COMPARATIVE BIOEQUIVALENCE AND PHARMACOKINETICS OF CIPROFLOXACIN IN HEALTHY MALE SUBJECTS

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ABSTRACT
Pharmacokinetics and bioequivalence studies of two ciprofloxacin tablet brands *(trial batch of ciprofloxacin(Test) & Reference)* were conducted in 14 healthy male volunteers after oral administration. Each brand (test and reference) consisted of 500 mg of ciprofloxacin. The drug was analyzed in plasma samples with a microbiological assay using *Streptococcus faecalis* as test organism. The elimination half-life of 3.00 ± 0.21 and 3.28±0.11 h was calculated for both brands. The peak plasma concentrations of (3.59±0.26 ug/mL) and (3.34±1.20 ug/mL) was attained in about 1.48±0.11 hour and 1.47±0.05 for both Test and Reference ciprofloxacin respectively. The mean ± SE values for total area under the curve (AUC O-∞) were 26.15 ±1.35, and 24.95±0.93 hmg/1 for both test and reference tablets respectively. The mean ± SE values of clearance were 24.83±1.63 and 24.73±1.11 1/h for both formulations respectively. The ratio of elimination rate constant Kel [l/h] was 1.14 percent difference between the test and reference tablets and likewise, half-life (t1/2β) expressed in hours showed the ratio of 0.91 percent. This study indicated that all the pharmacokinetic and bioequivalence parameters for both ciprofloxacin formulations are statistically non-significant, hence both formulations are bioequivalent.

Keywords: Pharmacokinetics, bioequivalence, bioassay of ciprofloxacin test and reference.

INTRODUCTION

Post oral solid dosage form, tablets and capsules are prescribed most widely through out the world and are very effective means of providing drugs to the patients. A basic assumption is that when an oral solid dosage formulation is used by a patient, the drug from the formulation is released, dissolved, and is absorbed promptly and consistently. Drug product quality is needed for this to be a valid assumption, and bioavailability and bioequivalence become important consideration in this context. The drug product quality judgment through product selection among available brands of drug products, involves informed selection of drug products available from different manufacturers and substitution of one product for another, whether it involves an innovator-to-generic, generic-to-innovator, or generic-to-generic change. Even lot-to-lot consistency with in one manufacturer's product can influence product quality considerations. Infectious diseases remain a constant threat to human and animal's health throughout the world. The problems are more prevalent in developing countries because of poor hygienic conditions and lack of education. Prevention of infectious diseases is a consistent endeavor to enhance the quality of health and life. Antibiotics play a significant role to check infectious diseases and are one of the extensively used drugs throughout the world but more so in. the developing countries. Development of antibiotic resistance in bacteria continuously incites the scientists to modify the existing drugs or to develop newer remedies, which has resulted in a constant flow of the products in the market.

Absorption and disposition kinetics studies are important to compare the rate and extent of systemic absorption of a drug manufactured by different manufacturers. Variations in excepients and manufacturing process can affect the disintegration and dissolution rate of tablets given through the oral route. Since, local population shows distinct nutritional habits and thrives in particular environments; therefore, there is a likelihood of differences in bio-disposition of Ciprofloxacin. Seth *et al.* (1995) recorded disposition kinetics of Ciprofloxacin and suggested the need to be cautious while treating patients with renal problems and proposed to use lower doses in Indian patients to achieve desirable results. Therefore, it is always advisable to perform disposition kinetics and renal handling studies in the target population and environments.

In view of the importance of the process of drug absorption as a direct determinant of drug efficacy and safety, and since bioavailability determination has not yet been adopted by official compendia as an efficacy indicating test, in Pakistan the present study has been conducted, to study the bioequivalence, relative bioavailability and disposition kinetic of trial batch of ciprofloxacin tablets with marketing imaging Ciproxin in healthy male volunteers.

MATERIALS AND METHODS

The study was performed in accordance with Good Clinical Practice guidelines regulated by FDA. Volunteers enrolled for this study were apprised in details about all

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aspects of the study in easy understandable language and terminologies. Those who agreed voluntarily were registered for further studies. More than 20 years of age, healthy non-smoker male subjects with homogenous age and body weight were enrolled for the study.

Drug information

Test drug: Ciprofloxacin 500 mg Tablets
B. No. Trial
Mfg. November 2002.
Exp. Use within five years.
For Experimental use only.
Reference drug:
Ciprofloxacin 500 mg
Batch No. 204-A
Mfg. Date 04-2000
Exp. Date 03-2005

After an overnight fast, subjects were randomized to receive a single dose of 500-mg Ciprofloxacin standard or test tablet with 240 ml of water. The volunteers were randomly divided into 2 groups of 14 subjects in each group. A replicated-crossover design for the bio-equivalence/Pharmacokinetics studies with two formulations was used. A seven day washout period was provided between dosing of test and reference tablets.

Sample collection and handling

Before drug administration, a control/blank venous blood sample was collected from each volunteer through a sterile venous Branula 18G (J Vasocan® Braniile®, B. Braun Melsungen AG Malaya). Following drug administration, serial blood samples were drawn at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 8.0 and 12 hours in heparinized centrifuge tubes specially prepared for this purpose. These tubes were chilled and centrifuged under refrigeration for 15 minutes at approximately 2000 rpm. The plasma was separated and stored at <-20 °C until analysis.

Demographic and clinical data

The age, weight, height, blood pressure (Systolic/ Diastolic), temperature and body surface area (BSA) of each volunteer was recorded. The Body surface area was calculated with the following formula as used by Hue *el al.* (2003): BSA = (W 0.425 x H 0.725) x 0.007184 Where, 'W stands for weight and 'H' stands for height.

The clinical data including Glucose, Blood urea, Serum Creatinine, Cholesterol, Bilirubin total, SGPT, SCOT, and CPK of all the volunteers was also determined to check the health status of individuals under study.

Microbiological agar diffusion method

Ciprofloxacin concentration in the plasma samples was calculated with bioassay technique. This method has the advantage to detect the microbiologically active moieties of drug in biological samples, hence, considered a valid method for assay of most of antibiotics.

For assay of Ciprofloxacin, the Disc Agar Diffusion Method was standardized and validated for accuracy and precision by using *Streptococcus faecalis* as test organism according to the method of Arret *et al.* (1971). The samples were run at least in duplicate. The zones of inhibition were measured with Zone Reader and the concentrations of Ciprofloxacin and its metabolites in the plasma samples were calculated by sample zones with standard curve regression equation (fig. 1). The standards were run with each analysis. The curve shows the value of regression coefficient ($R^2 = 0.9918$).

Statistical calculations

a) Pharmacokinetics parameters

For computation and analysis of Ciprofloxacin in plasma, the computer software programme "Microsoft Excel 7.0" was used. The plasma concentration of Ciprofloxacin and its metabolites from each volunteer was plotted on linear plot against time. The plasma concentration versus time data was used to calculate pharmacokinetics and bioavailability parameters with the help of a PC-Computer Program, APO, MWPHARM version 3.02 a MED1WARE product Holland. Calculations also included area under curve (AUC) from time t to ∞ (infinity) calculated with poly-exponential and trapezoidal methods.

b) Bioequivalence/Bioavailability parameters

(Bioavailability parameters such as C_{max}, T_{max} and AUC were determined) Bioequivalence comparisons were performed using Student t-test: paired two samples for means. For the ratios of the mean bioavailability parameters, models were used to construct 90% confidence intervals for test versus reference tablet.

RESULTS

The demographic data of individuals who pariprofloxacin Test and Reference formulations is represented in fig. 2. This is evident from the data that volunteers in both study groups are homogenous in terms of mean ± SE age (22.4 & 21.1 years), weight (58.7 & 65.9 kg), height (167.5 & 168.2 cm), and body surface area (BSA) (1.7 & 1.8 m^2). Composite plasma drug concentration-versus-time profiles collected from study individuals following oral administration of Ciprofloxacin are presented in fig. 3. The mean plasma concentration (ug/ml) of ciprofloxacin test and reference in 14 healthy male subjects were presented in table 1. The peak plasma concentrations of (3.59±0.21 ug/mL) and (3.34±0.10 ug/mL) was attained in about 1.48 ± 0.11 hour and 1.47±0.05 for both Test and Reference ciprofloxacin respectively. The mean ± SE

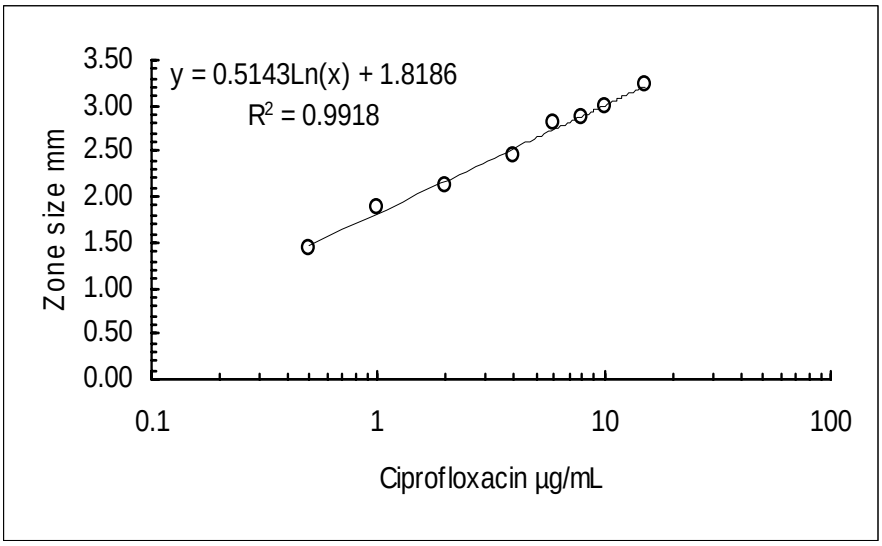
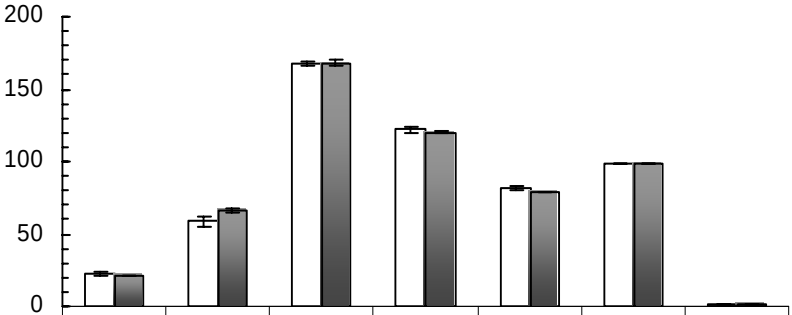


Fig. 1: Standard curve of Ciprofloxacin in plasma.



	Age Years	Weight Kg	Height Cm	Syst mmHg	Diast mmHg	Temp oF	BSA m2
Test	22.4	58.7	167.5	122.1	81.4	98.4	1.7
reference	21.1	65.9	168.2	120.3	79.0	98.2	1.8

Fig. 2: Showing mean values for age, body weight, height, blood pressure, body temperature and body surface area of all healthy male volunteers used for the study of bioequivalence of Ciprofloxacin.

values for total area under the curve (AUC O-∞) were 26.15 ±1.35 and 24.95 ±0.93 hmg/1 for both test and reference tablets respectively. Mean pharmacokinetic data for both Ciprofloxacin preparations are presented in table 2. The mean ± SE values of clearance were 24.83±1.63 and 24.73±1.11 1/h for both formulations respectively. The ratio of elimination rate constant Kel [l/h] was 1.14 percent difference between the test and reference tablets and likewise, half-life (t1/2β) expressed in hours showed the ratio of 0.91 percent. This is evident from results reflected in table 4 that all the pharmacokinetic parameters for both ciprofloxacin formulations are statistically non-significant.

The comparison of mean ± SE "bioequivalence" parameters of Ciprofloxacin Test and Reference formulations have been presented in table 3, while table 4 presents pharmacokinetics and bioavailability parameters comparison for both Test and Reference ciprofloxacin. Statistical appraisal of the bioequivalence between the Unavailability parameters of two formulations did not reveal any significant differences.

DISCUSSION

Ciprofloxacin has become an extremely popular quinolone antimicrobial agent for use in human (Owens *et al*, 1997), dogs, cats, pigs, cattle and poultry (Brown 1996). The availability of this important drug in various brands in Pakistan raises the need to conduct pharmacokinetic and bioequivalence studies for various formulations in target population. The present study was undertaken to investigate the disposition and bio-

Table 1: Plasma concentration (µg/mL) of Ciprofloxacin trial tablet (Test) and 500 mg reference tablet in 14 healthy male subjects.

Time Hours	0.5	1	1.5	2	2.5	3	4	5	6	8	12
Test Mean ± SE	2.24 ± 0.12	3.51 ± 0.21	3.47 ± 0.21	3.38 ± 0.15	3.04 ± 0.11	2.67 ± 0.10	2.24 ± 0.07	1.75 ± 0.08	1.56 ± 0.08	0.93 ± 0.06	0.39 ± 0.05
Reference Mean ± SE	2.03 ± 0.12	3.11 ± 0.12	3.33 ± 0.12	3.22 ± 0.07	3.03 ± 0.05	2.56 ± 0.06	2.17 ± 0.04	1.65 ± 0.04	1.48 ± 0.03	0.93 ± 0.04	0.39 ± 0.02
Ratio T/R	1.11	1.13	1.04	1.05	1.00	1.04	1.03	1.06	1.05	1.00	1.00

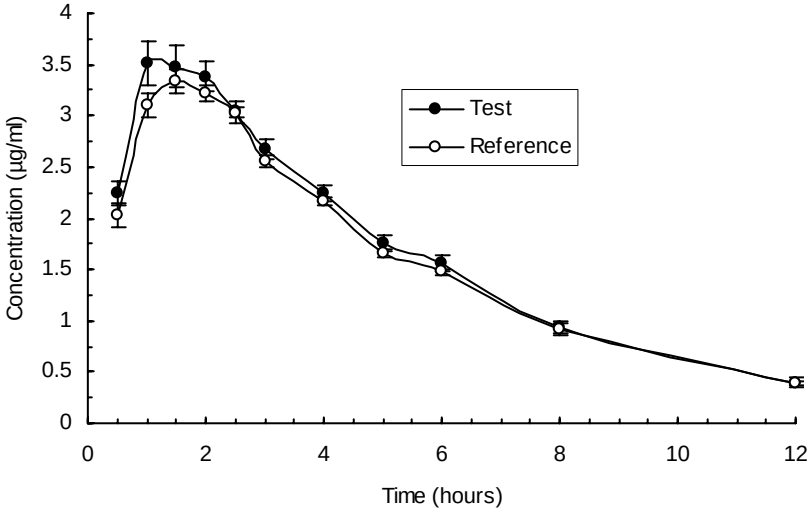


Fig. 3: Showing mean ± SE values of the plasma concentration of Ciprofloxacin after 500 mg oral dose of Test and Reference Tablets given to 14 volunteers on both ordinary graph scale.

equivalence of two orally administered formulations of Ciprofloxacin.

There is controversy in literature regarding selection of suitable compartmental model to best describe the disposition of Ciprofloxacin. The kinetics of Ciprofloxacin in domestic animals was mainly described with two compartment open model, as reported in chickens (Anadon *et al.,* 1995), horses (Garcia Ovando *et al,* 1996), pigs and bovines (Nouws *et al.,* 1988) and ponies (Dowling *et al.,* 1995). However, Pharmacokinetics behavior of orally administered Ciprofloxacin has been described in terms of three compartmental model in volunteers (Hoftken *et al.*, 1985), in patients subjected to lung surgery for bronchial epithelioma (Breilh *et al.,* 2001) and by two compartmental model in healthy male volunteers (Abdallah *et al.,* 2002). Pharmacokinetics of Ciprofloxacin has also been studied by using non compartmental model in healthy volunteers (Maya *et al.,* 2003). In the present study, pharmacokinetics parameters determined by two compartmental open model and non compartment analysis did not reveal any significant differences. However, a decision about two or three compartmental model seems to depend on the frequency of blood sampling during the initial phase of experiments. In case of three compartmental models, frequent sampling within first hour makes it possible to distinguish between two distribution phases (Xia *et al.,* 1983).

The half life of a drug is a derived parameter that changes as a function of both clearance and volume of distribution (Booth and McDonald, 1998). In present study the mean values of $t_{1/2}$ B of test and reference drugs was 3.00, and 3.28 h respectively (table 4). These values are comparable to 4.02 ±0.89 h (Breilh *et al.,* 2001), 4.2 h (Catchpole *et al*., 1994), and 5.37±0.82 h (Lubasch *et al.,* 2000) in healthy volunteers. The mean + SE values of clearance measured in 1/h were 24.8 and 24.73 for both brands of ciprofloxacin respectively (table 4). These values are also similar to 29.1±17.5 1/h in patients after oral administration of ciprofloxacin (Garrelts *et al.,* 1996).

Table 2: Mean ± SE bioequivalence parameters of ciprofloxacin trial tablet (Test) and reference tablet in 14 healthy male subjects.

Bioequivalence parameters	Units	Test Mean ± SE	Reference Mean ± SE	Ratio T/R	% Difference
AUC	[h.mg/l]	21.20 ± 1.36	20.60 ± 0.71	1.03	2.94
$Ln_{(AUC)}$	h.mg/l]	3.03 ± 0.07	3.02 ± 0.04	1.00	0.39
T_{max}	[h]	1.48 ± 1.11	1.47 ± 0.05	1.01	0.90
C_{max}	[mg/L]	3.59 ± 0.21	3.34 ± 0.10	1.07	7.35
$Ln(C_{max})$	[mg/L]	1.26 ± 0.06	1.20 ± 0.03	1.05	4.67

Table 3: Critical Bioequivalence metrics comparison of bioavailability (Bioequivalence) of Ciprofloxacin trial tablet (Test) and reference tablet in 14 healthy male subjects

Bioequivalence parameters	Units	Test	Reference	Test % of Reference	90 % CI Limits	
					Lower	Upper
AUC*	[h.mg/l]	21.20	20.60	102.91	86.6	117.7
$Ln_{(AUC)}$*	h.mg/l]	3.03	3.02	100.33	95.0	105.2
T_{max}*	[h]	1.48	1.47	100.68	86.3	113.4
C_{max}*	[mg/L]	3.59	3.34	107.49	92.7	121.6
$Ln(C_{max})$*	[mg/L]	1.26	1.20	105.00	92.3	117.2

*Critical Bioequivalence metrics that should not differ beyond 80-125 percent.

Bioequivalence is a comparison of the Bioavailability of two or more drug products. The two products or formulations containing the same active ingredient are bioequivalent if their rates and extents of absorption are same. For bioequivalence studies, C_{max}, T_{max} and AUC are commonly used parameters (tables 2 and 3). After oral administration of ciprofloxacin, the mean peak plasma concentrations (C_{max}) of 3.95±0.34 ug/mL and 3.34 ± 1.20 ug/mL were attained in about (3.59 ± 0.26 ug/mL) and (3.34 ±1.20 ug/mL) was attained in about 1.48±0.11 hour and 1.47±0.05 for both Test and Reference ciprofloxacin respectively (fig. 3). These values are comparable to the literature values of 3.9±1.7 mg/L (Catchpole *et al.*, 1994) and 2.9 ug/ml (Lebel, 1998) after a single 500 mg oral dose. In present study the mean±SE values for area under the curve (AUC O-∞) were 26.15±1.35, and 24.95±0.93 hmg/1 for both test and reference tablets Ciprofloxaein formulations respectively. This parameter is similar to the reported values of 20.7±16.6 ug.h/ml (Garrelts *et al.*, 1996) and greater than 12.11 mg. h/l (Escobar and Hoyo, 2003).

It has been reported that the time at which plasma or biological fluid concentrations of antibiotic exceed minimum inhibitory concentration (MIC) is highly correlated with success of therapy for antibacterial agents exhibiting time-dependent activity (Rao *et al.*, 2002). Previous studies suggest that fluoroquinolones kill bacteria in a concentration-dependent manner and area under inhibitory curve (AUIC) calculated by AUC/M1C is highly correlated with the outcome of successful treatment (Drusano *et al.*, 1993, Aliabadi and Lees, 1997). For effective eradication of bacteria and good clinical therapy, it has been suggested that an AUIC > 100 is required for gram-negative bacteria and > 30 is needed for gram-positive organisms (Nightingale *et al.*, 2000; Walker, 2000). Although MIC values of ciprofloxacin for many pathogens of genus *Pasturella, Escherichia, Haemophilus, Moraexella*, and *Salmonella* are reported to be in the range of .0.01-0.06 ug/ml (Prescott and Yielding, 1990; Bottner e*t al.*, 1995). On the basis of MIC reported for highly sensitive pathogens (0.01-0.06 ug/ml) and AUC (21.20±1.36, and 20.60±0.71 h.mg/L) determined in the present study, AUIC would be much greater than 100.

In present study the critical bioequivalence parameters included AUC, T_{max} and C_{max} of both test and reference ciprofloxacin are within the range of 80 to 125% (table 3) this study concludes that the bioequivalence metrics between the Bioavailability parameters of both ciprofloxacin formulations did not show significant differences; hence both test and reference formulations are bioequivalent.

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Table 4: Pharmacokinetics/Bioavailability parameters of Ciprofloxacin trial tablet (Test) and reference tablet in 14 healthy male subjects.

Kinetic Parameters	AUC inf	Ln (AUC inf)	AUC polyexponential (t= 12)	AUC trapezoidal rule (t= 12)	(AUCTail)	Ln (AUCTail)	AUCxtr %	Clearance (CL) [l/h]	Half-life phase 1 [h]	Half-life phase 2 [h]	Elimination rate constant [1/h]	Mean Residence Time (MRT) [h]	Absorption rate constant (ka) [1/h]	Absorption half-life [h]
Test Mean ± SE	26.15 ± 1.35	3.25 ± 0.05	19.67 ± 1.03	19.65 ± 1.04	4.95 ± 0.14	1.59 ± 0.03	19.55 ± 1.13	24.83 ± 1.63	0.33 ± 0.06	3.00 ± 0.21	0.25 ± 0.02	5.19 ± 0.18	1.42 ± 0.26	0.77 ± 0.15
Reference Mean ± SE	24.95 ± 0.93	3.21 ± 0.03	19.12 ± 0.56	18.90 ± 0.57	4.35 ± 0.02	1.47 ± 0.01	17.64 ± 0.57	24.73 ± 1.11	0.47 ± 0.03	3.28 ± 0.11	0.21 ± 0.01	5.39 ± 0.09	1.13 ± 0.18	0.81 ± 0.13
Ratio T/R	1.05	1.01	1.03	1.04	1.14	1.08	1.11	1.00	0.71	0.91	1.14	0.96	1.25	0.95

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