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In-vitro In-vivo Correlation Models for Glibenclamide after Administration of Metformin/Glibenclamide Tablets to Healthy Human Volunteers

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Abstract

In this study, level C and A in-vitro in-vivo correlation (IVIVC) models were developed for glibenclamide. In-vitro dissolution data were collected for the glibenclamide component of three metformin/glibenclamide tablets using a USP Type II apparatus. In-vivo plasma concentration data were obtained after administration of the prototype formulations to 24 healthy volunteers and subject to deconvolution analysis to obtain percentage in-vivo absorbed profiles. Multiple linear level C models were developed for CMAX and AUC(0–48) using percentage in-vitro dissolved data at 10, 45 and 120 min. Initially, the level A model was constructed for the first 2 h only, based on availability of in-vitro data. Another level A model was attempted using a time-scaled approach, with percentage in-vivo absorbed at time t and percentage in-vitro dissolved at time t/I as the correlating data. Internal predictability was evaluated for the level C and time-scaled level A models.

For all level C approaches, linear regression models with $r^2 > 0{\cdot}99$ were determined. The prediction errors (% PE) for C_{max} and $AUC_{(0-48)}$ were less than 1% for all formulations at all three chosen time points. The deconvolution analysis indicated biphasic absorption for glibenclamide, with one phase occurring at 2–3 h and another at 6–12 h after dose administration. The level A model using 2-h data was not unique for all formulations and was therefore not developed. The time-scaling factor I correlated highly ($r^2 = 0{\cdot}99$) with in-vitro mean dissolution time (MDT). A linear regression time scaled model ($r^2 = 0{\cdot}97$) was successfully developed using in-vitro and in-vivo data from all 3 formulations. However, the internal predictability of the time-scaled model was poor, with % PE values for C_{max} and $AUC_{(0-48)}$ being as much as 30·5% and 18·7%, respectively.

The results indicate that level C models have good internal predictability. Though a time-scaled level A IVIVC model was successfully developed, the model was found to have poor internal predictability.

Glibenclamide is a widely used orally administered sulphonylurea hypoglycaemic agent. Metformin hydrochloride, available as Glucophage, is also a widely used biguanide hypoglycaemic agent. A recent report (Hermann et al 1994) suggests that co-administration of metformin and a sulphonylurea may produce a synergistic hypoglycaemic effect. A fixed dose metformin/glibenclamide tablet may provide for better patient compliance and ease of administration. Three such immediate-release metformin/glibenclamide tablet prototypes were formulated and evaluated recently for their pharmacokinetics and bioavailability. This report examines the feasibility of developing in-vitro in-vivo correlation (IVIVC) models only for the glibenclamide component of the metformin/glibenclamide tablet, since all prototypes were identical with respect to the metformin component.

Correlation between in-vitro dissolution and in-vivo absorption may provide models applicable in formulation development and regulatory submissions. A recent regulatory guidance (U.S. FDA 1997) classifies IVIVC models into three different levels: A, B, and C. The level A correlation uses the

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entire time course of in-vitro dissolution and in-vivo absorption to obtain a continuous time-point-to-time-point correlation. For a level B correlation, mean dissolution times are correlated for the in-vitro and in-vivo processes. For level C models, in-vivo pharmacokinetic parameters such as C_{max} and AUC are correlated to single dissolution points, such as time to 50% dissolution in-vitro. Whereas level A models are regarded as most useful for regulatory submissions such as biowaivers and setting dissolution specifications, level C models may nevertheless be applicable in formulation development. This study developed and evaluated the internal predictability of level C and level A IVIVC models for glibenclamide.

Methods

Formulations

Three metformin/glibenclamide tablet prototypes, A, B and C, were formulated. These prototypes differed principally in the particle-size specifications for glibenclamide. All tablet prototypes contained 500 mg metformin hydrochloride and 2·5 mg glibenclamide.

In-vitro dissolution

The in-vitro dissolution tests for the metformin/glibenclamide tablet prototypes were based on a previously reported method (Blume et al 1993). Briefly, a USP apparatus II (paddle method) was used, with 1000 mL dissolution medium at pH 7·4 and a paddle speed of 75 rev min^{-1}. Samples were drawn at regular time points for up to 120 min after introduction of the tablet formulations into the dissolution apparatus. No sampling was done later than 120 min, since sink conditions were absent in the dissolution medium beyond this time. The assay of glibenclamide from these samples was performed using a validated HPLC system consisting of a Zorbax-Rx C8 column, a mobile phase of 0·25 M monobasic ammonium phosphate : acetonitrile (50 : 50) pH 5·3, with detection at 230 nm. Six tablets were used for obtaining the in-vitro dissolution profiles of each protoytpe.

In-vivo study in humans

A randomized, complete crossover in-vivo study was conducted in 24 healthy volunteers to evaluate the performance of the metformin/glibenclamide tablet prototypes. The protocol was approved by an Investigational Review Board. Subjects were administered a total dose of 1000 mg metformin hydrochloride and 5 mg glibenclamide (i.e. each subject received two metformin/glibenclamide tablets of the appropriate prototype during each period after an overnight fast). All doses were administered with 240 mL of a 20% glucose solution. Further, 60 mL of the 20% glucose solution was administered at 15-min intervals up to 4 h post dosing. Glucose administration was necessary to avoid hypoglycaemia in the healthy volunteers. Plasma samples were collected for the analysis of metformin and glibenclamide before, and at the following time points after, dosing: 0·5, 1·0, 2·0, 2·5, 3·0, 3·5, 4·0, 4·5, 5·0, 6·0, 8·0, 10·0, 12·0, 16·0, 24·0, 30·0, 36·0 and 48·0 h. Though pharmacokinetics of both metformin and glibenclamide were evaluated in the in-vivo study, this work examines IVIVC models only for the glibenclamide component of the metformin/glibenclamide tablet since all prototypes were identical with respect to the metformin component. A validated liquid chromatography tandem mass spectrometry LC/MS/MS method was used for the analysis of glibenclamide in plasma samples. For this assay method, the lower limit of quantitation (LLQ) of glibenclamide was determined to be 1 ng mL^{-1}. Noncompartmental pharmacokinetic methods were used to evaluate the maximum plasma concentration, C_{max}, and the linear trapezoidal area under the curve from 0 to 48 h, $AUC_{(0-48)}$. No extrapolation was done beyond the 48-h time point for the area under the curve calculations since the terminal elimination half-life of glibenclamide was not discernible in many subjects.

Development of IVIVC models

Level C IVIVC models. Initially, multiple level C models were attempted for glibenclamide using mean C_{max} and $AUC_{(0-48)}$ as the in-vivo parameters and mean percentage dissolved at the various time points. The chosen time points of 10, 45 and 120 min were taken as representative of early, middle and late phases of the in-vitro dissolution of glibenclamide. A linear correlation model was developed for these selected time points.

Level A IVIVC models. To develop a level A IVIVC model, the in-vivo absorption of glibenclamide was obtained for all subjects using the deconvolution module of the Kinetica software package (version 2.0.2, Innaphase, France). Mean intravenous glibenclamide data, reported in a previous study (Rogers et al 1982), were fitted to a two-compartment model and used as the reference treatment for performing the deconvolution procedure.

A preliminary inspection of the percentage in-vivo absorption vs time profile indicated that in-vivo absorption of glibenclamide occurred for 10–20 h on average, and up to 24 h for some subjects, after dose administration. Since in-vitro dissolution data was available for only 2 h, the initial level A correlation plot of mean percentage in-vivo absorption vs mean percentage in-vitro dissolved was undertaken only for the common time points (i.e., for the 0-, 0·5-, 1·0- and 2·0-h time points).

Since the in-vitro dissolution data was available for only 2 h and in-vivo absorption occurred for at least 10–20 h on average, it was apparent that these two processes occurred over different time scales. To correct for these differences, a time-scaling technique used in previous reports (Levy 1964; Mojaverian et al 1992) was attempted for glibenclamide in this study. An intensity factor (also referred to as time scaling factor), I, was calculated for each of the three metformin/glibenclamide tablets using the formula shown in Equation 1.

$$I = \frac{\text{Time required for 50\% absorption in-vivo}}{\text{Time required for 50\% dissolution in-vitro}} \quad (1)$$

For all formulations, mean in-vitro dissolution and mean in-vivo absorption did not reach 100% of dose at the respective last sampling points. Therefore, normalized plots of in-vitro dissolution and in-vivo absorption were constructed for all formulations by normalizing the percentage in-vitro dissolved or percentage in-vivo absorption at the last sampling point to 100%. Computations of the time for 50% absorption in-vivo and 50% dissolution in-vitro, used in Equation 1, were based on the normalized plots. The calculated I values were plotted as a function of mean in-vitro dissolution time, MDT, to examine whether in-vitro dissolution is predictive of I. For all formulations, MDT values were calculated by the method of Brockmeier (1984). The time-scaled level A IVIVC model was developed by plotting % in-vivo absorption at time t vs percentage in-vitro dissolved at time t/I, with I calculated from Equation 1. Dissolution data at different t/I points were obtained using linear interpolation. Linear regression was used to develop a single time-scaled IVIVC model using data from all three formulations.

Evaluation of internal predictability for IVIVC models

Level C model. Using the linear correlation level C models developed above, mean C_{max} and $AUC_{(0-48)}$ were internally predicted for the various metformin/glibenclamide tablet formulations. Percent prediction error (% PE) was calculated for all formulations as shown in Equation 2.

$$\%\ PE = \frac{(\text{Observed} - \text{Predicted})}{(\text{Observed})} \times 100 \quad (2)$$

Level A model. The linear regression equation, developed using the time-scaled model, that correlates % absorbed at time t to % dissolved at time t/I was used to construct the predicted % in-vivo absorption time profile for the various formulations. Predicted in-vivo absorption rate, $r_{pred\text{-}vivo}$, between any two time points t_1 and t_2 was calculated as shown in Equation 3.

$$r_{pred\text{-}vivo} = \frac{\%\text{In-vivo absorption } (t_2) - \text{ In-vivo absorption } (t_1)}{(t_2 - t_1)} \quad (3)$$

Finally, using the convolution equation shown in Equation 4, it was possible to internally predict the mean plasma concentration profile for the three formulations.

$$Ct = \int_0^t C_{\delta iv}(t-u).\ r_{pred\text{-}vivo}(u).du \quad (4)$$

where $C_{\delta iv}(t)$ is the intravenous bolus concentration data obtained from a previous report (Rogers et al 1982), $r_{pred\text{-}vivo}$ is the predicted in-vivo absorption rate, Ct is the predicted concentration at time t, and u is the dummy convolution variable. For prototype C, plasma concentration data were predicted for 36 h only since the t/I value at 48 h exceeded 2 h and the % in-vitro dissolved data was not available beyond 2 h.

Using the plasma profiles predicted from Equation 4, it was possible to obtain predicted mean C_{max} and $AUC_{(0-48)}$. For prototype C, C_{max} and $AUC_{(0-36)}$ were calculated. Similar to the level C models, % PE values were calculated for mean C_{max} and AUC of all formulations. In these % PE calculations, the observed data for C_{max} and AUC were obtained from mean plasma profiles only and not by averaging C_{max} and AUC values from all subjects.

Results

Mean in-vitro dissolution profiles and mean plasma concentration profiles for glibenclamide are shown in Figures 1A and 1B, respectively. The profiles in Figure 1B indicate the presence of double peaks for glibenclamide after administration of all three

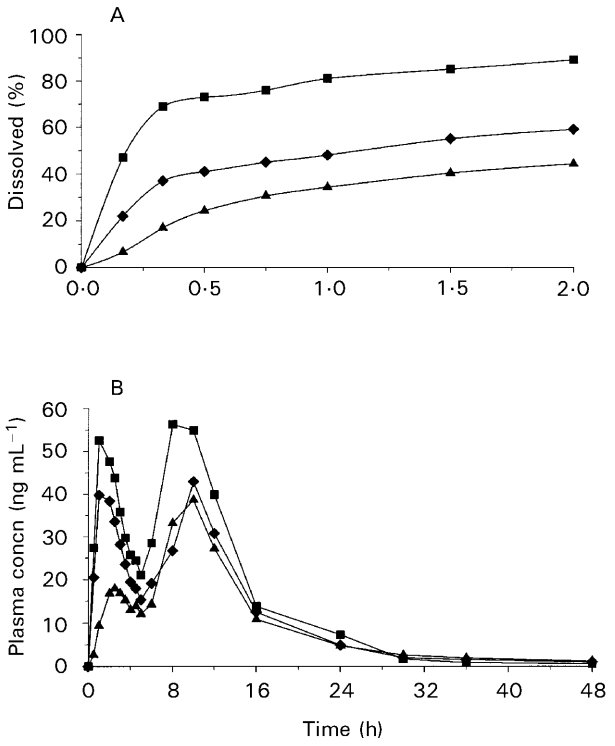

Figure 1. Mean in-vitro dissolution data (A) and in-vivo plasma concentration data (B) for glibenclamide from metformin/glibenclamide tablets. In-vitro data are mean of 6 tablets and in-vivo data are mean of 24 healthy volunteers for formulations A (◆), B (■) and C (▲), respectively.

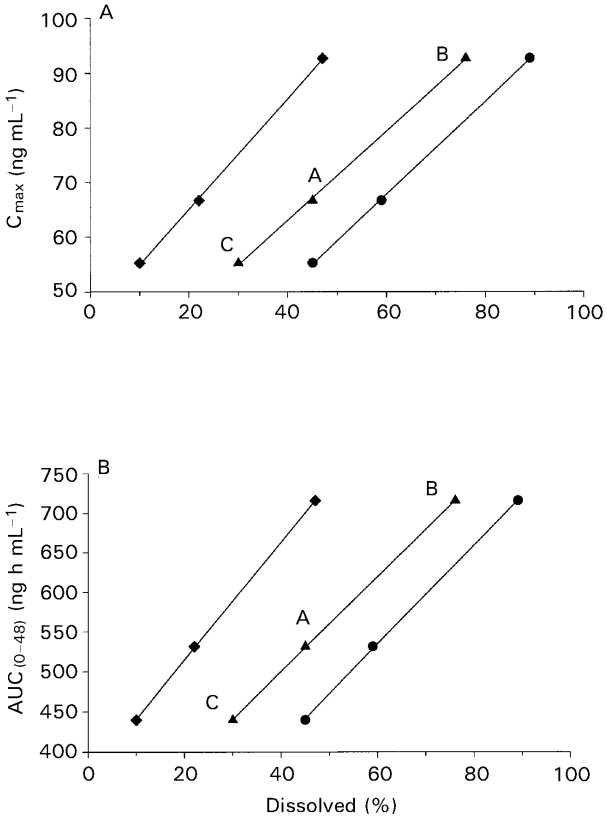

Figure 2. Level C IVIVC models for glibenclamide. Models for mean observed C_{max} and $AUC_{(0-48)}$ are shown in A and B, respectively. In-vitro dissolution data were at 10 (◆), 45 (▲) and 120 min (●), respectively. The rank order in formulations for both C_{max} and $AUC_{(0-48)}$ was B > A ≥ C as shown. Lines are linear regressions of data points, with r^2 values greater than 0·99 for all models.

metformin/glibenclamide tablet prototypes. Level C IVIVC models using mean C_{max} and $AUC_{(0-48)}$ are shown in Figures 2A and 2b, respectively. The % PE values, determined from the level C IVIVC models, are shown in Table 1. These results indicate highly predictive level C models with % PE values for C_{max} and $AUC_{(0-48)}$ not exceeding 1% for all formulations.

The mean in-vivo absorption profiles for glibenclamide from the three metformin/glibenclamide tablet prototypes are shown in Figure 3. Evidently, the availability of glibenclamide in-vivo (as a % of dose) is formulation dependent and incomplete. Also, glibenclamide in-vivo absorption continues for 10–20 h after dosing and may be biphasic (i.e., absorption occurs at different rates over time). A level A IVIVC plot for glibenclamide using 2-h dissolution and in-vivo absorption data only, is shown in Figure 4A. The 2-h level A model shown in Figure 4A indicates that glibenclamide in-vivo absorption in the initial 2 h was relatively low compared with the eventual percent of total dose available at 48 h. Further, there is no unique level A model, as seen from the different relationships for the three formulations. Therefore, the level A model based on 2-h data only is of limited utility and was not developed further.

The time required for 50% in-vitro dissolution

Table 1. Absolute % PE values for Level C models for glibenclamide following administration of metformin/glibenclamide tablets.

Variable	Formulation	Time point for correlation (min)		
		10	45	120
C_{max}	A	0·71	0·78	0·49
	B	0·17	0·18	0·11
	C	0·58	0·63	0·40
$AUC_{(0-48)}$	A	0·24	0·19	0·45
	B	0·06	0·05	0·11
	C	0·20	0·15	0·37

and in-vivo absorption for the three formulations, and their respective intensity factor (I) values, are shown in Table 2. A linear regression model with an r^2 value of 0·99, that was determined for I as a function of in-vitro MDT, is also shown in Table 2. Using this relationship between I and MDT it is possible to predict I for new prototypes or new

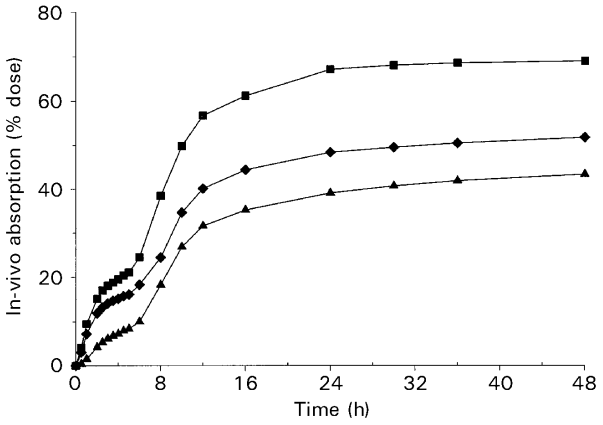

Figure 3. Mean % in-vivo absorption profile for glibenclamide. Data are mean of 24 healthy volunteers for formulations A (◆), B (■) and C (▲), respectively.

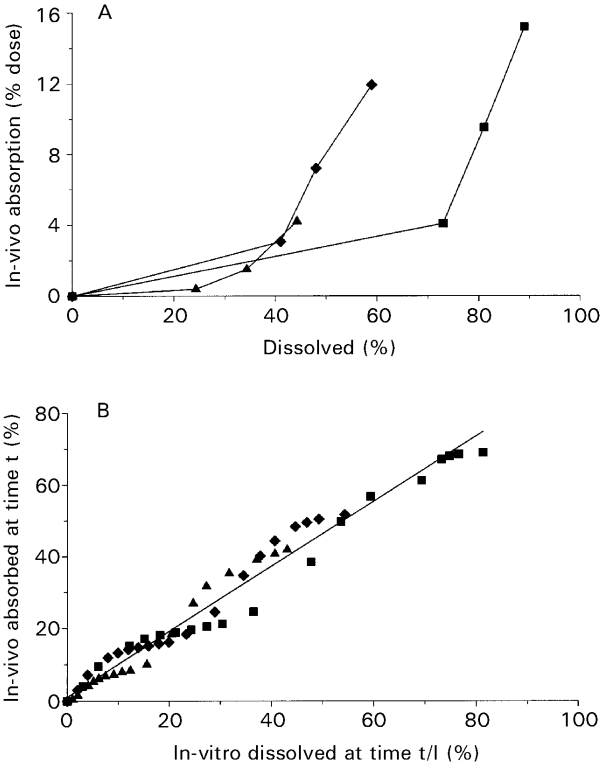

Figure 4. Level A IVIVC models for glibenclamide. A, 2-h model; B, time-scaled. For the time-scaled model, line is a linear regression IVIVC model ($r^2 = 0{\cdot}97$) of the data points, with the following equation: $y = 0{\cdot}91x + 1{\cdot}05$. Mean in-vitro data from 6 tablets and mean in-vivo data from 24 subjects were used for formulations A (◆), B (■) and C (▲), respectively.

batches within a given prototype. A time-scaled level A IVIVC model constructed using % in-vivo absorption at time t vs % dissolved in-vitro at time t/I is shown in Figure 4B. An IVIVC model encompassing all three formulations was developed using linear regression. Using this model, and the convolution integral shown in Equation 4, predicted concentrations were obtained for each formulation. In the case of formulation C, plasma concentration data were predicted until 36 h only, since the t/I value at the 48-h time point exceeded 2 h and the percentage in-vitro dissolved data was not available beyond 2 h.

Table 2. Calculation of time-scaling factor, I, for glibenclamide following administration of metformin/glibenclamide tablets.

Formulation	$T_{50\%}$ in-vivo (h)	$T_{50\%}$ in-vitro (h)	I	MDT* (h)
A	8·27	0·25	33·1	0·48
B	7·42	0·16	46·4	0·33
C	8·77	0·44	19·9	0·62

*A linear regression equation, $I = -91 \times MDT + 76{\cdot}4$, with $r^2 = 0{\cdot}99$, was determined.

Predicted and observed plasma concentration profiles for glibenclamide for all three formulations are shown in Figures 5A, 5B and 5C, respectively. The predicted profiles, obtained using the time-scaled level A IVIVC model, do not account for the double peaks in the observed data. Prediction errors (% PE) calculated for C_{max} and $AUC_{(0-T)}$ are shown in Table 3. The recent regulatory guidance (U.S. FDA 1997) outlined three stages for IVIVC models, namely the development, evaluation, and application stages. In the present case, large prediction errors in C_{max} and $AUC_{(0-T)}$ indicate that despite successful development of a time-scaled level A IVIVC model for glibenclamide, the current model is not predictive of the entire time course of in-vivo performance.

Discussion

The objective of this study was to develop and evaluate the internal predictability of level C and A IVIVC models for glibenclamide after administration of three metformin/glibenclamide prototype tablets to healthy human volunteers. Linear level C IVIVC models with high correlation coefficient (r^2) values were developed for both the C_{max} and $AUC_{(0-48)}$ of glibenclamide. Three different models were developed using 10, 45 and 120 min in-vitro dissolution data, which were considered as representative of the early, middle and late portions of the in-vitro dissolution profile, respectively. Since all of the above three models had high r^2 values, level C models may be developed using in-vitro dissolution data at any time point.

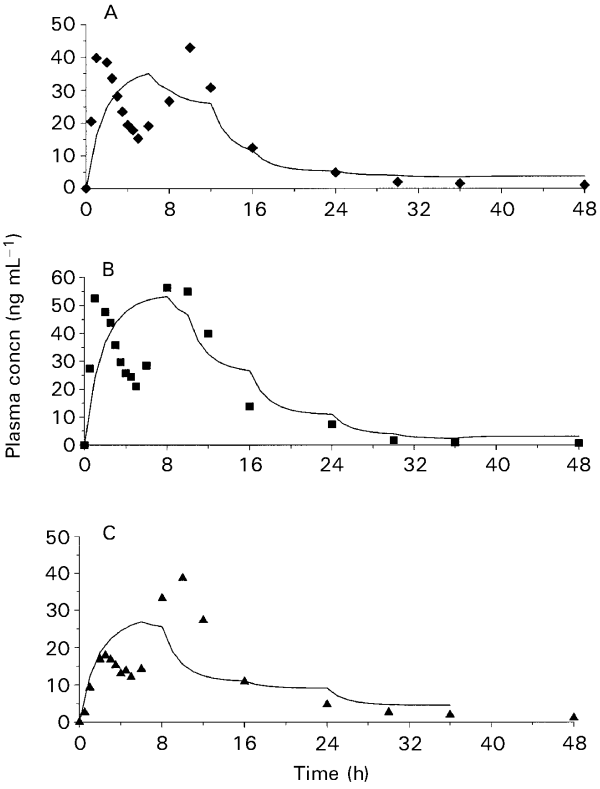

Figure 5. Predicted and observed mean plasma concentration values for glibenclamide. Predictions were done by incorporating the time-scaled level A IVIVC model shown in Figure 4B into Equation 4 shown in text. Panels A, B and C show data for formulations A, B and C, respectively. Symbols are observed mean plasma concentration data and lines are mean predicted data.

Table 3. Absolute % PE values for time-scaled level A model, for glibenclamide following administration of metformin/glibenclamide tablets.

Variable	Formulation	% PE
C_{max}	A	18·5
	B	5·5
	C	30·5
$AUC_{(0-48)}$*	A	1·7
	B	16·7
	C	0·7

*For prototype C, % PE values were calculated using AUC (0–36)

For developing a level A model, the first step was to obtain in-vivo absorption for glibenclamide from the three metformin/glibenclamide tablet formulations. Since plasma concentration data from a reference intravenous treatment was not available in this study, average intravenous data parameters for a two-compartment model, obtained from a previous study (Rogers et al 1982), were used to generate intravenous plasma concentration data and taken as the reference treatment for the deconvolution procedure. The results from the deconvolution analysis indicate that absorption of glibenclamide from the metformin/glibenclamide tablet prototypes is biphasic, insofar as a fraction of the dose is absorbed within 2–3 h and another fraction is absorbed 10–20 h after dose administration. This erratic absorption pattern results in glibenclamide plasma profiles having delayed peaks, as reported previously (Ikegami et al 1985; Negebauer et al 1985). The double peak phenomenon observed for glibenclamide plasma profiles in this study can be due to two reasons, either poor absorption in certain regions of the gastrointestinal tract or poor dissolution of glibenclamide, whose solubility is low and dependent on pH and particle size (Lehto et al 1996). An earlier study (Brockmeier et al 1985) showed that glibenclamide is absorbed from all sites in the gastrointestinal tract. In contrast, gliben-clamide dissolution is less than 25% at pH 2–6 (Lehto et al 1996). Since the pH in the proximal gastrointestinal tract is also in the 2–6 range, it is likely that there is poor dissolution of glibenclamide in this region. At more distal sites in the gastrointestinal tract, such as the ileum and colon, the pH is within the 6–8 range, enabling higher dissolution rates, absorption and the occurrence of secondary peaks. The additional presence of metformin in the metformin/glibenclamide tablet may also influence the dissolution behaviour of glibenclamide, although this effect has not been examined in detail in this study. Based on the above arguments, it is likely that the occurrence of late peaks in the glibenclamide plasma concentration profiles is a result of the pH-dependent dissolution of glibenclamide from the metformin/glibenclamide tablet prototypes.

In our study, in-vivo absorption and in-vitro dissolution of glibenclamide occurred in different time scales. While in-vivo absorption occurred up to 15–20 h after dose administration, the in-vitro dissolution data was available for only 2 h. The level A IVIVC model developed using the in-vitro and in-vivo data available in the common time frame (0–2 h) is inappropriate since the in-vivo absorption at 2 h is not representative of the in-vivo absorption eventually occurring at 48 h. Further, there is no unique model applicable to all formulations, with the IVIVC model being dependent on the in-vitro dissolution rate.

For such cases where in-vitro dissolution and in-vivo absorption occur in different time scales, an IVIVC model that incorporates a time-scaling factor may be appropriate. The time-scaling factor corrects for differences in in-vitro dissolution and in-vivo absorption and has been used by other

investigators (Levy 1964; Levy & Hollister 1965; Mojaverian et al 1992) to develop IVIVC models. Using the above approach, a linear level A IVIVC model was developed, with the % in-vivo absorbed at time t correlated to % in-vitro dissolved at time t/I. The IVIVC guidance document (U.S. FDA 1997) indicates that the time-scaling factor, I, should be the same for all formulation prototypes. In the present study, the time-scaling factor, I, was not the same for all formulations. In this aspect, the current results are in accordance with other reports (van Bommel at al 1991; Mojaverian et al 1992, 1997) that conclude that the time-scaling factor is not the same for all formulations in a given series. Nevertheless, the linear regression relationship of I as a function of MDT in our study indicates that it is possible to a-priori determine the value of I for a new prototype.

Few reports in the literature have determined the predictability of a level A IVIVC model. The recent IVIVC guidance (U.S. FDA 1997) indicates that assessment of internal and external predictability is required in advance of the application of IVIVC models for regulatory submissions. In the current study, only internal predictability was assessed since new formulation prototypes were not available to test the external predictability. For level C models, % PE values for all three models (i.e. models developed using % in-vitro dissolution at 10, 45 and 120 min, respectively) did not exceed 1% for both C_{max} and $AUC_{(0-48)}$. Such low values for % PE suggest that these models may be useful to predict C_{max} and $AUC_{(0-48)}$ for new prototypes, or, for new batches within a given prototype. For the time-scaled level A model, predicted mean concentrations of glibenclamide were not similar to the observed profiles. The double-peak profiles that were observed in the in-vivo data could not be predicted using the time-scaled IVIVC model. The % PE for the mean C_{max} values were as high as 18·5% for prototype A and 30·5% for prototype C, respectively. Also, the % PE value for $AUC_{(0-48)}$ of prototype B was 16·7%. Based on the 15% limit in % PE as specified in the recent guidance (U.S. FDA 1997), the time-scaled IVIVC model has poor internal predictability and may not be useful for further applications or for regulatory submissions.

The reason for the poor internal predictability for the time-scaled IVIVC model is evident. Although the time-scaled model apparently adjusts for time differences between in-vitro dissolution and in-vivo absorption, it cannot model the pH-dependent dissolution and discontinuous absorption of glibenclamide observed in-vivo. It is important to design alternative dissolution tests for which the medium pH changes as a function of time. Additionally, it may be necessary to include surfactants and other ions to mimic the in-vivo dissolution profile of the dosage forms. The exact in-vitro dissolution conditions need to be optimized using the in-vivo absorption profile obtained in this study as the reference. With such alternate in-vitro data it may be possible to develop a 1 : 1 level A IVIVC model with good internal predictability for the metformin/glibenclamide tablets that does not require mathematical techniques such as time scaling.

A review of glibenclamide pharmacokinetics (Pearson 1985) indicates that glibenclamide absorption, though dissolution-limited, is complete. As discussed previously, the solubility of glibenclamide is poor and dependent on pH and particle size. Therefore, as in the proposed (Amidon et al 1995) Biopharmaceutical Classification System (BCS), glibenclamide is a low-solubility high-permeability (Class II) drug. For a Class II drug, a successful IVIVC is expected unless the dose is high relative to drug solubility. The findings of our study are in agreement with the proposed BCS and level C models with good internal predictability having been developed. However, alternate dissolution tests that mimic the in-vivo absorption profile are required to develop predictive level A IVIVC models for glibenclamide.

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