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Optimization of Sustained-release Diltiazem Formulations in Man by use of an In-vitro/In-vivo Correlation

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Abstract

In-vitro/in-vivo correlations (IVIVC) are useful for predicting in-vivo results from in-vitro data. An IVIVC has been used to optimize a hydrocolloidal-based matrix tablet designed to be bioequivalent to an existing once-daily diltiazem HCl product (Dilacor XR 240 mg; Rhone-Poulenc Rorer).

Data from a preliminary formulation dosed to fasted and fed subjects were used to establish the IVIVC. The correlation was then used during reformulation of the dosage forms to predict changes in the maximum plasma concentration (C_{max}) and the area under the plasma-concentration–time curve (AUC) for fasted and fed subjects using in-vitro dissolution data.

The IVIVC adequately predicted plasma profiles of two optimized formulations in studies with fasted and fed subjects.

The appeal of sustained-release formulations within the pharmaceutical industry is evident from the growing number of sustained- and extended-release products available commercially. The use of sustained-release dosage forms helps physicians to provide optimum treatment by better patient compliance and safer systems with lower peak/trough ratios.

Hydrocolloids are key components of many oral sustained-release formulations. Guar gum, derived from the endosperm of seeds of *Cyamopsis tetragonolobus* or *C. psoraloides*, is a useful controlled-delivery hydrocolloid matrix material which has been used as a disintegrant or binder in pharmaceutical applications (Eatherton et al 1955; Feinstein & Bartilucci 1966; Sakr & Elsabbagh 1975; Elsabbagh et al 1978; Iqbal et al 1979; Rudnic et al 1981). It is generally recognized as safe by the FDA. The advantages of guar gum as a sustained-release matrix are its high viscosity, low cost and commercial availability (Goldstein et al 1973; Yu et al 1996b). The product has proven useful as a once-daily matrix material in formulations for sustained release of diltiazem (Altaf et al 1996).

By establishing in-vitro-in-vivo correlations (IVIVC), it is possible to reduce or even eliminate the need for clinical trials. This approach has received considerable attention in recent years and has led to FDA guidelines specifically for IVIVC (FDA 1997).

The purpose of this study was to optimize an existing guar gum diltiazem formulation utilizing preliminary in-vitro and in-vivo data. The ultimate goal of these studies is to develop a sustained-release formulation yielding pharmacokinetic data for fasted and fed subjects to establish bioequivalence to a reference product, Dilacor XR 240 mg (Rhone-Poulenc Rorer).

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Materials and Methods

Materials

Diltiazem HCl (Reddy-Cheminor, Ridgewood, NJ) was used in all formulations. Guar gum (Supercol G3-NF) was supplied by Aqualon (Hercules, Wilmington, DE), Plasdone K-25 (Povidone USP) by ISP Technologies (Wayne, NJ), hydroxypropylmethylcellulose (Methocel K100LV) by Dow Chemical (Midland, MI), and magnesium stearate by Whittaker, Clark and Daniels (South Plainfield, NJ).

Formulation development

The compositions of the dosage forms used in this study are shown in Table 1. A wet granulation procedure was used to prepare the powder mixtures. The resulting granules were compressed into 785-mg caplets and encapsulated into size 00

gelatine capsules. Dissolution of diltiazem was determined by use of a USP II (paddle) apparatus at 100 rev min^{-1} and 900 mL deionized water at 37 ± 0.5°C. Samples were collected after 1, 2, 4, 6, 8, 10 and 24 h with $n \geq 4$ replicates. Samples were diluted (1 : 10) and assayed by UV spectrophotometry at 240 nm.

In-vitro-in-vivo modelling

A simple, one-compartment, Wagner–Nelson model (Wagner & Nelson 1964; Gibaldi & Perrier 1982; Mojaverian et al 1987) was used to calculate diltiazem absorption profiles from blood plasma profiles. This model is valid for diltiazem which is known to be well absorbed throughout the gastrointestinal tract (Zelis & Kinney 1982; Ochs & Knuchel 1984).

Diltiazem plasma levels were converted to fraction of diltiazem absorbed by use of the Wagner–Nelson method.

$$A(t) = \frac{C(t)K \int_0^t C(t)dt}{K \int_0^\infty C(t)dt} \quad (1)$$

where A(t) is the fraction of drug absorbed at time t, C(t) is the concentration of drug in the plasma at time t and K is the elimination rate constant. The integrals in equation 1 were obtained by the trapezoidal rule. The elimination rate constant, K, was calculated from clinical data from formulations A, B and C (Table 1). The in-vivo absorption values were directly related to in-vitro dissolution data to complete the IVIVC.

Clinical study design

The clinical trials on fasted and fed subjects were designed as three-period randomized crossover studies. The study was approved by the Institutional Review Board of Corning Besselaar (now Covance). Nine healthy volunteers, male and female, were enrolled for the fasted study, twelve for the fed study. No one subject was used in both fed and fasted trials. Volunteers abstained from caffeine-containing food and drink from 48 h before dosing until discharge from the clinic. One of three 240-mg diltiazem capsule formulations (test formulations D and E and Dilacor XR was given to each subject with 240 mL water according to a computer-generated randomized schedule. Each volunteer was dosed at the same time of day in each treatment period with a minimum of one week for a washout. Blood samples (10 mL) were drawn via venipuncture of antecubital veins after 0, 0·5, 1, 1·5, 2, 3, 4, 6, 8, 10, 12, 14, 16, 20, 24, 28, 32 and 36 h. For the fed state a standard high-fat breakfast was given 30 min before dosing. The meal included an egg, a buttered English muffin, a slice of Canadian bacon, a slice of American cheese, hash browns, whole milk and orange juice. All subjects were given meals approximately 4·5, 7·5, 11 and 14 h post-dose on the first day. Meals on the second day were given after the 24-h post-dose blood sample, approximately 25, 29, 31·5 and 35 h post dose.

Blood samples were collected into 10-mL sodium heparin Vacutainer tubes and centrifuged within 20 min of collection at approximately 3000 rev min^{-1} for 7 min at 4°C. For each sample exactly half of the separated plasma was transferred into each of two polypropylene tubes and stored at temperatures < -70°C pending analysis. Determination of diltiazem, desmethyldiltiazem and desacetyldiltiazem was performed by Corning Besselaar (now Covance) by use of a validated HPLC assay. Standard pharmacokinetic parameters for the plasma diltiazem and its two metabolites were determined for each volunteer.

The parameters peak plasma concentration (C_{max}) and extent of absorption (AUC, the area under the plasma concentration–time curve) were calculated using a standard spreadsheet program (Microsoft Excel). Analysis of variance and the 90% confidence intervals for comparing the formulations were calculated using Biopak software (Scientific Consulting, Cary, NC).

Table 1. Guar gum-based sustained-release diltiazem formulations.

Ingredient	Formulation				
	A	B	C	D	E
Diltiazem HCl, USP	31·00	31·00	31·00	30·60	30·60
Guar gum (Supercol G3-NF)	62·00	–	62·00	64·60	57·15
Purified guar gum* (Supercol G3-NF)	–	67·00	–	64·60	57·15
Methocel K100LV	5·00	–	–	2·50	10·00
Polyethylene oxide (Polyox, MW 8 000 000)	–	–	5·00	–	–
Povidone (PVP K-25)	–	–	–	0·25	0·25
Stearic acid	2·00	2·00	2·00	–	–
Magnesium stearate, NF	–	–	–	2·00	2·00
Total weight (mg)	785	785	785	785	785

Except for total weight data in the table are percentages. *See Gebert & Friend (1997).

Results and Discussion

The data used to establish an IVIVC were obtained from a fasted and fed state pilot pharmacokinetic trial (Parasrampuria et al 1996). Table 2 lists the AUC and C_{max} values obtained. A subsequent food-effect study showed an increase in C_{max} of approximately 20% for formulation A compared with Dilacor XR, the AUC remaining within the bioequivalence limit (Table 2). On the basis of these data methods were examined to bring the C_{max} closer to the reference product under both fasted and fed conditions. Firstly, increasing the rate of drug release over the first 4–6 h followed by a period of slow release compared with the reference product (i.e. fast–slow formulation) was hypothesized. In this circumstance more drug should be available in the early hours after dosing, bringing the C_{max} down later. The second approach was to reduce the release rate at all times, i.e. a slower-release formulation. On the basis of these two approaches two new diltiazem formulations were developed (formulations D and E, Table 1). The in-vitro dissolution profiles of the two new formulations are shown in Figure 1.

To confirm the selection of these two optimized diltiazem formulations, the IVIVC was established on the basis of formulations A, B and C in the fasted state and formulation A in the fed state (fed clinical data were unavailable for other formulations). The primary purpose of the reformulation was to reduce the C_{max} of formulation A in both the fasted and fed states relative to that of Dilacor XR. For accurate use of the data from both the fasted and fed IVIVC, a set of multipliers was calculated which enabled conversion of in-vitro release data into in-vivo absorption data and vice versa. Thus, when the percent released–time data from a dissolution curve was multiplied by the appropriate multiplier set, both fasted and fed absorption–time

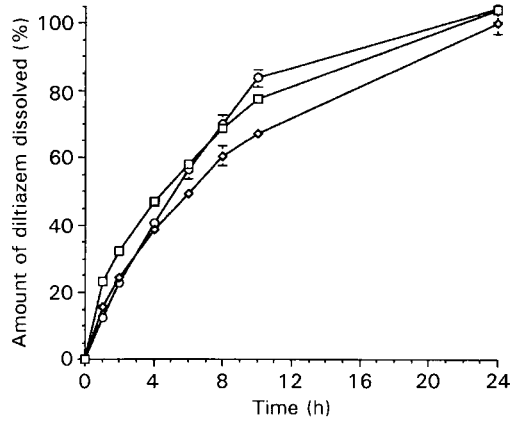

Figure 1. Diltiazem dissolution release profiles of optimized sustained-release formulations D (□) and E (◇) and of Dilacor XR 240 mg (○) (data are means ± s.d., n = 12).

Table 2. Geometric mean pharmacokinetic parameters and 90% confidence intervals (upper, lower) for initial diltiazem formulations.

Formulation	$AUC_{(0-36)}$ (ng h mL^{-1})	C_{max} (ng mL^{-1})
Dilacor XR	1340	69·5
A	1484 (0·91, 1·35)	79·0 (0·91, 1·41)
B	1588 (0·97, 1·44)	83·6 (0·97, 1·49)
C	1599 (0·98, 1·45)	81·1 (0·94, 1·45)

curves were generated. This process is illustrated in Figure 2.

The absorption curves were then converted into drug concentrations in blood plasma–time curves by use of a rearranged form of the Wagner–Nelson method:

$$C(t) = A(t) \times K \int_0^{\infty} C(t)\,dt - K \int_0^{t} C(t)dt \qquad (2)$$

$$C(t) = A(t) \times AUC - K \int_0^{t} C(t)dt \qquad (3)$$

where the AUC is the area under the curve calculated from clinical data. For the fasted correlation AUC is an average $AUC_{0-\infty}$ from formulations A, B and C whereas for the fed correlation it is the $AUC_{0-\infty}$ from formulation A. Because it is not possible to isolate the term C(t), equation 3 must be solved iteratively; this was accomplished by use of a computer spreadsheet (Microsoft Excel).

In Figure 3 the fasted in-vivo absorption rate is plotted against the in-vitro dissolution rate for the three original guar-gum formulations and Dilacor XR. It is apparent that the IVIVC were similar for all three guar gum-based sustained-release formulations. The Dilacor XR IVIVC was slightly different from those for the guar-gum formulations only very late in the release profile. The fed IVIVC for formulation A and Dilacor XR is shown in Figure 4; this shows that for in-vivo drug release between 25 and 75% the amount of drug absorbed for formulation A seemed to be significantly less than for Dilacor XR. This could be because of differences in transit through the gastrointestinal tract for the different dosage forms.

With the IVIVC established, the dissolution profiles of the new formulations could be processed by calculations resulting in a predicted clinical profile (Figures 5 and 6). Formulations D and E gave predicted C_{max} and AUC values suggesting their potential bioequivalence to Dilacor XR for both fasted and fed subjects. Thus, these two formulations were evaluated in a second fed and fasted trial.

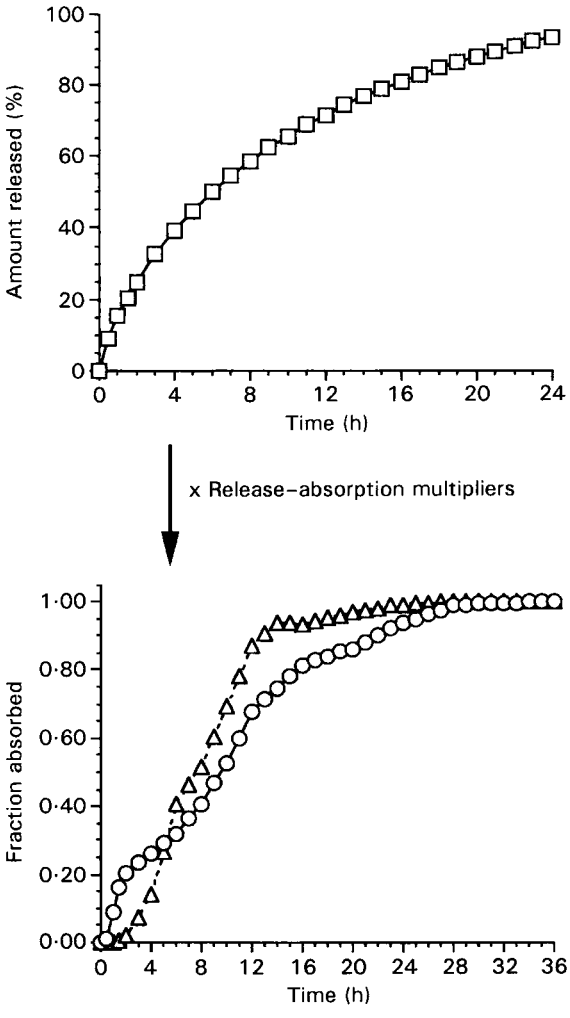

Figure 2. Generation of absorption–time curves for fasted (○) and fed (△) subjects by use of an appropriate multiplier set on a plot of percent released against time dissolution data from formulation E (□).

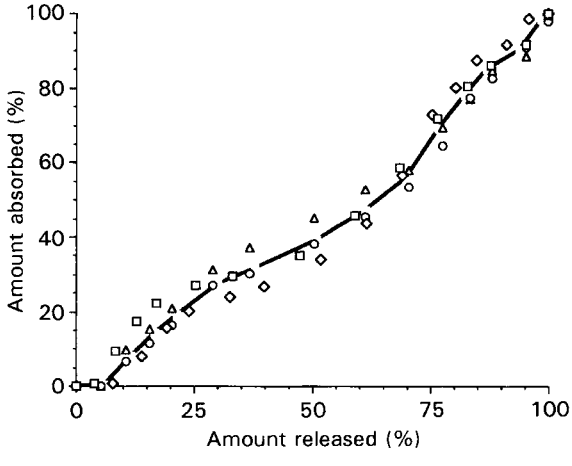

Figure 3. Plot of in-vivo absorption (%) against in-vitro release (%) from diltiazem formulations A (◇), B (△) and C (○) and from Dilacor XR (□) for fasted subjects. The line represents the mean from all four formulations.

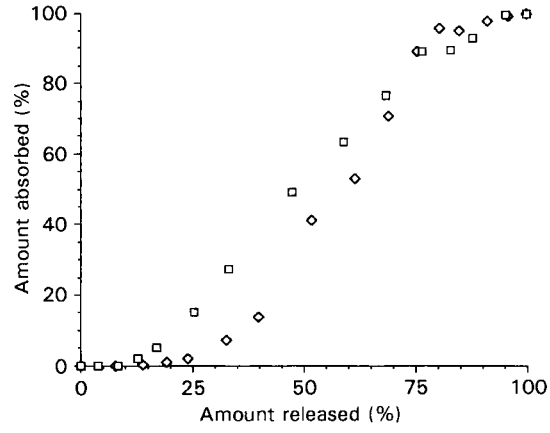

Figure 4. Plot of fed-state amount absorbed in-vivo (%) against in-vitro amount (%) released for formulation A (◇) and Dilacor XR (□).

All the enrolled subjects completed the three-period crossover studies. There were no serious adverse events. The mean plasma diltiazem concentrations after oral administration of Dilacor XR, D and E to fasted and fed subjects are plotted in Figure 7. Absorption of diltiazem from formulations D and E was similar to that from the reference product in both the fasted and fed states.

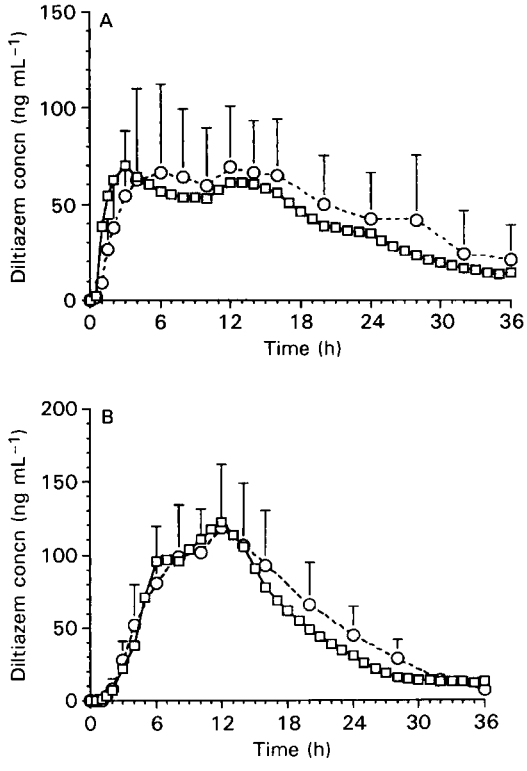

Figure 5. Predicted diltiazem plasma profiles (□) for fasted (A) and fed (B) subjects for optimized formulation D compared with actual clinical results (○). Error bars are s.d. (n = 12).

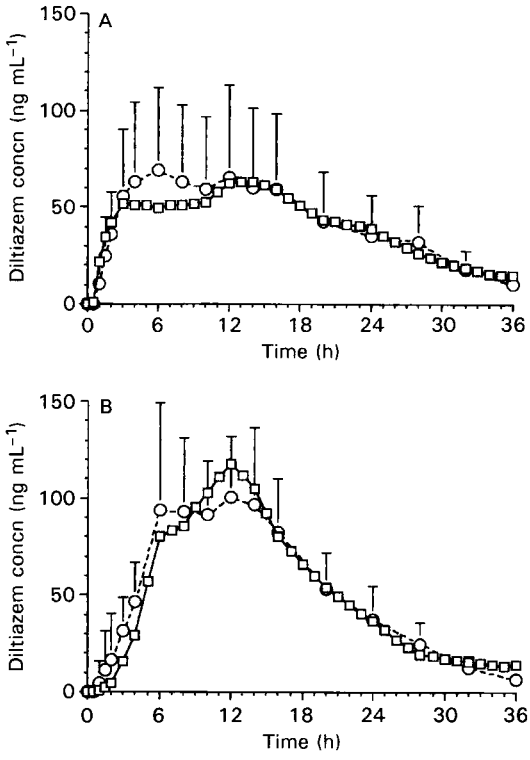

Figure 6. Predicted diltiazem plasma profiles (□) for fasted (A) and fed (B) subjects for optimized formulation E compared with actual clinical results (○). Error bars are s.d. (n = 9).

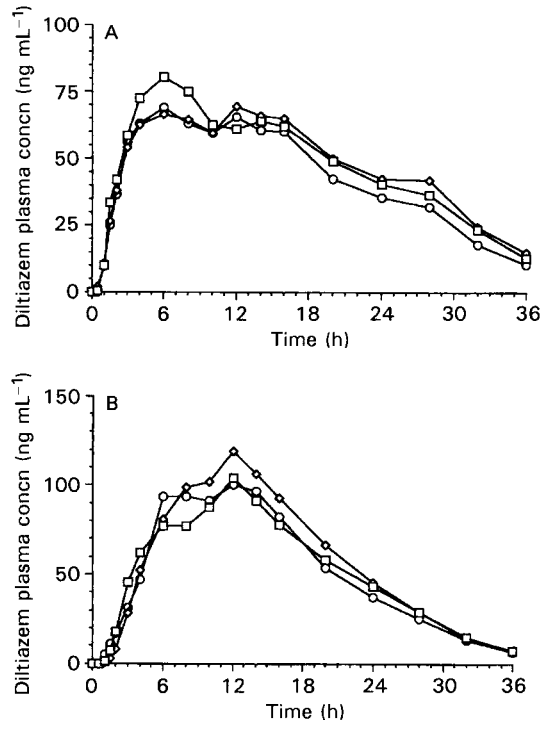

Figure 7. Mean plasma diltiazem concentrations from formulations D (◇) and E (○) and from Dilacor XR (□) in fasted (n = 12) (A) and fed (n = 9) (B) subjects.

The metabolite profiles of formulations D and E were also similar to that of the reference product (data not shown). Some variation in the metabolism of diltiazem to desacetyldiltiazem for all three formulations tested was observed for fasted and fed states. In each instance two subjects metabolized diltiazem to desacetyldiltiazem to a greater extent than the other participants in their respective groups. The geometric means used for bioequivalence analysis of D and E with the fasted and fed data, including the two metabolites, are given in Tables 3 and 4, respectively.

The measured diltiazem plasma profiles are compared with the predicted profiles in Figure 5. It can be seen that the IVIVC developed for guar gum-based sustained-release diltiazem formulations adequately predicted the plasma concentrations. The IVIVC could be improved by exploring a wider variety of dissolution conditions (Liu et al 1996). Different dissolution conditions might be particularly relevant for the fed state where greater physical agitation and longer gastric retention times might be expected. In addition, improvements in the way in-vivo data is analysed could be incorporated into the IVIVC. For example, the inclusion of a time-lag parameter would correct for differences between the onset of drug absorption in fasted and fed subjects (Yu et al 1996a).

Conclusions

On the basis of data collected under fed and fasted conditions the release of diltiazem from formulations D and E was similar to that from Dilacor XR. In addition, an IVIVC was used to predict changes in C_{max} and AUC under fed and fasted conditions. Despite some variability in desacetyldiltiazem absorption, overall results were comparable with those from Dilacor XR. The IVIVC applied to the in-vitro dissolution curves of D and E predicted the in-vivo release profiles. The slight differences between observed and predicted blood–plasma profiles could be partially attributable to error present in the small number of subjects tested (nine and twelve in the fasted and fed studies, respectively).

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Table 3. Geometric means, ratios, and 90% confidence intervals of diltiazem for formulations D and E under fasted conditions.

Parameter	Test	Reference	Ratio (%) (T/R)	90% Confidence interval	
				Lower	Upper
Formulation D with Dilacor XR as reference					
$AUC_{(0-36)}$ (ng h mL^{-1})	1545	1553	99·5	0·87	1·13
$AUC_{(0-\infty)}$ (ng h mL^{-1})	1654	1702	97·2	0·85	1·11
C_{max} (ng mL^{-1})	77·5	76·0	101·9	0·86	1·21
Formulation E with Dilacor XR as reference					
$AUC_{(0-36)}$ (ng h mL^{-1})	1342	1553	86·4	0·76	0·98
$AUC_{(0-\infty)}$ (ng h mL^{-1})	1470	1702	86·3	0·76	0·99
C_{max} (ng mL^{-1})	73·3	76·0	96·4	0·81	1·14

$AUC_{(0-36)}$ is the area under the plasma concentration–time curve between times 0 and 36 h; $AUC_{(0-\infty)}$ is the area under the plasma concentration–time curve between times 0 and ∞; C_{max} is the maximum plasma concentration.

Table 4. Geometric mean diltiazem ratios for formulations D and E under fed conditions.

Parameter	Test	Reference	Ratio (%) (T/R)
Formulation D with Dilacor XR as reference			
$AUC_{(0-36)}$ (ng h mL^{-1})	1992	1753	113·6
$AUC_{(0-\infty)}$ (ng h mL^{-1})	1984	1809	109·7
C_{max} (ng mL^{-1})	122·7	108·1	113·5
Formulation E with Dilacor XR as reference			
$AUC_{(0-36)}$ (ng h mL^{-1})	1798	1753	102·6
$AUC_{(0-\infty)}$ (ng h mL^{-1})	1854	1809	102·5
C_{max} (ng mL^{-1})	119·1	108·1	110·2

$AUC_{(0-36)}$ is the area under the plasma concentration–time curve between times 0 and 36 h; $AUC_{(0-\infty)}$ is the area under the plasma concentration–time curve between times 0 and ∞; C_{max} is the maximum plasma concentration.

Clinical Research Unit, Madison, WI. The plasma samples were analysed by Hazelton Wisconsin, Madison, WI.

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