Bioequivalence and Pharmacokinetic Study of Two Oral Formulations of Ciprofloxacin Tablets in Healthy Male Volunteers

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ABSTRACT

Objective: The objective of this study was to compare different pharmacokinetic parameters of a locally manufactured (Quinox) and reference (Ciproxin) formulation of ciprofloxacin 250 mg tablets after oral administration of a single dose under fasting condition.

Method: Fourteen blood samples were collected from each of 24 healthy male Bangladeshi volunteers over 12 hours after oral administration of the drugs. Serum ciprofloxacin concentrations were determined by high-performance liquid chromatography (HPLC) assay using ultraviolet (UV) detection, and pharmacokinetic parameters were determined by the non-compartmental method.

Results: Mean plus or minus standard deviation (SD) of peak plasma concentration (C_{max}), area under the serum concentration-time curve (AUC_{0-12}), area under the serum concentration-time curve extrapolated to infinity ($AUC_{0-\alpha}$), serum elimination half-life ($t_{1/2}$), and elimination rate constant (k_{el}), were 1.49 ± 0.085 and 1.46 ± 0.032 μg/mL, 5.82 ± 0.38 and 5.79 ± 0.67 hr.μg/mL, 6.86 ± 0.93 and 6.92 ± 0.92 hr.μg/mL, 4.96 ± 1.19 and 4.52 ± 0.66 hr, and 0.147 ± 0.033 and 0.156 ± 0.022 hr^{-1} for the locally manufactured (test) and reference formulation, respectively. For both formulations time to reach peak serum concentration (T_{max}) was found to be 1.2 (± 0.27) hr. From the paired *t*-test, the *P*-values for the two formulations were found to be 0.624, 0.784, and 0.460 for AUC_{0-12}, $AUC_{0-\alpha}$, and $C_{max,}$ respectively. The 90% confidence intervals of the mean of the difference between log-transformed values for AUC_{0-12}, $AUC_{0-\alpha}$, and C_{max} were within the bioequivalence accepted range of 80% to 125%, namely: 97.99% and 103.18%; 96.47% and 101.73%; and 99.96% and 103.69%, respectively.

Conclusion: The results indicate that the two formulations are bioequivalent for both the rate and extent of absorption.

Table 1. Precision and Accuracy of the Method for Determining Ciprofloxacin Levels in Human Plasma (n=5)

Concentration (ng/mL)		Relative error*	Intra-day	Inter-day
Added	Found	(%)	RSD (%)	RSD (%)
10	10.45	4.54	2.86	10.87
50	55.01	10.03	8.35	6.45
500	486.99	-3.82	1.68	2.26

*Relative error=(mean measured concentration - added concentration) X 100/added concentration
RSD=relative standard deviation

INTRODUCTION

Ciprofloxacin [1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid] is a quinoline carboxylic acid derivative with broad antibacterial activity against both gram-positive and gram-negative bacteria.[1-4] This compound was found to be substantially 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.[1,5] A single-dose pharmacokinetic study of ciprofloxacin showed that an oral dose of ciprofloxacin was absorbed well and rapidly and exhibited excellent tissue penetration.[6] Peak plasma concentrations occur at 47 ± 20 minutes.[7] Various enteral feeding can decrease ciprofloxacin C_{max} by 26% to 47% and *AUC* by 58% to 73%.[8-10] The aim of this study was to compare, under fasting conditions, the rate and extent of absorption of two 250-mg tablet formulations of ciprofloxacin, a locally manufactured (test) formulation, Quinox (SKF, Eskayef Bangladesh Ltd., Dhaka, Bangladesh) and a reference formulation, Ciproxin (Bayer Health Care Pharmaceuticals, United Kingdom).

SUBJECTS AND METHODS

Subjects

Twenty-four healthy, nonsmoking, adult Bangladeshi male volunteers (mean age ± SD, 25 ± 1.3; range, 24-27 years) were randomly selected for enrollment in the study. The mean body weight and height of the subjects was 68.4 ± 5.18 kg (range, 64-75 kg) and 1.69 ± 0.06 m (range, 1.62-1.78 m) respectively, producing a mean body mass index (BMI) of 23.9 ± 1.45 kg/m^2 (range, 21.5-25.1 kg/m^2). Subjects were selected after their medical history was obtained and they underwent physical examination, chest X-ray, electrocardiogram (ECG), serological screening for infectious disease, and urine analysis. Participation in the study was limited to those with no evidence of significant abnormal hematology and serum chemistry. Exclusion criteria included any history of a significant gastrointestinal condition that could potentially impair the absorption or disposition of the study medicine, previous history of allergy to any fluoroquinolone, need for any chronic medication [eg, theophylline, antacids, glibenclamide (glyburide), phenytoin, iron, or vitamins], donation of blood within 30 days preceding the first dose of the study, or use of a investigational agent within 30 days of study entry. Potential subjects were also excluded if they use any medication within 1 day before administration of the first dose. The volunteers were asked to abstain from taking any medication (including nonprescription drugs) throughout the study; and from smoking and taking alcohol or caffeine or con-

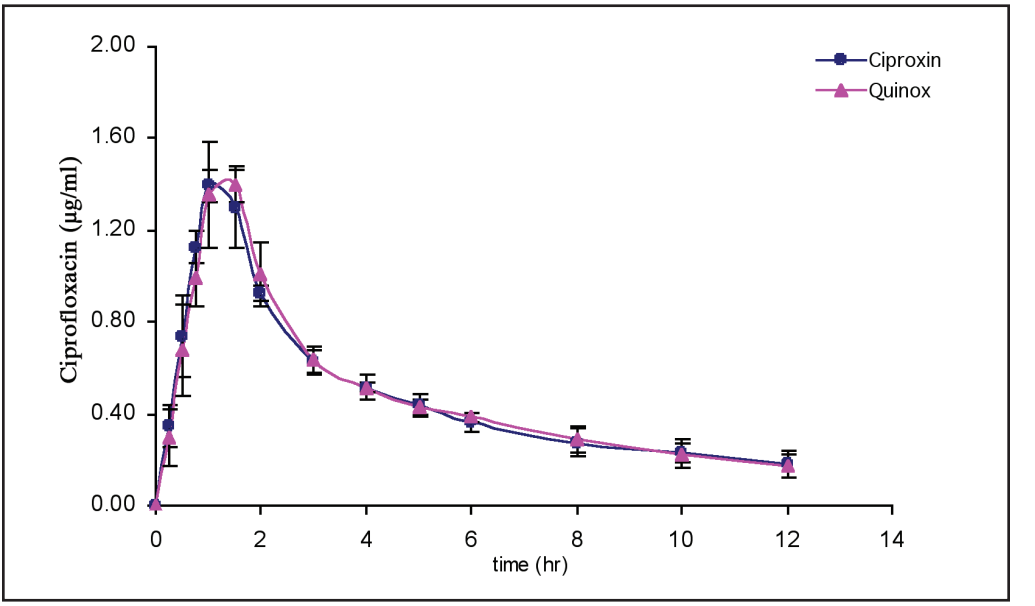

Figure 1. Mean plasma concentrations of ciprofloxacin at different time intervals after single oral administration of 250-mg tablet of Ciproxin and Quinox to 24 healthy male volunteers.

suming xanthene-containing beverages or food for at least 48 hours prior to, and throughout, the study. Any incidence of vomiting or any other adverse events resulted in the exclusion of the subject from the study. They were informed about the risks, benefits, procedures, and aims of the study, as well as their rights as research subjects. The study was conducted according to the Declaration of Helsinki (1964). Each volunteer signed an informed consent document before entering the study. Ethical permission was taken to approve the protocol and consent form of this study from the Ethical Review Committee of Pharmacy Faculty, Dhaka University.

Study Drugs

As described above, the test formulation was 250-mg tablets of Quinox (batch # 5002); the reference formulation was 250-mg tablets Ciproxin (batch # IT401DU).

Study Design

Twenty-four volunteers were selected randomly. All volunteers received single 250-mg film-coated tablet of both formulations, reference formulation (A) or test formulation (B). Volunteers were randomly divided into 2 groups consisting of 12 volunteers in each group. Group 1 received treatment A followed by treatment B with a 7-day washout period. This sequence of treatment is denoted by AB. Group 2 received treatment B followed by treatment A after the same washout period. This sequence of treatment is denoted as BA. In the first period, group 1 received treatment A and group 2 received treatment B. The study used a crossover design in the second period in that group 1 received treatment B and group 2 received treatment A.[11] Each volunteer received the treatment with 250 mL of water in the morning after overnight fasting. A standard lunch was allowed after 4 hours of dosing. The volunteers were ambulatory during the study but were prohibited from strenuous activity. Volunteers were monitored constantly for the period of 12 hours by a medical doctor.

Table 2. Mean Pharmacokinetic Parameters of Ciproxin 250-mg Tablet. (A) Reference Formulation and (B) Quinox 250-mg Tablet (Locally Manufactured Formulation)

(A)	Reference Formulation, Ciproxin 250-mg Tablet						
Pharmacokinetic parameters (no of subjects=24)	**Geo-metric mean**	**Median**	**Mean**	**SD**	**CV (%)**	**Max**	**Min**
C_{max} (µg/mL)	1.46	1.47	1.46	0.03	2.34	1.50	1.41
t_{max} (hr)	1.18	1.00	1.20	0.27	22.82	1.50	1.00
AUC_{0-12} (hr · µg/mL)	5.76	5.51	5.79	0.67	11.54	6.98	5.42
$AUC_{0-\alpha}$ (hr · µg/mL)	6.88	6.48	6.92	0.92	13.34	8.49	6.18
$t_{1/2}$ (hr)	4.48	4.42	4.52	0.67	14.73	5.52	3.79
k_{el} (hr^{-1})	0.15	0.16	0.16	0.02	14.02	0.18	0.13
$AUMC_{0-12}$ (hr^2.µg/mL)	23.76	22.54	23.89	2.98	12.46	28.87	21.69
$AUMC_{0-\alpha}$ (hr^2.µg/mL)	42.62	39.29	43.78	12.36	28.24	65.47	35.75
MRT (hr)	6.34	6.06	6.38	0.79	12.36	7.71	5.79
C_{max} /$AUC_{0-\alpha}$	0.21	0.22	0.21	0.02	11.30	0.23	0.17

C_{max}= peak plasma concentration; t_{max}= time to reach peak serum concentration; AUC_{0-12}=area under the serum concentration-time curve; $AUC_{0-\alpha}$=the area under the serum concentration-time curve extrapolated to infinity; $t_{1/2}$=serum elimination half-life; K_{el}=elimination rate constant; $AUMC_{0-12}$=area under the first moment versus time curve from $t = 0$ to t; $AUMC_{0-\alpha}$= area under the first moment versus time curve from $t = 0$ to α; MRT= mean resident time; SD=standard deviation; CV=coefficient of variation

(B)	Test Formulation						
Pharmacokinetic parameters (no of subjects=24)	**Geo-metric mean**	**Median**	**Mean**	**SD**	**CV (%)**	**Max**	**Min**
C_{max} (µg/mL)	1.49	1.49	1.49	0.08	5.68	1.62	1.39
t_{max} (hr)	1.18	1.20	1.00	0.27	22.82	1.50	1.00
AUC_{0-12} (hr• µg/mL)	5.81	5.82	5.73	0.38	6.55	6.39	5.46
$AUC_{0-\alpha}$ (hr• µg/mL)	6.81	6.86	6.67	0.93	13.61	8.48	6.18
$t_{1/2}$ (hr)	4.85	4.96	4.33	1.19	24.05	6.46	3.90
k_{el} (hr-1)	0.14	0.15	0.16	0.03	22.26	0.18	0.11
$AUMC_{0-12}$ (hr^2• µg/mL)	28.96	32.85	23.29	21.76	66.25	71.67	21.39
$AUMC_{0-\alpha}$ (hr^2• µg/mL)	39.65	41.69	36.14	16.13	38.68	69.49	28.41
MRT (hr)	6.75	6.88	6.06	1.53	22.28	8.63	5.50
C_{max} /$AUC_{0-\alpha}$	0.22	0.22	0.22	0.03	15.06	0.26	0.17

C_{max}= peak plasma concentration; t_{max}= time to reach peak serum concentration; AUC_{0-12}=area under the serum concentration-time curve; $AUC_{0-\alpha}$=the area under the serum concentration-time curve extrapolated to infinity; $t_{1/2}$=serum elimination half-life; K_{el}=elimination rate constant; $AUMC_{0-12}$=area under the first moment versus time curve from $t = 0$ to t; $AUMC_{0-\alpha}$= area under the first moment versus time curve from $t = 0$ to α; MRT= mean resident time; SD=standard deviation; CV=coefficient of variation

Blood Sampling

The timing of blood collection was planned according to the previously reported value of time to reach peak serum concentration (T_{max}) and serum elimination half-life ($t_{1/2}$).[12-16] Venous blood samples were collected before and at 0.25, 0.50, 0.75, 1.00, 1.50, 2, 3, 4, 5, 6, 8, 10, and 12 hours after drug administration. An intravenous cannula was

Table 3: P-values for Different Pharmacokinetic Parameters of 2 Formulations Calculated by Paired t-test (No. of subjects=24)

Pharmacokinetic	AUC_{0-12}	$AUC_{0-\alpha}$	C_{max}	t_{max}	kel	$t_{1/2}$	MRT	$AUMC_{0-12}$	$AUMC_{0-\alpha}$
P-values	0.624	0.784	0.460	1.000	0.350	0.270	0.589	0.352	0.850

AUC_{0-12}=area under the serum concentration-time curve; $AUC_{0-\alpha}$=the area under the serum concentration-time curve extrapolated to infinity; C_{max}= peak plasma concentration; t_{max}= time to reach peak serum concentration; K_{el}=elimination rate constant; $t_{1/2}$=serum elimination half-life; MRT= mean resident time; $AUMC_{0-12}$=area under the first moment versus time curve from t = 0 to t; $AUMC_{0-\alpha}$=area under the first moment versus time curve from t = 0 to α

placed into the volunteers' forearm vein before drug administration and left in place until the 12-hour blood sample was collected. The blood samples were collected in coded, evacuated tubes, kept 30 minutes for clotting, and centrifuged at room temperature at 2500 rpm for 10 minutes. (Mikro-20, Hettich, Zentrifugen, Germany). The serum was collected in coded Eppendorf tubes and serum protein was separated by precipitation with ethanol followed by centrifugation at 10,000 rpm for 5 minutes. The serum was collected and stored at -80°C until analyzed.

Determination of Ciprofloxacin Level

Ciprofloxacin was separated at room temperature on a 5-µm (particle-size), 3 x 50-mm Xterra C_{18} column with Guard Pak pre-column module and Nova-Pak C_{18} 4-µm insert (XTerra column, Waters, Ireland). The compounds of interest were detected using a 996 photo-diode array detector set at 278 nm (Waters Alliance HPLC Systems, Waters, Ireland). The mobile phase consists of 0.025 M phosphoric acid buffer (pH adjusted to 4.0 ± 0.01 with 5.0 M sodium hydroxide) and acetonitrile (80:20 v/v) and was delivered at a flow rate of 1.0 mL/min. Samples were injected in the high performance liquid chromatographic (HPLC) system by an autosampler. The retention time was 4.2 ± 0.013 minutes.

The standard curves were linear over the concentration ranges of 10 to 1000 ng/mL, with a mean correlation coefficient of 0.9985. The lower limit of quantification (LLOQ) of ciprofloxacin in the serum was found to be 10 ng/mL. All the blood samples were analyzed within 1 week of collection. The precision and accuracy were investigated with quality control (QC) samples at concentrations of 10, 50, and 500 ng/mL. (Results are shown in Table 1.) The intra-day and inter-day coefficients of variation for 5 QC samples were satisfactory, with relative standard deviations (RSD) less than 10.87 %. The determined values deviated from the declared concentration with a relative error less than 10.03%.

PHARMACOKINETIC ANALYSIS

The following pharmacokinetic parameters were directly calculated by the standard noncompartmental analysis: (a) C_{max} and T_{max}; (b) $t_{1/2}$ was calculated as $t_{1/2}=(\ln 2)/K_{el}$, where K_{el} is the apparent elimination rate constant and K_{el} was calculated by using the software WinNonlin (Version 2.1) (Pharsight Corp, Mountain View, CA);[17] (c) area under the serum concentration-time curve (AUC_{0-12}), area under the first moment curve ($AUMC$), and mean residence time (MRT) were calculated from the measured levels, from time zero to the time of last quantifiable level, by the linear trapezoidal rule; (d) area under the serum concentration-time curve extrapolated to infinity ($AUC_{0-\alpha}$) was calculated according to the following formula: $AUC_{0-\alpha} = AUC_{0-t} + C_t/K_{el}$, where C_t is the last quantifiable serum level; and (e) the rate of absorption was evalu-

Table 4. *P*-values for Sources of Variations Obtained from Analysis of Variance (ANOVA)

Sources of Variations	AUC_{0-12}	$AUC_{0-\alpha}$	C_{max}	t_{max}	k_{el}	$t_{1/2}$	$C_{max}/AUC_{0-\alpha}$
Formulations	0.6899	0.8513	0.0921	1.000	0.3151	0.3272	0.5384
Period	0.4648	0.8273	0.0384	1.000	0.8618	0.8844	0.5984
Sequence	0.5327	0.4882	0.3404	0.495	0.7461	0.7461	0.3600
Subjects	0.0960	0.0530	0.0620	0.0912	0.0770	0.0790	0.0970

AUC_{0-12}=area under the serum concentration-time curve; $AUC_{0-\alpha}$=the area under the serum concentration-time curve extrapolated to infinity; C_{max}=peak plasma concentration; t_{max}=time to reach peak serum concentration; K_{el}=elimination rate constant; $t_{1/2}$=serum elimination half-life

ated by means of the ratio of $C_{max}/AUC_{0-\alpha}$. Pharmacokinetic parameters were calculated using Microsoft Excel (Version 2000) (Microsoft Corp, Redmond, WA) and WinNonlin (Version 2.1).

STATISTICAL ANALYSIS

Let y_{ijk} be the observed value of a pharmacokinetic parameter corresponding to the subject k in period j of group i. The following model is assumed for y_{ijk}:

$$y_{ijk}=\mu + S_{ik} + \Pi_j + \tau_{d[i,j]} + \lambda_{d[i,j-1]} + \varepsilon_{ijk}, \quad (1)$$

where μ is the general mean, S_{ik} is the random effect of subject k in group i, is the effect of period j, $\tau_{d[i,j]}$ is the effect of treatment administered in period j of group i, $\lambda_{d[i,j-1]}$ is the carryover (sequence) effect of the treatment administered in period j-1 of group i with λ [i,0]=0 and ε_{ijk} is the random error term. It is assumed that random terms S_{ik} and ε_{ijk} follow normal distribution with same mean 0 and variance σ^2 and σ^2_s, respectively. Carryover effect can be tested by comparing corresponding mean sum of squares with the between-subject mean sum of squares (σ^2_s), and period of treatment effects are tested by comparing corresponding mean squares with the within-subject mean squares ($\hat{\sigma}^2$).

In our analysis, the log-transformed value of the pharmacokinetic parameters AUC_{0-12}, $AUC_{0-\alpha}$, C_{max}, K_{el}, $t_{1/2}$, and $C_{max}/AUC_{0-\alpha}$ are used in Model 1 above. Model 1 can be fitted by using standard statistical software. We have used statistical software R (R Development Core Team. *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing, Vienna, Austria, 2005) for fitting the model and drawing inferences about the parameters.[18] Besides fitting the model, we also reported the approximate 90% confidence interval for the difference between two formulations only for the pharmacokinetic parameters AUC_{0-12}, $AUC_{0-\alpha}$, C_{max}, and $C_{max}/AUC_{0-\alpha}$.

RESULTS

The mean (± SD) serum concentration-time profile of the 2 formulations, shown in Figure 1, was similar and superimposable.

Central and dispersion measures for all pharmacokinetic parameters for both formulations are shown in Table 2. From this, the mean values of C_{max} were found to be 1.46 (± 0.032 standard deviations [SD]) μg/mL for the reference product and 1.49 (± 0.0845) μg/mL for the locally manufactured (test) product. For t_{max} (hr), the mean values were found to be similar for both the reference and local product and the value was 1.2 (0.273)

Table 5. Large Sample-Based 90% Confidence Intervals (CI) for Different Pharmacokinetic Parameters from Log-Transformed and Untransformed Data for Assessment of Bioequivalence

	Test (Quinox) /Reference (Ciprox)					
	Untransformed			Log Transformed		
Parameters	Mean Ratio (Test/Reference)	90% CI		Mean Ratio (Test/Reference)	90% CI	
AUC_{0-12} (hr · µg/mL)	103.25%	88.23%	120.84%	100.55%	97.99%	103.18%
$AUC_{0-\alpha}$ (hr · µg/mL)	98.35%	83.90%	115.30%	99.06%	96.47%	101.73%
C_{max} (µg/mL)	98.02%	95.26%	100.85%	101.81%	99.96%	103.69%
C_{max} /$AUC_{0-\alpha}$	122.78%	123.83%	124.89%	102.77%	99.13%	106.54%

AUC_{0-12}=area under the serum concentration-time curve; $AUC_{0-\alpha}$=the area under the serum concentration-time curve extrapolated to infinity; C_{max}= peak plasma concentration; CI=confidence interval

hr. The mean values of AUC_{0-12} were found to be 5.79 (± 0.67) µg.hr/mL for reference and 5.82 (± 0.38) µg.hr/mL for local product. AUC is important in determining the bioavailability and bioequivalence of a drug product. The values of AUC_{0-12} for all volunteers were found to be greater than 80% of $AUC_{0-\alpha}$. The mean $AUC_{0-\alpha}$ values were found to be 6.92 (± 0.92) µg/hr/mL and 6.858 (± 0.932) µg.hr/mL for the reference and locally manufactured product, respectively. Other pharmacokinetic parameters such as $t_{1/2,}$ $k_{el,}$ $AUMC_{0-12,}$ $AUMC_{0-\alpha}$, and MRT were also determined.

Table 3 shows that the change in $C_{max,}$ $AUC_{0-12,}$ and $AUC_{0-\alpha}$ was found to be insignificant (P>0.1).

Table 4 shows the analysis of variance (ANOVA) for Model 1. As it shows, after controlling the effects of period, sequence, and subject there is no significant difference between the 2 formulations for all the pharmacokinetic parameters we considered other than C_{max}. Period effects were found to be insignificant for all the parameters except C_{max}. The insignificant sequence effects indicate no carryover effect of the 2 formulations. Subject variations are found to be significant at a 10% level.

Table 5 shows the 90% confidence intervals of the ratios (test/reference) between the 2 formulations regarding AUC_{0-12}, $AUC_{0-\alpha}$, C_{max} and $C_{max}/AUC_{0-\alpha}$.

DISCUSSION

Assessment of bioequivalence of local 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 drugs 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.[19]

The aim of this study was to compare the bioavailability of 2 formulations of ciprofloxacin 250-mg tablets, a locally manufactured (test) formulation, Quinox, and a reference formulation, Ciproxin. The study revealed that at a 90% confidence interval (Table 5) AUC_{0-12}, $AUC_{0-\alpha}$, and C_{max} were found to be 97.99% and 103.18%; 96.47% and 101.73%; and 99.96% and 103.69%, respectively, from log-transformed data, and all values are within the bioequivalence accepted range of 80%-125%.[20-21] Moreover, a further evaluation of the rate of absorption was performed by

analyzing the $C_{max}/AUC_{0-\alpha}$, since this parameter has been proposed to better reflect the absorption rate.[22] The 90% confidence intervals for this parameter also indicated bioequivalence.

In conclusion, the two formulations can be considered bioequivalent in regard to the extent and rate of absorption and therefore interchangeable.

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REFERENCES

1. Bauernfeind A, Petermüller C. In vitro activity of ciprofloxacin, norfloxacin and nalidixic acid. *Eur J Clin Microbiol*. 1983;2:111-115.
2. Chin NX, Neu HC. Ciprofloxacin, a quinolone carboxylic acid compound active against aerobic and anaerobic bacteria. *Antimicrob Agents Chemother.* 1984;25:319-326.
3. Goodman LJ, Fliegelman RM, Trenholme GM, Kaplan RL. Comparative in vitro activity of ciprofloxacin against *Campylobacter* spp. and other bacterial enteric pathogens. *Antimicrob Agents Chemother.* 1984;25:504-506.
4. Van Caekenberghe DL, Pattyn SR. In vitro activity of ciprofloxacin compared with those of other new fluorinated piperazinyl-substituted quinoline derivatives. *Antimicrob Agents Chemother.* 1984;25:518-521.
5. Borner K, Lode H, Elvers A. Determination of apalcillin and its metabolites in human body fluids by high-pressure liquid chromatography. *Antimicrob Agents Chemother.* 1982;22:949-953.
6. Crump B, Wise R, Dent J. Pharmacokinetics and tissue penetration of ciprofloxacin. *Antimicro Agents Chemother.* 1983;24:784-786.
7. Keller I, Lubasch A, Rau M. Comparative pharmacokinetics of ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin, and trovafloxacin after a single in healthy volunteers [abstract 30]. 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, Sep 26-29, 1999.
8. Healy D, Brodbeck M, Clendening C. Ciprofloxacin absorption is impaired in patients given enteral feedings orally and via gastrostomy and jejunostomy tubes. *Antimicrob Agents Chemother.* 1996;40:6-10.
9. Mueller B, Brierton G, Abel S. Effect of enteral feeding with ensure on the bioavailabilities of ofloxacin and ciprofloxacin. *Antimicrob Agents Chemother.* 1994; 38:2101-2105.
10. Noer B, Angaran D. The effect of enteral feedings on ciprofloxacin pharmacokinetics. *Pharmacotherapy*. 1990;10:254.
11. Jones B, Kenward MG. *Design and Analysis of Cross-Over Trials*. 2nd ed. 2003. Boca Raton, FL: Chapman & Hall/CRC.
12. Food and Drug Administration. *Tequin Tablets (Gatifloxacin), Tequin Injection (Gatifloxacin)*. Washington, DC: Department of Health and Human Services; 1999.
13. Hutchinson TA, Shahan DR, Anderson ML. *Drugdex System*. Englewood, CO: Micromedex; 2001.
14. Panacea Biotec Ltd. MYGAT (Gatifloxacin infusion– 2 mg/mL). New Delhi, India; 2003.
15. Nakashima M, Uematsu T, Kosuge K. Single and multiple-dose pharmacokinetics of AM-1155, a new 6-fluoro-8-methoxy quinolone, in humans. *Antimicrob Agents Chemother.* 1995;39:2635-2640.
16. Liang H, Kays M, Sowinski K. Separation of levofloxacin, ciprofloxacin, gatifloxacin, moxifloxacin, trovafloxacin and cinoxacin by high performance liquid chromatography: application to levofloxacin determination in human plasma. *J Chromatogr.* 2002;772:53-63.
17. Gibaldi M, Perrier D. *Pharmacokinetics*. 2nd ed. New York; Dekker, 1982:433-434.
18. R Development Core Team. *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing, Vienna, Austria, 2005. Available at: http://www.r-project.org. Accessed April 25, 2007.
19. Food and Drug Administration. *Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations*. Rockville, Md; 2002.
20. Hauschke D, Steinijans VW, Diletti EA. Distribution-free procedure for the statistical analysis of bioequivalence studies. *Int J Clin Pharmacol Ther Toxicol.* 1990;28:72-78.
21. Food and Drug Administration. *Guidance for Industry: Bioanalytical Method Validation*. Rockville, Md, 2001.
22. Endrenyl L, Fritsch S, Yan W. C_{max}/AUC is a clearer measure then C_{max} for absorption rates in investigations of bioequivalence. *Int J Clin Pharmacol Ther*. 1991;29:394-399.