd. (India), was provided by Stadmed Pharmaceuticals (India). Magnesium stearate, talcum powder and silicon dioxide (Aerosil) were manufactured by Loba Chemicals and provided by Stadmed Pharmaceuticals (India).

**Formulations** Three extended-release matrix formulations of 5 mg glipizide were developed by non aqueous wet granulation method using hydroxypropyle methylcellulose (HPMC K 4M, HPMC K 15M and HPMC K 100M) as the release-rate-controlling excipient. Lactose (grade 315, 316) was used as filler and magnesium stearate, talcum powder and Aerosil as lubricant. These formulations were designed to release glipizide at three different rates, referred as fast (release up to 12 h), moderate (release up to 18 h) and slow (release up to 24 h). The high-viscosity HPMC (K 100M), medium-viscosity HPMC (K 15M) and low-viscosity HPMC K 4M) were used for slow, moderate and fast release, respectively. Final weight of the fast release formulation was 220 mg with average hardness of 6.0 kg cm\(^{-2}\). The average weight of the moderate release formulation was 190 mg with an average hardness of 7.0 kg cm\(^{-2}\). External validation was carried out based on the data obtained from the extended-release matrix tablet designed to release up to 15 h, optimized by using response surface methodology (RSM). This optimized formulation was comprised of mixture of low viscosity grade of hydroxypropyle methylcellulose (HPMC K 4M) and medium viscosity grade of hydroxypropyle methylcellulose (HPMC K 15M) and the average weight and hardness was 180 mg and 6.5 kg cm\(^{-2}\) respectively.

**Dissolution Testing** The dissolution behavior of glipizide extended-release matrix tablets (fast, moderate and slow) was continuously recorded using a semi-automatic dissolution apparatus (Electrolab, USPXXIII, TDT 06P). The release characteristics of the formulations were determined using United States Pharmacopeia (USP) Apparatus II at 50 and 100 rev. min\(^{-1}\) in 0.1 M HCl or pH 6.8 phosphate buffer maintained at 37 °C. Dissolution tests were performed on six tablets and the amount of drug release was analyzed by validated reverse phase high performance liquid chromatography (HPLC) method at 275 nm. Dissolution samples were collected at the following times: 0, 0.5, 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 12, 18 and 24 h.

**Bioavailability Study** The bioavailability study was an open level, fasting, single dose and four-way cross over study (n=6) using normal healthy subjects. Subjects provided informed consent to participate in the study. The study was approved by the Institution ethical committee of Jadavpur University, Kolkata, India. Twenty four male, non smoking subjects were enrolled in the study and received three extended-release 5 mg glipizide matrix tablets (fast, moderate and slow), once per day. All three formulations were given in a randomized fashion. In addition to the extended release formulations, an immediate-release 5 mg glipizide tablet (GLIPY, manufactured by Alembic, India) was also administered. In order of drug administration was randomized in four sequences (ABCD, BADC, CDBA and DCAB) in blocks of four. Blood samples were obtained at seventeen time points from pre dose (0 h) until 48 h post dose (0, 0.5, 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 12, 18, 24, 48 h). Subjects fasted for 12 h prior to administration of drugs. A washout period of 1 week was allowed between dose administrations. The plasma samples were stored at −20 °C until assayed.

**Assay Method for Glipizide** An analytical method for the determination of glipizide and gliclazide (as internal standard) in human plasma was developed and validated using high performance liquid chromatography (HPLC; Model No. K 2501; Knauer, Germany, Eurochrom software). The method determined the concentrations of glipizide using a calibration range of 0.02—1.0 μg ml\(^{-1}\). The accuracy of the assay for glipizide (as determined from the calibration standards and control samples) was in the range 98.12—102.34% and 98.28—101.59%, respectively.

**In Vitro Dissolution Data Analysis** The in vitro dissolution data was analyzed by estimation of a similarity factor, the \(f_2\) metric and parameterized by the sigmoid Emax model. The dissolution profiles were compared using the similarity factor, \(f_2\) presented in the following equation.\(^{15}\)

\[
f_2 = 50 \log \left( 1 + \frac{1}{n} \sum_{i=1}^{n} (R_i - T_i)^2 \right)^{0.5} \times 100
\]

Where \(R_i\) and \(T_i\) are the cumulative percent dissolved at each time point for the reference product and the test product, respectively. FDA has set a public standard of 50<\(f_2<100\) to indicate similarity between two dissolution profiles.

**In Vivo Data Analysis** The glipizide concentration–time data were evaluated by analysis of plasma samples by validated HPLC method. The measured plasma concentrations were used to calculate the area under the plasma concentration–time profile from time zero to last concentration time point (\(AUC_{0→\infty}\)). The \(AUC_{0→\infty}\) was determined by the trapezoidal method. Area under the plasma concentration–time curve from zero to infinity (\(\infty\)), \(AUC_{0→\infty}\), was determined by the following equation:

\[
AUC_{0→\infty} = AUC_{0→t} + C(t)/K_e
\]

Where \(K_e\), the elimination rate constant, was estimated by fitting the logarithm of the concentration versus time to a straight line over the observed exponential decline. The Wagner–Nelson method\(^{10}\) was used to calculate the percentage of the glipizide dose absorbed:

\[
F(t) = C(t) + K_e AUC_{0→t}
\]

Where, \(F(t)\) is the amount absorbed. The percent of dose absorbed is determined by dividing the amount absorbed at any time by the plateau value, \(K_e AUC_{0→\infty}\) and multiplying this ratio by 100.

\[
% \text{dose absorbed} = \left[1 + (C(t) + K_e AUC_{0→t})/K_e AUC_{0→\infty}\right] \times 100
\]

**In Vitro–in Vivo Correlation** The data generated in the bioavailability study were used to develop the IVIVC. The percent of drug dissolved was determined using the aforementioned dissolution testing method and the fraction of drug absorbed was determined using the method of Wag-
ner–Nelson\textsuperscript{10} from the glipizide plasma concentration vs. time data following the slow, moderate and fast release formulations. The deconvolution procedure was used to obtain \textit{in vivo} input profiles of glipizide using immediate-release data as the reference treatment. Correlation models were developed using mean fraction dissolved and mean fraction absorbed data from various combinations of the formulations including: 

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

Linear regression analysis was used to examine the relationship between percent of drug dissolved and percent of drug absorbed. The percent of drug unabsorbed was calculated from the percent absorbed. The percent of drug unabsorbed \textit{versus} time was plotted on a semi log paper. The slope of the best-fit line for the semi-log treatment of this data was taken as the first order rate constant for absorption ($K_d$) where slope is equal to negative $K_d$ divided by 2.303, the dissolution rate constant ($K_{diss}$) was determined from percent cumulative released \textit{versus} the square root of time. Linear regression analysis was applied to the IVIVC plots and coefficient of determination ($R^2$), slope and intercept values were calculated.

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

The IVIVC model predicted glipizide plasma concentration was determined by the following procedure. First, best fitting line was drawn between the cumulative percent dissolved and square root of time. The slope of the best fitting line was used as rate of dissolution. The \textit{in vitro} dissolution rates were then converted to \textit{in vivo} dissolution rates by using the different (S/M, S/F, M/F and S/M/F) IVIVC models (\textit{i.e.}, slope, intercept). The prediction of the plasma glipizide concentrations from the \textit{in vitro} dissolution profiles was accomplished by convolution of the \textit{in vitro} dissolution rates and the pharmacokinetic model for the immediate release administration of the drug.

The prediction of the plasma glipizide concentration was accomplished using the following curve fitting equation:

$$y=\text{const} \times (\text{dose}) \times K_d/K_a \times K_e(e^{-K_d t} - e^{-K_e t})$$

Where $y$ = predicted plasma concentration (ng ml$^{-1}$); const. = the constant representing $F/V_d$, where $F$ = fraction absorbed, and $V_d$ is the apparent volume of distribution; $K_a$ = absorption rate constant; $K_e$ = overall elimination rate constant. The deconvolution was accomplished on a spreadsheet in Excel.

To further assess the predictability and the validity of the correlations, we determined observed and IVIVC model-predicted $C_{\text{max}}$ and AUC\textsubscript{0--\infty} values for each formulation. The percent prediction errors for $C_{\text{max}}$ and AUC\textsubscript{0--\infty} were calculated as follows:

$$\%\text{PE}_{C_{\text{max}}}=\left[\frac{C_{\text{max(adv)}}}{C_{\text{max(pred)}}}\right]C_{\text{max(obs)}} \times 100$$

$$\%\text{PE}_{\text{AUC}_{0--\infty}}=\left[\frac{\text{AUC}_{0--\infty(adv)}}{\text{AUC}_{0--\infty(pred)}}\right]C_{\text{AUC}_{0--\infty(obs)}} \times 100$$

Where $C_{\text{max(adv)}}$ and $C_{\text{max(pred)}}$ are the observed and IVIVC model predicted maximum plasma concentration, respectively; and $\text{AUC}_{0--\infty(adv)}$ and $\text{AUC}_{0--\infty(pred)}$ are the observed and IVIVC model-predicted $\text{AUC}_{0--\infty}$ for the plasma concentration profiles, respectively. The IVIVC was considered valid if the average absolute % prediction error is <10 for $C_{\text{max}}$ and AUC and if the % prediction error for each formulation does not exceed 15%.

**External Validation of the IVIVC** The external validation was accomplished by the optimized extended-release matrix formulation of glipizide containing 5 mg active ingredient, selected to provide a $C_{\text{max}}$ of the reformulated product equivalent to the $C_{\text{max}}$ obtained from the fast, moderate and slow tablets, and to re-test the re-formed product against the fast, moderate and slow tablets in another bioavailability study in human subjects.

**Statistical Analysis** All the results were expressed as mean±standard deviation (S.D.). The values of $C_{\text{max}}, T_{\text{max}}$ and $\text{AUC}_{0--\infty}$ obtained from three formulations were analyzed using one-way analysis of variance with WinNonlin (version 4.1, Pharsight) software to determine statistically significant differences. The $\text{AUC}_{0--\infty}$ and $C_{\text{max}}$ values were logarithmically transformed before statistical analysis. $p\leq0.5$ denoted statistical significance.

**RESULTS AND DISCUSSION**

**In Vitro Studies** Mean profiles of the cumulative glipizide fraction dissolved from the slow, moderate and fast formulation are illustrated in Figs. 1 and 2. The dissolution testing methods were Apparatus II, pH 6.8 phosphate buffers at 50 and 100 rev. min$^{-1}$ (Fig. 1), Apparatus II, 0.1 M HCl at 50 and 100 rev. min$^{-1}$ (Fig. 2). The associated $f_2$ metrics, which determines the similarity of the various formulations are shown in Table 1. A $f_2$ value between 50 and 100 suggests that two profiles are similar. Eddington \textit{et al.} (1998) reported that it is imperative to utilize a dissolution methodology that discriminates between formulations and the mimics the \textit{in vivo} release profile in the process of developing an IVIVC.\textsuperscript{9} Accordingly, Apparatus II, pH 6.8 at 100 rev. min$^{-1}$ were found to be the most discriminating dissolution methods. Cumulative percent glipizide release \textit{versus} square root of time (Higuchi Kinetics) profiles for fast, moderate and slow release tablets at different dissolution parameters (50, 100 rev. min$^{-1}$, pH 6.8 phosphate buffer; 50, 100 rev. min$^{-1}$, 0.1 M HCl) gave the straight line (regression coefficient, $R^2>0.98$) and the slopes were used as dissolution rate constant ($K_{diss}$). The value of $K_{diss}$ at pH 6.8 phosphate buffer with 100 rev. min$^{-1}$ for fast, moderate and slow release formulation was found to be 29.328±0.18, 23.516±0.64 and...
In Vivo Studies

Twenty four male subjects completed the study. The mean ± S.D. age, height and weight of the subjects were 32.8 ± 5.4 years, 168.5 ± 15.2 cm and 58.3 ± 4.9 kg, respectively. There were no serious adverse reactions reported in the study. Mean pharmacokinetic parameters are summarized in Table 2 and mean glipizide plasma concentration versus time profiles after each formulation and the immediate-release formulation are presented in Fig. 3. The rank order of release observed in the dissolution testing was also apparent in the plasma glipizide concentration profiles with a mean $C_{\text{max}}$ of 451.529, 439.609, and 411.957 ng/ml for the slow, moderate and fast releasing formulations. In addition, a rank order was also apparent in the $AUC_0-\infty$ (Table 2). The $AUC_0-\infty$ from immediately release tablets (2059.316 ± 43.821 ng·h·m l$^{-1}$) was somewhat less than the $AUC_0-\infty$ from the extended release formulation ($p<0.01$), probably due to shorter residence time of the immediately release tablet than the extended release tablets or drug–excipient interaction from the immediate release tablet.

IVIVC Correlation Development

A Level A IVIVC was investigated using the percent absorbed data versus percent dissolved for both the fast, moderate and slow formulations, using both 0.1 M HCl and pH 6.8 phosphate buffer dissolution media at 50 rev. min$^{-1}$ and 100 rev. min$^{-1}$. A good linear regression relationship was observed between the percent dissolved in the dissolution testing using phosphate buffer pH 6.8 at 50 rev. min$^{-1}$ and the percent absorbed for the combined data of the three dosage ($y=3.3863x−2.5871$; $r^2=0.98$).

15.900±0.29, respectively.

Table 1. $f_2$ Metric in Various Dissolution Testing Conditions for Extended Release Glipizide Formulations

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Formulations</th>
<th>$f_2$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1 M HCl, 50 (rev/min)</td>
<td>Fast</td>
<td>Moderate</td>
</tr>
<tr>
<td>0.1 M HCl, 50 (rev/min)</td>
<td>Fast</td>
<td>Slow</td>
</tr>
<tr>
<td>0.1 M HCl, 50 (rev/min)</td>
<td>Moderate</td>
<td>Slow</td>
</tr>
<tr>
<td>0.1 M HCl, 100 (rev/min)</td>
<td>Fast</td>
<td>Moderate</td>
</tr>
<tr>
<td>0.1 M HCl, 100 (rev/min)</td>
<td>Fast</td>
<td>Slow</td>
</tr>
<tr>
<td>0.1 M HCl, 100 (rev/min)</td>
<td>Moderate</td>
<td>Slow</td>
</tr>
<tr>
<td>pH 6.8, 50 (rev/min)</td>
<td>Fast</td>
<td>Moderate</td>
</tr>
<tr>
<td>pH 6.8, 50 (rev/min)</td>
<td>Fast</td>
<td>Slow</td>
</tr>
<tr>
<td>pH 6.8, 50 (rev/min)</td>
<td>Moderate</td>
<td>Slow</td>
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<tr>
<td>pH 6.8, 100 (rev/min)</td>
<td>Fast</td>
<td>Moderate</td>
</tr>
<tr>
<td>pH 6.8, 100 (rev/min)</td>
<td>Fast</td>
<td>Slow</td>
</tr>
<tr>
<td>pH 6.8, 100 (rev/min)</td>
<td>Moderate</td>
<td>Slow</td>
</tr>
</tbody>
</table>

Table 2. Mean Pharmacokinetic Parameters for Glipizide from Slow, Moderate, Fast and Immediate Release Formulations

<table>
<thead>
<tr>
<th>Formulation</th>
<th>$C_{\text{max}}$ (ng/ml)</th>
<th>$T_{\text{max}}$ (h)</th>
<th>$AUC_0-\infty$ (ng · h/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate release</td>
<td>360.51±21.57</td>
<td>2.67±0.37</td>
<td>2059.32±43.82</td>
</tr>
<tr>
<td>Fast release</td>
<td>411.96±29.07</td>
<td>4.58±0.49**</td>
<td>3746.04±57.51*</td>
</tr>
<tr>
<td>Moderate release</td>
<td>439.61±33.91</td>
<td>5.12±0.52**</td>
<td>4904.17±63.09**</td>
</tr>
<tr>
<td>Slow release</td>
<td>451.53±27.19</td>
<td>5.53±0.61**</td>
<td>6861.48±72.91*</td>
</tr>
</tbody>
</table>

Values are presented as mean ± S.D., $n=6$. *$p<0.01$; **$p<0.001$ vs. immediate release.
correlation coefficient ($r^2=0.9483$). Another good linear regression relationship was observed between the percent dissolved in the dissolution testing using phosphate buffer pH 6.8 at 100 rev. min$^{-1}$ and the percent absorbed for the combined data of the three dosage ($y=2.8008x−5.1494$; correlation coefficient ($r^2$)=0.9522).

It was also observed that the *in vivo* absorption rate constant, $K_a$ values for slow, moderate and fast formulations correlated with the dissolution rate constant, $K_{\text{diss}}$ values of the pH 6.8 phosphate buffer at 100 rev. min$^{-1}$. Dissolution testing using pH 6.8 phosphate buffers at 100 rev. min$^{-1}$ was more representative of the *in vivo* absorption profiles and linear regression relationships were developed. There was good linear correlation for these models, with $r^2$ values $>0.95$ for the IVIVC models. Each correlation was found to be significant and the combination of the fast and slow formulation displayed the strongest relationship ($r^2=0.9982$). Conversely, the correlation for the slow and moderate formulations was less descriptive as compared to other correlation models ($r^2=0.9689$).

**Internal Validation** The internal validation was performed by convolution of the dissolution data (*i.e.*, pH 6.8 phosphate buffers at 100 rev. min$^{-1}$) that corresponded to each formulation (S/M/F). Each of the IVIVC model predicted glipizide plasma concentration *versus* time profiles were compared to the experimental data points using prediction error metrics. The validity of the correlations was also assessed by determining how well the IVIVC models could predict the rate and extent of glipizide absorption as characterized by $C_{\text{max}}$ and $AUC_{0-\infty}$. Tables 3 and 4 present the errors estimated for the difference between the observed and predicted $C_{\text{max}}$ and $AUC_{0-\infty}$ values for all the IVIVC models. None of the IVIVC model predicted parameters deviated from the experimental values by more than 10%.

**External Validation** The external validation was accomplished by the optimized extended-release matrix formulation of glipizide containing 5 mg active ingredient and to predict the plasma concentration of the new formulation all four IVIVC models (S/M/F, S/M, M/F and S/F) were used. The actual (observed) maximum average plasma concentration of the new formulation at steady state was determined to be $446.059\pm38.431$ ng/ml by *in vivo* study ($n=6$). The errors estimated for the difference between the observed and predicted $C_{\text{max}}$ and $AUC_{0-\infty}$ values of the new formulation for all the IVIVC models ranged between (−)8.91 to 7.02% and (−)5.59 to 6.17%, respectively.

**Discussion** The FDA-IVIVC Guidance and the USP/AAPS/FDA-Workshop II, which examined the scale-up of oral extended release dosage forms, stated that the objective of an IVIVC was the use of dissolution as a surrogate for bioequivalency testing and as an aid in setting dissolution specifications. In the process of developing an IVIVC, it is imperative to utilize dissolution methodology that discriminates between formulations and mimics the *in vivo* release profiles. We examined the various dissolution testing methods to characterize the release of the three formulations of glipizide. The initial IVIVC development began with using the USP defined dissolution methodology for glipizide (*i.e.*, Apparatus II, phosphate buffer pH 6.8 at 50 rev. min$^{-1}$). These dissolution methods produced a curvilinear relationship (Fig. 4A) between percentage dissolved and percentage absorbed and the dissolution results were not representative of the *in vivo* glipizide absorption profile. The release profile generated lagged behind the absorption profile. An increase in the shear force or velocity of the testing system was required to approximate the absorption profile. Dissolution testing with Apparatus II, phosphate buffer pH 6.8 at 100 rev. min$^{-1}$ provided percentage dissolved data that was predictive of the percentage absorbed data (Fig. 4B). It appears that the increase in agitation generated from this in
vitro dissolution system appropriately simulated the erosion that occurred in vivo with this formulation. Once identified, the dissolution methodology should be used in any further evaluation of the correlation, such as external validation.

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

The predictability of the correlations developed was tested by internal validation which consisted of calculating percentage prediction errors (%PE\text{C}_{\text{max}} and %PE\text{AUC}_{0-\infty}). The realistic measurement of the validation is the ability of the IVIVC models to estimate the observed rate and extent of absorption. All IVIVC models predicted the observed C\text{max} and AUC\text{0-\infty} within 10% (Tables 3, 4). The lowest percent prediction error for C\text{max} (2.63%) was found for the slow formulation using the S/F IVIVC model. The S/F IVIVC model provided the best estimate of AUC\text{0-\infty} for the fast formulation (2.59%). The relatively low percent prediction errors (C\text{max} and AUC\text{0-\infty}) found strongly suggest that the glipizide IVIVC are valid. The average percent prediction error of less than 10% indicates that the correlation is predictive and is acceptable according to the FDA-IVIVC guidance.

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