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Bioequivalence of Two Oral Extended Release Formulations of Ciprofloxacin Tablets in HealthyMale Volunteers under Fed and Fasting Conditions

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Abstract

The bioavailability of a single dose of ciprofloxacin 1000 mg Extended release (XR) tablets manufactured by a Jordanian manufacturer (Hikma PLC), was compared with a reference ciprofloxacin 1000 mg XR tablets (Cipro® XR, Bayer-health care, Germany) in two different studies (under fasting and fed conditions). In each study, 28 healthy, male, Jordanian volunteers were enrolled. However, only 25 subjects in fasting study and 23 subjects in fed study completed the crossover. Each study was designed as single-center, open-label, randomized, single-dose, two-way crossover study. Nineteen blood samples were taken during 24hrs. Samples were frozen and kept until time of analysis. Ciprofloxacin concentrations in subjects' plasma were determined by using a validated HPLC fluorescence technique. Confidence intervals (90%) for the peak plasma concentration (C_{max}) and area under the concentration-time curve (AUC0-t) were determined by calculating log-transformed Test/Reference ratio using standard non-compartmental method and ANOVA statistics. The 90% CI result in fasting study for C_{max} was 88.87 (82.17 - 96.10)% and for AUC0-t was 87.60 (80.38-95.46)%. In fed study the results were 102.09 (92.77-112.34)% and 104.06 (100.01-108.27)% for $_{Cmax}$ and AUC0-t, respectively. In conclusion, it is evident that the 90% CI for the primary pharmacokinetics parameters was within the bioequivalence acceptable boundaries of 80-125%, while for AUC0-t, and 75.-133% for C_{max}. Therefore, it was concluded that both products were bioequivalent.

Keywords: Ciprofloxacin; Extended Release; Pharmacokinetics; Bioavailability; Bioequivalence

Introduction

Ciprofloxacin is a quinoline carboxylic acid derivative with broad antibacterial activity against both gram-positive and gram-negative bacteria. Chemically it is 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid] [3, 5,11]. It was found to be more active against enterobacteriaceae than the older drugs of this class, such as nalidixic acid, with minimum inhibitory concentrations ranging from 0.008 to 2.0 mg/l [3,4]. The adverse effects are also less likely [7]. Ciprofloxacin extended release is indicated only for the treatment of urinary tract infections, including acute uncomplicated pyelonephritis, caused by susceptible strains. Ciprofloxacin XR and ciprofloxacin immediate-release tablets are not interchangeable [6].

Once-daily ciprofloxacin XR was safe, effective, and noninferior to twice-daily ciprofloxacin immediate-release (IR) in the treatment of acute UTI. Additionally, ciprofloxacin XR was associated with significantly reduced frequencies of nausea and diarrhea. [8,12,15,19,14]. [18] showed that ciprofloxacin XR possessed larger AUCs than levofloxacin. Patients' compliance improvement using ciprofloxacin XR and thus decrease the risk of treatment failure and the spread of antibiotic resistance are also reported [17]. Furthermore, since economic considerations are increasingly important and using XR treatments prove convenient and effective in this regards [12]. Maximum plasma ciprofloxacin concentrations are attained between 1 and 4 hours after dosing with Ciprofloxacin XR. In comparison to the 250 mg and 500 mg ciprofloxacin IR BID treatment, the C_{max} of Ciprofloxacin XR 500 mg and 1000 mg once daily are higher than the corresponding BID doses, while the AUCs over 24 hours are equivalent. The IT decreases the rate, but not the extent, of drug absorption. Antacids containing magn-esium, aluminum and/or calcium decrease the bioavailability of ciprofloxacin. The plasma half-life is about 3.5-4.5 hours and there is an evidence of modest accumulation [6].

Studies to establish bioequivalence (BE) between two products are important for certain changes before approval regulatory submissions. In BE studies, an applicant compares the systemic exposure profile of a test drug product to that of a reference drug product. For two orally administered drug products to be bioequivalent, the active drug ingredient or active moiety in the test product must exhibit equivalent rate and extent of absorption to that of the reference drug product. Product quality BE frequently relay on pharmacokinetics measures such as AUC and C_{max} that are reflective of systemic exposure [9]. For modified-release products, the following studies are recommended: (1) a single-dose, nonreplicate, fasting study comparing the highest strength of the test and reference listed drug product and (2) a food-effect, nonreplicate study comparing the highest strength of the test and reference product. For immediate release products, a single-dose, fasting study is recommended. In addition, in vivo BE studies are to be accompanied by in vitro dissolution profiles on all strengths of each product.

Literature showed many bioequivalence studies for ciprofloxacin immediate release tablets [2,1], while no bioequivalence studies were published on the 1000 mg XR formulation. The aim of this study was to determine bioequivalence of two XR tablet formulations: Ciprofloxacin

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XR 1000mg tablet (Hikma pharmaceutical-PLC) relative to [6] tablets (Bayer Health care-Germany) after oral administration to healthy volunteers under both fed and fasting conditions.

Subjects and Methods

Subjects

Table 1 shows number and demographic data for subjects enrolled in the two studies, fast and fed. In either study, 28 subjects were enrolled, however, 3 in fasting and 5 in fed withdrew due to personal reasons or medical conditions before study drug administration. Consequently, a total of 25 and 23 subjects completed the crossover in fast and fed, respectively. All subjects were healthy, adults, male Jordanian volunteers. Clinical results of the screened laboratory examinations (biochemistry, serology, hematology and urine analysis) were within normal ranges. All subjects were informed with the objectives, drugs, potential risks, dates and activities during the clinical part of the study. A written consent form was signed by each subject. Any subject having drug allergy, alcohol abuse, GIT conditions that may have significantly affected drug absorption, etc., was excluded. The use of either prescription or OTC drugs was abstained 2 weeks before study time.

Both Fasting and fed studies were approved by The Institutional Review Board (IRB) of IPRC, Amman, Jordan, which operates in accordance with the principles and requirements described in Guidelines on Research Involving Human Subjects. The study protocols were reviewed by IRB of IPRC, approved and given the code Nos.CIP-T015 and CIP-T016 for fasting and fed studies respectively.

Study drugs

Two products of Ciprofloxacin 1000mg XR tablets were studied. The test product was Ciprofloxacin 1000mg XR tablets (Hikma-Pharma, Jordan, B# JE5-P9, Exp date: 04/10). The reference was [6] 1000mg (Bayer-Health care, Germany, B# BXBX721, Exp. Date: 01/09). The same batches were used for fasting and fed studies.

Methods

The method was designed as single dose, two-treatment, two-period, two-sequence crossover with a 7-days washout period for each study. Subjects were admitted the night before the study drug administration, supervised for at least 10 hours overnight fasting, and confined until collecting the 24 hour sample. On day 1 of each study period, each subject was given either one tablet of Ciprofloxacin 100mg XR tablet (test product) or Cipro XR 1000mg (Reference product) according to a randomization plan, along with 240ml of water. Diet consumption before and after drug administration are shown in Table 2.

Characteristic	Fasting study	Fed study
No. enrolled	28	28
No. completed study	25	23
Mean age (yr)±SD	29±7.66 range18-43yr	25±5.92 range19-43yr
Mean body wt (Kg)±SD	70±7.44 range54-85kg	75±11.59 range60-100kg
Mean height (cm)±SD	171±5.69 range163-186cm	175±6.48 range163-190cm

Table 1: number of subjects enrolled in the study and their demographic characteristics.

day	Meal	Fasting study	Fed study
-1	Dinner	Finished at least 10 hours before time of drug administration in day 1	Finished at least 10 hours before time of drug administration in day 1
1	Breakfast	None	0.5hours before drug administration
1	Lunch	4 hours after drug administration	5 hours after drug administration
1	Snack	8 hours after drug administration	9 hours after drug administration
1	dinner	12 hours after drug administration	13 hours after drug administration

Table 2: Food times before and after drug administration.

The consumption of alcohols, methylxanthin-containing beverages (coffee, etc.) or grapefruits were prohibited enough time prior to drug administration. Physical activities were controlled throughout the study period. For blood samples collection, a cannula was inserted to each subject's forearm vein and remain there until the 24-hour sample. Eight milliliters blood was collected each sample as follows: immediately before at 0.00 (predose) and at 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00, 20.00 and 24.00 hours. Blood samples were collected into tubes containing heparin as an anticoagulant (Dispo™, AFMA, Jordan), slightly shaken and centrifuged (at approximately 3500 rpm) for 10 minutes, transferred immediately to plastic tube (Dispo™, AFMA, Jordan) and stored at -20°C. The total amount of blood loss during the whole study did not exceed 317.5ml.

Ciprofloxacin concentrations in human plasma were determined by a specific high performance liquid chromatography (HPLC) with fluorescence detection method. The technique was developed at IPRC laboratories. After spiking 200 µl of plasma samples with levofloxacin as internal standard, a protein precipitation technique using 1 ml methanol was employed to extract both analytes. Supernatants then were centrifuged, evaporated to dryness under nitrogen gentle stream and reconstituted with 800 µl mobile phase. Only 20 µl were injected into a prepacked C18, 5 µm (3.9x150 mm) reversed phase analytical column. Mobile phase was composed of 7% glacial acetic acid, 5% acetonitrile and 88% (0.025 M sodium acetate trihydrate), with flow rate at 1.50 ml/min. Separations were monitored at 280 and 440 nm as excitation and emission wavelengths, respectively. Analysis was accomplished at column oven temperature 25°C. Chromatography separation and drug determination was accomplished by using Shimadzu (Japan) HPLC composed of LC-10AD vp pump, RF- 10A XL fluorescence detector and SCL-10A vp system controller.

The method was validated according to the FDA current bioanalytical guidance. Accordingly the method validation was evaluated in terms of specificity, selectivity, linearity, sensitivity, inter and intraday accuracy and precision, recovery and stability under different conditions. Samples from 25 subjects in fasting study and 23 subjects in fed study were analyzed.

Pharmacokinetic calculations

Pharmacokinetic parameters of ciprofloxacin were estimated using standard non-compartmental methods. The maximal plasma concentration (C_{max}) and the time to the peak plasma concentration (t_{max}) of ciprofloxacin were taken directly from the measured data. The area under the plasma concentration-time curve (AUC_{0-t}) was calculated from measured data points from time of administration to time of last quantifiable concentration (C_{last}) by the linear trapezoidal rule. The area under the plasma concentration-time curve extrapolated to infinity ($AUC_{0-\infty}$) was calculated according to the following formula: $AUC_{0-\infty} = AUC_{0-t} + C_{last}/[\ln 2/t_{1/2e}]$ where C_{last} is the last quantifiable concentration. The ratio AUC_{0-t} / $AUC_{0-\infty}$ as a percent was determined as an indicator for the adequacy of sampling time. The elimination

half-life ($t_{½e}$) was calculated as:$t_{½e}$ = Ln (2)/(-b), where b was obtained as the slope of the linear regression of the Ln-transformed plasma concentrations versus time in the terminal period of the plasma curve. The pharmacokinetic calculations were performed on a Pentium MMX MHz Computer using the computer program Kinetica™ 2000.

Statistical analysis

Statistical analysis was performed by using the Kinetica ™ 2000 program, with the aid of Microsoft® Excel (2002).The extent of absorption is determined by AUC_{0-t} and $AUC_{0-\infty}$. The rate of absorption is determined by C_{max}. For the parametric analysis of bioequivalence for Ln-transformed data, the acceptance boundaries were set at 80.00-125.00% for both AUC_{0-t}, and $C_{max.}$ A multiplicative model with respect to the untransformed bioequivalence parameters was selected. A logarithmic transformation of the original data was used. Under the assumption of a logarithmic normal distribution, a parametric approach recommended by [16] based on the inclusion of the shortest 90% confidence interval in the bioequivalence range was adopted. An analysis of variance (ANOVA) tested for sequence, period, subject (sequence) and treatment effects was used. ANOVA was performed on AUC_{0-t}, $AUC_{0-\infty}$,C_{max}, t_{max}, $t_{1/2e}$, K_e, Ln AUC_{0-t}, Ln $AUC_{0-\infty}$ and Ln C_{max}.

A multiplicative linear model was used for the two-way crossover design:Yijk = log (Xijk) = μ + Gk Sik + Pj + F (j , k) + eijk,Where,Yijk = is a pharmacokinetic parameter of the ith subject (i = 1 , 2 , …n_k) in the sequence (k = 1, 2, … k) for the jth period (j = 1 , 2 , …p); μ: is the overall mean; Gk: is the fixed effect of the kth sequence; Sik: is the random effect of the ith subject in the kth sequence; Pj: is the fixed effect of the jth period; F (j, k): is the fixed effect of the formulation in the kth sequence, which is administered at the jth period; and, eijk: is the (within subject) random error in observing Yijk.It was assumed that {Sik} and {eijk} are mutually independent and normally distributed with mean zero and variances σs^2 and σe^2.

Results

The described analytical method was proved selective and specific. Retention times were 7.4 and 8.8 min for the internal standard and drug, respectively. No interferences were observed. Concomitant drugs do not interfere with ciprofloxacin or internal standard analysis. The method was proved sensitive and accurate for the determination of ciprofloxacin in human plasma. Under the described conditions, the limit of quantitation for ciprofloxacin was 50 ng/ml with 99.60 % accuracy and 15.06% CV. The method was found linear within the range 50 – 5000 ng/ml, with accuracy ranging 99.15 – 100.70% and precision 0.98 – 15.06 %. Correlations coefficients were 0.99. Intraday accuracy of ciprofloxacin method ranged from 94.93 to 97.80%, while precision ranged from 1.24 to 5.73%. Interday accuracy ranged from 95.00 to 99.3 1%, while the interday precision ranged from 4.07 to 7.58%. Mean recovery was proved 86.57 % with 7.74 % CV. Ciprofloxacin long-term stability was tested and was found stable for 90 days at -20°C (99.59 % with 1.09 % CV).

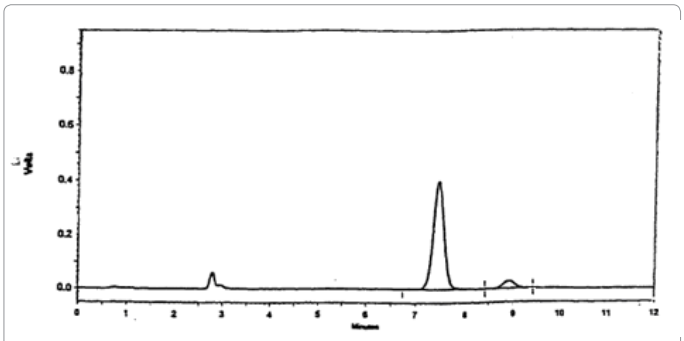

Figure 1: HPLC chromatogram showing human plasma containing 150 ng/ml ciprofloxacin at retention time 9 min and internal standard levofloxacin peak at 7 min.

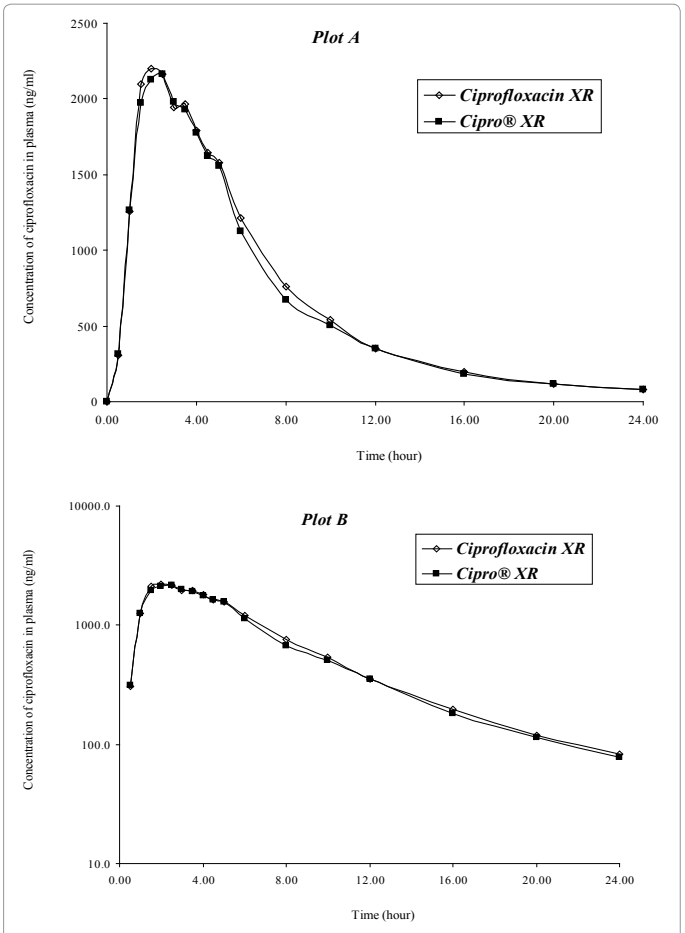

Figure 2: Ciprofloxacin mean plasma concentration after an oral dose administration of 1000 mg Ciprofloxacin from Ciprofloxacin XR, 1000 mg Ciprofloxacin per extended release tablet (Test Product) and Cipro® XR,1000 mg Ciprofloxacin per Tablet (Reference Product) to 25 healthy subjects under fed conditions (Plot A: plasma conc. vs time, Plot B: log transformed plasma conc vs time).

Drug plasma levels were designated as surrogate parameters to indicate clinical activity. Primary pharmacokinetic parameters were set to be C_{max} and AUC_{0-t} were also considered to be the bioequivalence determinants. Finally, K_e, $AUC_{0-\infty}$, t_{max} , AUC_{0-t}/ $AUC_{0-\infty}$ and $t_{½e}$ were set as the secondary pharmacokinetic parameters. The detailed results for fasting and fed studies are shown in Tables 3-6, respectively. Bioequivalence could be demonstrated for Ciprofloxacin within the prescribed 90% confidence interval of 80.00-125.00% for AUC_{0-t} and C_{max} with respect to the parametric method on log-transformed data. The results are shown in Figure 2 and 3 for fed and fasting studies, respectively.

Discussion

Assessment of bioequivalence of generic product to reference product is required to exclude any clinically important differences in the rate or extent at which the active entity of the drugs becomes available at the site of action. Two drug products are considered to

be bioequivalent if they are pharmaceutically equivalent and their bioavailability is so similar that they are unlikely to produce clinically relevant differences in regard to safety and efficacy [9].Food has been shown to alter the bioavailability of some drugs which can have negative impact on the interpretation of bioequivalence results between test and reference products [13]. Food can alter BA by various means, including delay gastric emptying, stimulate bile flow, change gastrointestinal (GI) pH, increase splanchnic blood flow, change luminal metabolism of a drug substance and physically or chemically interact with a dosage form or a drug substance [9]. This effect is more pronounced in case of modified release dosage forms due to their longer stay in GIT. FDA recommends that BE study under fed conditions should be conducted for all orally administered modified-release drug product [9].

In this study, the effect of food on the bioavailability of ciprofloxacin is somewhat more noticeable for reference product (Cipro® XR) than test product. This might be due to the difference in the formulation composition. That is, the test product formula contains Ciprofloxacin HCl only, while that of the reference product contains a combination of ciprofloxacin base and HCl. Thus test product will be less affected by change effect due to food. The AUC values in Table 3 and 4 shown to be higher under fasting than those under fed conditions. This effect can also be noticed if Figures 1 and 2 are compared. Furthermore, the values of C_{max} is shown to be higher in fasting than in fed conditions which reflects effect of food on the rate of drug absorption.

The results of this bioequivalence study showed the equivalence of the two studied products in terms of the rate of absorption as indicated

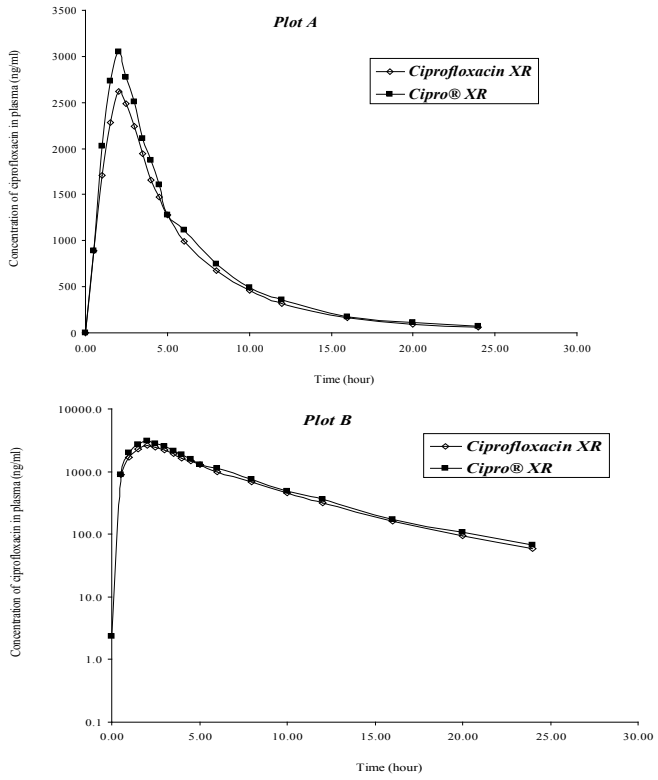

Figure 3: Ciprofloxacin mean plasma concentration after an oral dose administration of 1000 mg Ciprofloxacin from Ciprofloxacin XR, 1000 mg Ciprofloxacin per extended release tablet (Test Product) and Cipro® XR,1000 mg Ciprofloxacin per Tablet (Reference Product) to 24 healthy subjects under fasting conditions (Plot A: plasma conc. vs time, Plot B: log transformed plasma conc vs time).

Pharmacokinetic Parameter	90% Confidence intervals of parametric means		
	Point estimate %	Lower Limit %	Upper Limit %
C_{max}	102.09	92.77	112.34
$AUC_{0\rightarrow t}$	104.06	100.01	108.27

Table 3: Bioequivalence Confidence Intervals of Ciprofloxacin for fed study (*Ciprofloxacin XR* Tablet the Test Product versus *Cipro® XR* Tablet the Reference Product).

Pharmacokinetic Parameter	Treatment (Mean ± SD)	
	Test Product	Reference Product
C_{max} (ng/ml)	2946±1006.38	2839±684.14
$AUC_{0\rightarrow t}$ (ng.h/ml)	15757.3±3122.92	15178.8±3238.10
$AUC_{0\rightarrow\infty}$ (ng.h/ml)	16421.2±3308.73	15820.9±3393.12
t_{max} (h)	2.83±1.24	2.70±1.33
$t_{½e}$ (h)	5.14±0.62	5.26±0.69
$AUC_{0\rightarrow t}/AUC_{0\rightarrow\infty}$%	96.02±1.08	95.96±1.14
K_e (1/h)	0.1370±0.02	0.1338±0.02

Table 4: Pharmacokinetics Parameters of Ciprofloxacin for fed study (*Ciprofloxacin XR* Tablet the Test Product versus *Cipro® XR* Tablet the Reference Product).

Pharmacokinetic Parameter	90% Confidence intervals of parametric means		
	Point estimate %	Lower Limit %	Upper Limit %
C_{max}	88.87	82.17	96.10
$AUC_{0\rightarrow t}$	87.60	80.38	95.46

Table 5: Bioequivalence Confidence Intervals of Ciprofloxacin for fasting study (*Ciprofloxacin XR* Tablet the Test Product versus *Cipro® XR* Tablet the Reference Product).

Pharmacokinetic Parameter	Treatment (Mean ± SD)	
	Test Product	Reference Product
C_{max} (ng/ml)	2993±845.18	3319±675.16
$AUC_{0\rightarrow t}$ (ng.h/ml)	15423.8±5431.72	17163.9±4192.24
$AUC_{0\rightarrow\infty}$ (ng.h/ml)	16008.5±5582.25	17874.2±4318.83
t_{max} (h)	2.10±0.82	2.13±0.58
$t_{½e}$ (h)	5.25±1.29	5.24±0.99
$AUC_{0\rightarrow t}/AUC_{0\rightarrow\infty}$%	96.23±1.24	95.97±1.97
K_e (1/h)	0.1379±0.03	0.1369±0.03

Table 6: Pharmacokinetics Parameters of Ciprofloxacin for fasting study (*Ciprofloxacin XR* Tablet the Test Product versus *Cipro® XR* Tablet the Reference Product).

by C_{max} and in terms of the extent of absorption as indicated by AUC_{0-t} and $AUC_{0-\infty}$. The parametric 90% confidence intervals of the mean values for the Test/Reference ratio were in each case well within the bioequivalence acceptable boundaries of 80.00-125.00% for $AUC_{0\rightarrow t}$ and $C_{max.}$ ANOVA analysis on the log-transformed data, C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ and untransformed data for C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, K_e, $t_{1/2e}$ and t_{max} showed that sequence effect for all these parameters did not significantly influence the outcome of the study. The mean plasma curves of both products are almost superimposable suggesting that not only C_{max} and AUC_{0-t} but also the time course of plasma levels over the whole sampling period are identical.

Conclusions

In conclusion, pharmacokinetic parameters, namely, C_{max}, AUC_{0-t}

and $AUC_{0-\infty}$, of the two ciprofloxacin 1000mg extended release products showed comparable values indicating that they are bioequivalent.

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