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Bioequivalence Study of Two Formulations Containing 400 mg Dexibuprofen in Healthy Indian Subjects

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Key words

- **Anti-inflammatories, nonsteroidal**
- **Dexibuprofen, bioequivalence, pharmacokinetics**
- **CAS 51146-56-6**

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Abstract

Objective: **This study presents the results of two-period, two-treatment crossover investigations on 24 healthy Indian male subjects to assess the bioequivalence of two oral formulations containing 400 mg of dexibuprofen (CAS 51146-56-6). An attempt was also made to study the pharmacokinetics of dexibuprofen in the local population of Indian origin.**

Method: **Both of the formulations were administered orally as a single dose separated by a one-week washout period. The concentration of dexibuprofen in plasma was determined by a validated HPLC method with UV detection using carbamazepine as internal standard. The formulations were compared using the parameters area under the plasma concentration-time curve (AUC_{0-t}), area under the plasma concentration-time curve from zero to infinity ($AUC_{0-\infty}$), peak plasma concentration (C_{max}), and time to reach peak plasma concentration (t_{max}).**

Results: **The results of this investigation indicated that there were no statistically significant differences between the logarithmically transformed $AUC_{0-\infty}$ and C_{max} values of the two preparations. The 90 % confidence interval for the ratio of the logarithmically transformed AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} were within the bioequivalence limit of 0.8-1.25 and the relative bioavailability of the test formulation was 99.04 % of that of reference formulation■ok?.**

Conclusion: **Thus, these findings clearly indicate that the two formulations are bioequivalent in terms of rate and extent of drug absorption. Both preparations were well tolerated with no adverse reactions observed throughout the study.**

1. Introduction

Ibuprofen (CAS 15687-27-1) is one of the most frequently used, nonsteroidal anti-inflammatory drug (NSAID) that is effectively used for treating many different types of pain (osteoarthritis, rheumatoid arthritis and moderate to severe post operative pain) [1, 2]. Dexibuprofen (CAS 51146-56-6) is the S-(+)-isomer of ibuprofen, a chiral 2-arylpropionic acid derivative. In a recent collaborative meta-analysis with individual NSAIDs proved that ibuprofen had the smallest risk of serious gastrointestinal complications. However, several independent studies in which different *in-vitro* approaches were used to monitor the inhibition of the cyclooxygenases COX-1 and COX-2 by ibuprofen ■**incomplete sentence!** [3–7]. An interesting feature of ibuprofen, which is marketed in most countries as an equal mixture of R- and S-ibuprofen (racemate), is the unidirectional metabolic chiral inversion of the *in-vitro* inactive (not prostaglandin synthesis inhibiting) R-enantiomer to the prostaglandin synthesis inhibiting S-form [8–10]. This conversion of racemic ibuprofen to the active S-(+)-isomer may contribute to the variability in analgesia and may explain the poor relationship observed between plasma concentrations of ibuprofen and the clinical response in acute pain and rheumatoid arthritis. (■**Please check the latter and the following sentence**■) In [11–13] it has been reported that S-(+)-ibuprofen was more potent than the racemic formulation of ibuprofen with respect to its analgesic and anti-inflammatory properties, and it produced less acute gastric damage. Dionne and McCullagh [14] studied the analgesic effect of orally administered ibuprofen active S-(+)-isomer in the clinical oral surgery model of acute pain. The administration of 200 mg of S-(+)-ibuprofen resulted in a greater analgesic effect than that of a racemic mixture containing approximately the same amount of active isomer. The analgesic onset was faster and the peak analgesia with only a small incidence of adverse effects [14]■**ok?**

Several high performance liquid chromatography (HPLC) methods have been published for the individual determination of ibuprofen. Mehvar *et al.* [15] described one liquid-chromatographic assay of ibuprofen enantiomers in plasma with UV detection applying derivatization of ibuprofen with ethyl chloroformate and (S)-(–)-1(1-napthyl)ethylamine. Vinci *et al.* [16] described one LC-MS method for the determination of 14 NSAID including ibuprofen in animal serum and plasma. An HPLC method for the estimation of ibuprofen in dog plasma was reported by Wang *et al.* [17]. In the present study, a simple HPLC method with UV detection has been described using precipitation technology for the determination of dexibuprofen in human plasma.

Bioavailability and bioequivalence issues have been an increasing concern to drug regulatory authorities for the assessment of the safety and efficacy of drug products. As the number of synonym drug products increase, bioavailability issues become a major concern. Bioequivalence of two formulations of the same drug comprises equivalence with respect to the rate and extent of

absorption while the area under concentration time curve (AUC) generally serves as the characteristic of the extent of absorption [18, 19]. No individual parameter reliably measures the rate of absorption; for instance, the maximal drug concentration (C_{max}) has been widely used, but it depends more on the fraction absorbed than the rate of absorbtion; the time required to reach the maximal concentration (t_{max}) depends on both absorption and elimination rates [20].

The main purpose of the present study was to evaluate the relative bioavailability of 400 mg dexibuprofen tablet (test product) with that of the reference product, a tablet formulation also containing 400 mg dexibuprofen. In addition, an attempt was made to study the pharmacokinetics of dexibuprofen in the local population of Indian origin.

2. Materials and methods

2.1 Materials and reagents

Acetonitrile and potassium dihydrogen phosphate were purchased from Merck, Mumbai (India). All solvents used were of HPLC grade, whereas other chemicals and reagents were of analytical grade. Water was purified by a Milli-Q gradient system of Millipore (Elix, Milli-Q A10 Academic) until a resistance of 18 MΩ was achieved. Blank human plasma with EDTA-K_3 anticoagulant was collected from the Clinical Pharmacological Unit (CPU) of the Bioequivalence Study Centre, Jadavpur University, Kolkata (India).

2.2 Products studied

Test product: Dexibuprofen 400 mg tablet (batch No. DI-0601, expiry date: October 2008). The test product was obtained from its manufacturer, Everest Formulations, Saproon, Solan (India).

Reference product: Dexibuprofen 400 mg tablet (batch No. 10896039, expiry date: Jun, 2008. The reference product was purchased at a local pharmacy.

2.2 Study design

Twenty-four non-smoking, normal, healthy, Indian subjects took part in the study. They had not previously participated in another clinical trial nor donated blood during the preceding 3–4 months, and had no history of alcohol or drug abuse. None had received prescription or over the counter drugs for at least 4 weeks prior to the study day. They were aged between 18 and 45 years (24.8 ± 3.78 years) with a body mass index between 18 and 24 (22.11 ± 3.13). All of them underwent complete physical examination, vital signs (blood pressure and pulse) check-up, and electrocardiogram measurement with biochemical and hematological tests before enrolling for the study. None of them showed clinically significant abnormalities. The study was only initiated after the protocol and subject information forms had been approved by the Drugs Control General of India (DCGI), New Delhi and the Institutional Ethical Committee (IEC) of Jadavpur University, Kolkata (India). Informed consent was obtained from all the subjects prior to the start of the study. The study was in compliance with Good Clinical Practice (GCP) and the revised Declaration of Helsinki. The study design was randomized, single dose, fasting, two-period, two-sequence crossover with a one-week wash out period [21–24].

2.3 Drug administration and sample collection

All the subjects assembled in the CPU ward at 6 a. m. on the study day of each session, after overnight fasting of 10 h. They did not consume any caffeinated or alcoholic beverages for at least 72 h prior to drug administration or during the study days. They received either of the study preparations and each served as their own control. According to the US Food and Drug Administration (FDA) and European Agency for the Evaluation of Medicinal Products (EMEA) [25] regulations, the sampling schedule should be planned to provide a reliable estimate of the extent of absorption [26, 27]. This is generally achieved if $AUC_{0\text{-}t}$ is at least 80 % of $AUC_{0\text{-}\infty}$. Usually the sampling time should extend to at least three terminal elimination half-lives of the active ingredient. The time periods between the samplings should not exceed one terminal half-life [28]. A total of 12 blood samples were collected at 0 h (before drug administration) and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 6.0, 8.0, 10.0, 12.0 and 24.0 h (after drug administration) in the test tubes with EDTA at each time point. Breakfast, lunch, and dinner were provided 3 h, 6 h, and 13 h, respectively, after drug administration. Collected blood samples were centrifuged immediately; plasma was separated and stored frozen at –20 °C with appropriate labeling of subject code number, study date, and collection time, till the date of analysis.

2.4 Sample preparation

To 1.0 ml of plasma in a 10 ml test tube, 100 µl of internal standard (IS, carbamazepine, CAS 298-46-4) at 1.0 µg/ml was added and then the tube was vortexed. For protein precipitation 1.0 ml acetonitrile was added, samples were vortexed, placed in the refrigerator for 15 min and centrifuged at 4000 rpm for 10 min. The supernatant layer was separated of which 20 µl was injected onto the HPLC column. Peak areas of dexibuprofen and IS were recorded.

2.5 Chromatographic conditions

Plasma samples were analyzed for dexibuprofen by HPLC with UV detection. The HPLC system (Knauer, Berlin, Germany) consisted of a solvent delivery pump (K 1001), a Rheodyne injector and a variable UV-visible detector (K-2501) with Eurochrom 2000 software for integration. HPLC was carried out isocratically at room temperature using an analytical column, Luna C18 (250 x 4.6, 5 µm particle size) from Phenomenex, USA. Elution was achieved with acetonitrile:10 mmol phosphate buffer (45:55, v/v) as the mobile phase. The sample was injected through the Rheodyne injector system fitted with 20 µl fixed loop. The effluent was monitored using UV detection at 223 nm. The method was validated in compliance with standard guidelines [29].

2.6 Pharmacokinetic analysis

The following pharmacokinetic parameters were directly determined or calculated by a standard non-compartmental method. Both maximum plasma concentration (C_{max}) and time to peak plasma concentration (t_{max}) were obtained directly from the analytical data. The elimination half-life ($t_{1/2}$) was calculated as $0.693/K_e$, where K_e is the apparent elimination rate constant. K_e was, in turn, calculated as the slope of the linear regression line of natural log-transformed plasma concentrations. The last seven quantifiable levels were used to determine K_e. The area under the plasma concentration-time curve ($AUC_{0\text{-}t}$) was calculated from the measured levels, from time zero to the time of the last quantifiable level, by the linear trapezoidal rule. $AUC_{0\text{-}\infty}$ was calculated according to the following formula:

$$AUC_{0\text{-}\infty} = AUC_{0\text{-}t} + C_{last} / K_e$$

where C_{last} is the last quantifiable plasma level. The tolerability of dexibuprofen was assessed by monitoring and subjects interview regarding the potential presence of adverse events.

2.7 Statistical analysis

For each subject, descriptive statistics was used to evaluate- ■**ok?** the estimated pharmacokinetic parameters. $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$ and C_{max} values were considered primary variables for bioequivalence analysis. Their log-transformed data were analyzed by an analysis of variance (ANOVA), including treatment, period and subject. The bioequivalence analysis was made according to guidance of the Committee for Proprietary Medicinal Products (CPMP): the test product was considered bioequivalent to the reference product if the 90 % confidence interval (CI) for the ratio between each parameter fell within the predetermined equivalence range of 80 – 125 % [25]. In addition, the nonparametric 90 % interval of the median differences of t_{max} was determined according to Hauschke *et al.* [18]. Tolerance data (vital sings, analytical results) were evaluated by Student's t test of repeated measures. Statistical significance was considered at $p \leq 0.05$.

3. Results

During HPLC analysis, no interferences were observed in the chromatogram of the plasma sample (Fig. 1). The retention time for IS and dexibuprofen was 4.85 and 14.21 min, respectively. The limit of quantification for dexibuprofen in plasma was 100 ng/ml with a coefficient of variation (CV) of 6.52 %. The relationship between concentration and peak area ratio (dexibuprofen:IS) was found to be linear within the range of 0.100 to 30 µg/ml. Quality control points at low, medium, and high levels (0.200, 12.0 and 24.0 µg/ml) were used to determine stability, absolute recovery and within-day and between-day precision and accuracy. The within-day and between-day precision and accuracy data are summarized in Table 1.

Mean plasma concentration versus time curves after administration of reference and test products to healthy subjects are shown in Fig. 2. The original 24 subjects concluded the study. Table 2 summarizes the demographic and mean health parameters of all the participants. Mean values of pharmacokinetic parameters after administration of reference and test products to healthy subjects are summarized in Table 3. The limits of the 90 % CIs for the ratios of C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}\infty}$ for their log-transformed data fell within 0.80 to 1.25 (Table 3). Nonparametric analysis according to the Wilcoxon signed rank test did not show any statistically significant differences between test and reference products ($P < 0.05$). The observed t_{max} values for the test product were within the acceptable limits (± 20 % of the mean values of the reference product).

■ **Fig. 1+2, Tab. 1–3** ■

4. Discussion

The described analytical method used for the measurement of dexibuprofen was shown to be accurate and

sensitive. The linearity achieved for this assay (0.100 to 30 µg/ml) effectively covers the therapeutic range. The run time was 17.5 min (Fig. 1). The peak of dexibuprofen and IS were well resolved. Table 1 shows the data of between-day and within-day precision and accuracy. The mean (± SD) extraction recovery of dexibuprofen was 89.36 ± 4.28 %, whereas that of carbamezepine (IS) was 88.34 ± 3.87 %.

Throughout the stability tests, dexibuprofen proved stable in biological samples for at least three freeze and thaw cycles with a final mean recovery of 97.18 % and a coefficient of variation (CV) of 3.89 %. Dexibuprofen in plasma was stable at room temperature for at least 24 h.

It can be observed from Table 2 that the subjects formed a homogeneous population in terms of age, weight, and body mass index. Dexibuprofen was well tolerated and there were no dropouts. Gastrointestinal disorders, the most common adverse effect associated with the use of NSAID, were not reported.

The elimination half-life ($t_{1/2}$) of dexibuprofen was in the range 1.84 to 1.89 h. Thus, the one-week washout period was sufficient due to the fact that no sample prior to administration in phase 2 showed any dexibuprofen levels. The time to reach maximum plasma concentration (t_{max}) was 2.1 to 2.2 h after drug administration, and the last samples were sufficient for calculating at least 80 % of $AUC_{0-\infty}$. All calculated pharmacokinetic parameters summarized in Table 3 agree with the previously reported values [30]. Administration of the reference preparation produced a C_{max} of 27.944 ± 1.002 µg/ml at the time 2.208 ± 0.257 h (t_{max}), whereas the test product produced a C_{max} of 26.972 ± 1.274 µg/ml at the time 2.125 ± 0.311 h (t_{max}). AUC_{0-t} and $AUC_{0-\infty}$ of the test versus reference were 95.757 ± 2.928 µg · h/ml versus 96.687 ± 1.626 µg · h/ml and 97.441 ± 2.706 µg · h/ml l versus 98.406 ± 1.730 µg · h/ml, respectively. Administration of the reference product produced a K_e of 0.377 ± 0.014 h^{-1} with $t_{1/2}$ of 1.840 ± 0.509 h, whereas the test product produced a K_e of 0.367 ± 0.021 h^{-1} with $t_{1/2}$ of 1.889 ± 0.413 h. On the basis of the comparison of the AUC_{0-t} for dexibuprofen after single dose administration, the relative bioavailability of the test preparation was 99.04 % ■of■**(ok?)** that of the reference preparation.

The aim of the bioequivalence trials is to assure interchangeability between an innovator and a generic formula in terms of efficacy and safety. When a pharmacological effect is difficult to measure, the plasma levels of a drug may be used as an indicator of clinical activity. Therefore dexibuprofen plasma levels obtained in this study suggest an equal clinical efficacy of the two brands tested and provide pharmacokinetic data from the Indian population.

5. Conclusion

The 90 % CI of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were in the acceptable range of 0.80–1.25. ANOVA (subject, period,

treatment) was applied to the C_{max}, ln C_{max}, AUC_{0-t} and ln AUC_{0-t} values. There was no statistically significant difference for the treatment values. Both formulations were equal in terms of rate and extent of absorption. On the basis of pharmacokinetic parameters studied, it can be concluded that the test product is bioequivalent with the reference product.

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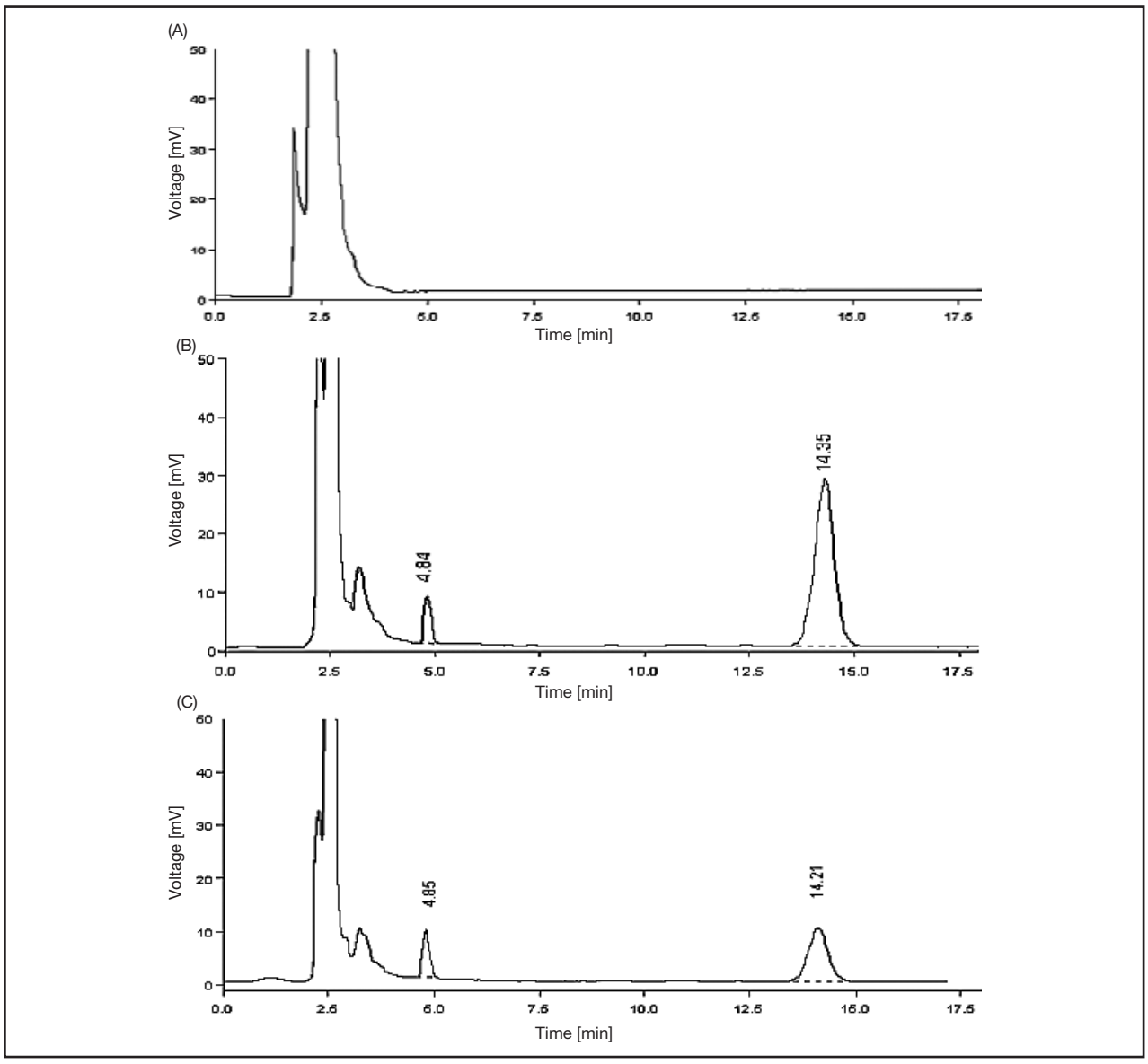

Fig. 1: Chromatograms of (A) blank plasma, (B) blank plasma spiked with 10.0 µg/ml of dexibuprofen, (C) subject plasma containing 4.9 µg/ml of dexibuprofen at 6.0bh after administration of 400 mg dexibuprofen tablet. Retention times of IS (carbamazepine) are 4.84 min (B) and 4.85 min (C); retention times of dexibuprofen are 14.35 min (B) and 14.21 min (C). No interfering peaks were observed at the retention times of IS and dexibuprofen in the chromatogram of blank plasma.

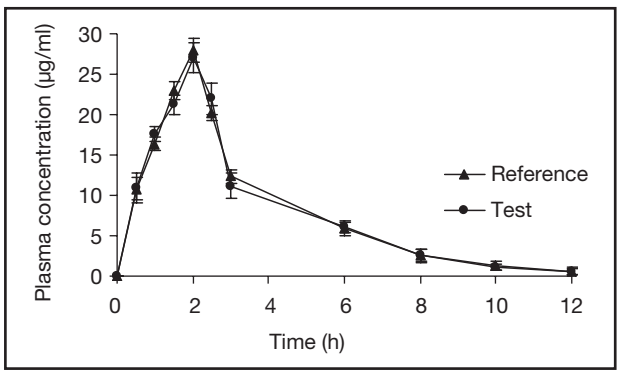

Fig. 2: Mean (± SD, n=24) plasma concentration-time profiles after administration of test and reference formulations in healthy Indian subjects. The curves were obtained by plotting time (h) on the x-axis and plasma concentration (µg/ml) on the y-axis.

Table 1: Within-day and between-day precision and accuracy of the HPLC method.

Concentration (µg/ml)	Within day (n = 6)		Between day (n = 18)	
	Accuracy (%)	Precision (CV%)	Accuracy (%)	Precision (CV%)
0.200	95.82	6.45	93.61	8.67
6.00	98.82	4.16	97.05	6.48
12.00	99.57	3.31	102.11	4.55

n = 6/18: mean value obtained after 6/18 determinations; CV = coefficient of variation expressed as %.

Table 2: Demographic and health parameters of healthy subjects considered in the bioequivalence study.

	Age (yr)	Weight (kg)	Height (cm)	BMI (kg/m^2)
Mean	24.8	60.2	165	22.11
SD	3.78	4.31	0.06	3.13

SD = standard deviation; BMI = body mass index.

Table 3: Mean (± SD, n = 24) pharmacokinetic parameters of 400 mg dexibuprofen tablets of the test and reference formulation.

Parameter	Test	Reference	90 % CI (log-transformed data)
AUC_{0-t} (µg · h /ml)	95.757 ± 2.928	96.687 ± 1.626	0.988919 – 1.008748
$AUC_{0-\infty}$ (µg · h /ml)	97.441 ± 2.706	98.046 ± 1.730	0.994422 – 1.011938
C_{max} (µg/ml)	26.972 ± 1.274	27.944 ± 1.002	0.977821 – 1.032926
t_{max} (h)	2.125 ± 0.311	2.208 ± 0.257	
K_e (h^{-1})	0.367 ± 0.021	0.377 ± 0.014	
$t_{1/2}$ (h)	1.889 ± 0.413	1.840 ± 0.509	

AUC_{0-t} = area under the plasma concentration-time curve from 0 to t h; $AUC_{0-\infty}$ = area under the plasma concentration-time curve from 0 to infinity; C_{max} = maximum plasma concentration; t_{max} = time to reach maximum plasma concentration; K_e = elimination rate constant; $t_{1/2}$ = elimination half-life; CI = confidence interval. Data are presented as mean values ± SD.

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