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Effect of piperine pre-conditioning on pharmacokinetics of marbofloxacin following subcutaneous administration in rats

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Abstract

The present study was conducted to evaluate the pharmacokinetics of marbofloxacin after single subcutaneous administration (5 mg/kg) in piperine pre-treated (10 mg/kg PO for 5 days) and normal rats. Plasma concentrations of the marbofloxacin were determined by a High Performance Liquid Chromatography. Following single dose subcutaneous administration of marbofloxacin at the dose rate of 5 mg/kg in normal rats, the plasma drug concentration ≥ 0.04 $\mu\text{g/ml}$ was detected up to 24 h, while plasma drug concentration ≥ 0.03 $\mu\text{g/ml}$ was detected up to 24 h in piperine pre-treated rats. After subcutaneous administration of marbofloxacin in piperine pre-treated and normal rats, absorption half-life ($t_{1/2Ka}$), mean apparent volume of distribution ($V_{d(\text{area})}$), area under plasma drug concentration-time curve ($\text{AUC}_{(0-\infty)}$) and area under first moment curve (AUMC) were 0.29 and 0.13 h; 6.80 and 4.79 L/kg; 8.68 and 9.35 $\mu\text{g.h/mL}$; 46.57 and 51.31 $\mu\text{g.h}^2/\text{mL}$, respectively. Elimination half-life ($t_{1/2\beta}$) and total body clearance (Cl_B) were 5.49 and 6.40 h; 0.60 and 0.52 L/h/kg, in piperine pre-treated and normal rats, respectively. The results showed that oral pre-treatment of piperine did not alter the pharmacokinetics of marbofloxacin after subcutaneous administration in rats.

Keywords: Piperine pre-conditioning, pharmacokinetics, marbofloxacin, subcutaneous administration

Introduction

Marbofloxacin is a fluorinated quinolone which is developed for exclusive use in Veterinary medicine [1]. It has bactericidal action by targeting the bacterial DNA topoisomerases II (gyrase) and IV, which are responsible for supercoiling of DNA around RNA core to provide a suitable spatial arrangement of DNA within the bacterial cell [2]. Marbofloxacin is having broad spectrum of antimicrobial activity against Gram-negative, Gram-positive bacteria and *mycoplasma* spp. [3, 4]. It has also shown a significant post antibiotic effect (PAE) for both Gram-positive and Gram-negative bacteria and it can kill bacteria during both stationary and growth phase of bacterial multiplication [5]. It differs from other fluoroquinolones by an oxadiazine ring, which may provide some pharmacokinetic advantages like larger volume of distribution, optimum AUC and C_{max} make it a potentially useful drug for the treatment of genital tract, respiratory tract, gastrointestinal tract, skin and soft tissue infections in domestic animals and birds [6-8]. Pharmacokinetics of newer fluoroquinolone, long acting moxifloxacin and levofloxacin were also studied in animal [9-12] as well as safety of morbofloxacin and levofloxacin was evaluated in normal and piperine pretreated rats [13-18]. Pharmacokinetic interaction is result of alterations of drug absorption, distribution, metabolism and elimination in combination therapy.

In current scenario, herbal medicines with newer fluoroquinolone antimicrobials are studied frequently and their clinically relevant interactions are increasingly attracting researchers for the drug resistance and safety impact [19, 20]. Many herbal compounds like quercetin, genistein, naringin, sinomenine, piperine and glycyrrhizin have demonstrated capability to enhance the bioavailability of other drugs [21, 22]. Furthermore, many of the dietary supplements and phytochemicals can modulate the activity of P-gp and drug metabolizing enzymes. It is needed to give more attention towards potential drug interactions due to dietary supplements. Among dietary products, black pepper and long pepper are one of the most common spices used by Indian people. Piperine, a major active component of black pepper and long pepper, has been reported to enhance bioavailability and alters the pharmacokinetics of the various antimicrobial agents like beta-lactams, ciprofloxacin, oxytetracycline, norfloxacin and ampicillin [23]. Piperine suppresses hepatic metabolizing enzymes (CYP3A4) [24], is prompting changes in the drug transporter P-glycoprotein also, hence increasing the maximum absorption

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concentration (C_{max}) and area under the plasma concentration-time curve (AUC) of celirolol and midazolam in rats which may increase bio-enhancing property [25]. Data are not available related to the effect of piperine on pharmacokinetics of marbofloxacin following subcutaneous administration in rats. With this background, the present study was planned to evaluate the influence of piperine pre-treatment on the disposition kinetics of marbofloxacin and to assess its impact on dosage regimen in rats.

Materials and methods

Experimental animals: The present study was conducted in 12 male albino rats. The rats were obtained from Cadila Pharmaceutical Pvt. Ltd., Dholka, Ahmedabad, Gujarat. They were maintained as per the guideline of the Committee for the Purpose of Control and Supervision of Experiments on Animals, 2003. The experimental protocol including number of rats and various procedures involved was approved by the Institutional Animal Ethics Committee (Protocol No. JAU/JVC/IAEC/SA/08/2016).

Animal husbandry: The rats were housed in standard polypropylene cages with stainless steel top grill which were changed at least thrice in a week. Animals were housed in the cool environmental temperature (23 to 26 °C) with relative humidity ranged between 40 to 55%. Twelve-hour dark and light cycle was maintained in animal room. Rat pelleted feed (VRK biological system, Vadodara) containing 18% protein was provided *ad libitum* to animals throughout the study period.

Drug and Chemicals: Marbofloxacin technical grade powder was obtained from Sigma Aldrich, USA. Marbofloxacin injection 100mg/ml, 30 ml vial (Intas Pharmaceuticals Ltd., Ahmedabad, India) was used in the study. Piperine was procured from Sigma Aldrich, Bangalore, India. Water, acetonitrile, ortho-phosphoric acid, perchloric acid and formic acid of HPLC grade were purchased from S. D. Fine Chem. Ltd., and Merck India Ltd., Mumbai.

Experimental design: Twelve albino rats were randomly divided based on body weight in two groups (6 animals in each group). Rats of group I were treated with single subcutaneous dose of marbofloxacin (5 mg/kg) and group II were treated with piperine (10 mg/kg, PO) for 5 days followed by single subcutaneous dose of marbofloxacin (5

mg/kg).

Collection of samples: Blood samples (approximately, 250 μ l) were collected from retro orbital plexus with help of glass capillary in test tubes containing heparin under light anesthesia at 0 minute (before drug administration), 5 (0.083 h), 15 (0.25 h) and 30 (0.5 h) minutes and at 1, 2, 4, 8, 12 and 24 h. Plasma was separated by centrifugation (Eppendorf 5430 R, Germany) from each blood sample at 14000 revolutions per minute (rpm) for 10 minutes at 4 °C. All plasma samples were transferred to cryo-vials (2 ml capacity) and then stored at -20 °C until assayed for marbofloxacin concentration using HPLC [26].

Marbofloxacin Assay: Plasma concentrations of marbofloxacin were determined by High Performance Liquid Chromatography (HPLC) system with UV detector.

Apparatus: The high-performance liquid chromatography apparatus of Shimadzu (Japan)-LC-2010 CHT comprising quaternary gradient delivery pump (LC-2010) and UV detector were used for assay. Chromatographic separation was performed using reverse phase C_{18} column (Thermo, ODS; 250 \times 4 mm ID, 5 micron) at 30 °C. The HPLC data integration was performed using LC solution version 1.25 (Shimadzu), japan.

Chromatographic condition: The mobile phase was a mixture of 10 mM formic acid (80%) and acetonitrile (20%) adjusted to pH 5.1 with ortho-phosphoric acid. Mobile phase was filtered by 0.45 μ size filter (Millipore India Pvt., Ltd., Bangalore) and degassed by ultra-sonication. The mobile phase was pumped into column at a flow rate of 0.75 mL/min at 30 °C temperature. The effluent was monitored at 295 nm wavelength.

Extraction procedure: The plasma samples were analysed for marbofloxacin concentration using a slight modification of method described by Carpenter *et al.* (2006) [27]. Briefly, 100 μ l of 0.8 M perchloric acid was added to 100 μ l of plasma. After mixing for 2-3 min, the samples were centrifuged at 12000 rpm for 10 min. The clean supernant was collected in to HPLC vial with insert. 20 μ l of supernant was injected in to HPLC system for analysis using auto sampler. The retention time of the marbofloxacin was 7.2 ± 0.2 minutes. Chromatograph of the drug is shown in figure 1.

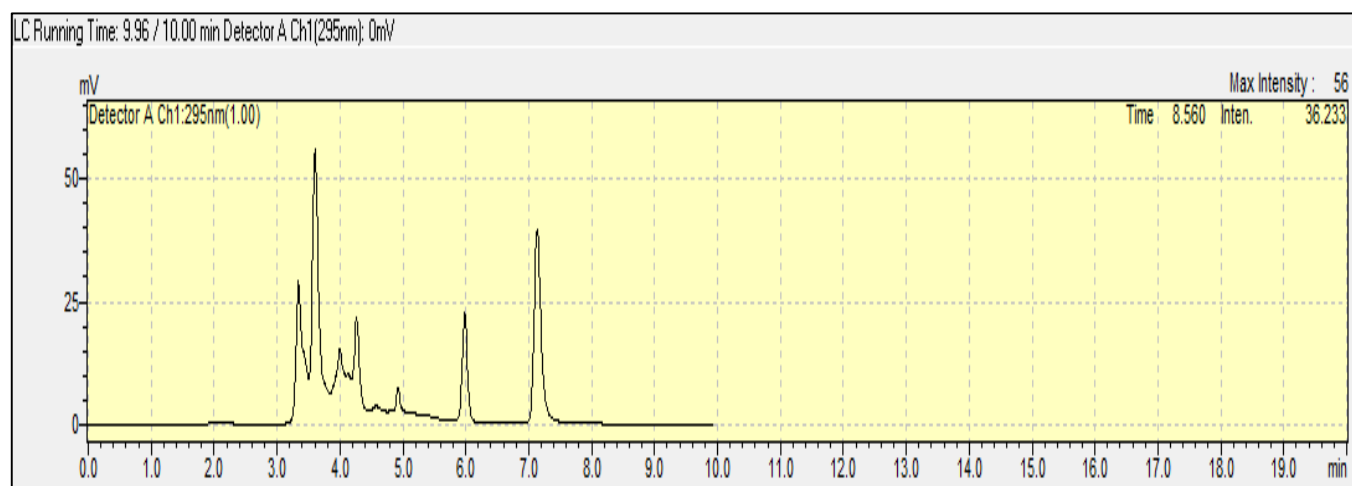


Fig 1: Chromatograph of marbofloxacin (Last peak) 5 μ g/mL standard in plasma of rat

Preparation of standard curve: For standardization, initially stock solution of marbofloxacin was prepared by adding 1 mg pure marbofloxacin powder in 1 ml HPLC water. The known standard solutions of marbofloxacin to construct the calibration graph were prepared by serial dilution of a stock standard solution (1000 µg/mL) in water. Stock solution was used to prepare standard marbofloxacin concentration of 20, 10, 5, 2.5, 1.25, 0.625, 0.312, 0.156, 0.078 and 0.039, µg/mL in drug free plasma rats. Each standard prepared in plasma was then treated by procedure as described earlier for extraction of marbofloxacin from plasma. Twenty microliters of each standard prepared in plasma was injected through auto sampler in HPLC [28].

Pharmacokinetic analysis: The plasma drug concentrations measured at various time intervals following subcutaneous administration of marbofloxacin given at the dose rate of 5

mg/kg body weight were employed for the calculation of various pharmacokinetic parameters like absorption half-life, distribution half-life, area under curve, area under under moment curve, elimination half-life, apparent volume of distribution, total body clearance, mean residence time and mean absorption time *etc* of the drug [29, 30].

Statistical analysis: All data obtained are presented as mean ± standard error (SE). Data were analyzed statistically by student's *t-test* to observe difference between treatment groups.

Results

Plasma drug concentrations following single dose subcutaneous administration of the marbofloxacin alone and with piperine pre-conditioning (10 mg/kg, PO for 5 day) in rats are presented in table 1 and depicted in figure 2.

Table 1: Comparison of plasma marbofloxacin concentrations (µg/mL) after subcutaneous administration (5 mg/kg) alone and with piperine pre-conditioning (10 mg/kg orally for 5 days) in rats (n = 6)

Blood collection time (h)	Marbofloxacin alone (Group I)	Piperine pre-conditioning + Marbofloxacin (Group II)
0.08333	0.94 ± 0.12	0.89 ± 0.22
0.25	2.05 ± 0.24	2.29 ± 0.19
0.5	2.89 ± 0.75	3.58 ± 0.28
1	2.21 ± 0.48	2.20 ± 0.21
2	1.46 ± 0.24	1.23 ± 0.20
4	0.59 ± 0.08	0.50 ± 0.06
8	0.22 ± 0.06	0.22 ± 0.02
12	0.12 ± 0.01	0.08 ± 0.02
24	0.04 ± 0.00	0.03 ± 0.01

The mean plasma concentrations of marbofloxacin with piperine were found to be higher at 0.08333, 0.25 and 0.5 hr (Figure 10), while they were found to be lower at 1, 2, 4, 8, 12, and 24 hr as compared to those after the administration of marbofloxacin alone. The plasma concentrations of marbofloxacin at 24 h alone and alone with piperine were ≥ 0.04 ± 0.00 and ≥ 0.03 ± 0.01 µg/mL, respectively. Further the mean values of peak plasma drug concentration (C_{max}) of marbofloxacin was found to be higher when administered

with piperine. However, Plasma drug concentrations of the marbofloxacin at different time internals in piperine pre-conditioning in rats were not significantly differ from those observed after single subcutaneous administration of marbofloxacin alone. The plasma levels of long acting moxifloxacin at different time intervals were comparable to previous studies in sheep [11]. Hiwale *et al.* (2002) [23] reported that piperine treatment did not altered the plasma levels at cefotaxime following IP administration in rats.

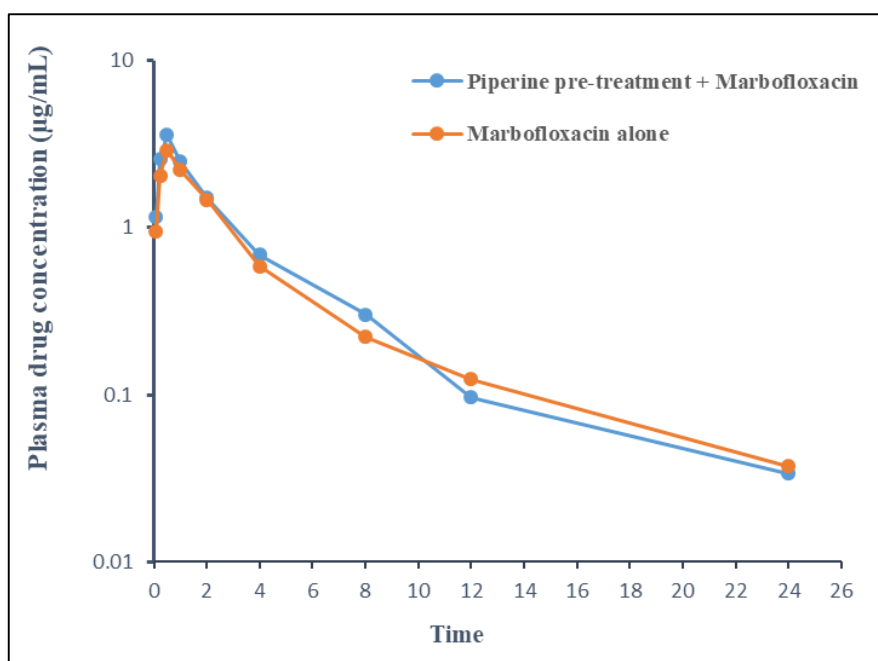


Fig 2: Semilogarithmic plot of plasma marbofloxacin concentrations after subcutaneous administration (5 mg/kg) alone and with piperine pre-conditioning (10 mg/kg orally for 5 days) in rats

Pharmacokinetic parameters of marbofloxacin following single dose subcutaneous administration alone and with piperine pre-conditioning (10 mg/kg, PO for 5 day) in rats are presented in table 2. After single subcutaneous administration of marbofloxacin in normal rats, the mean values of absorption rate constant (K_a) and elimination rate constant (β) were $6.11 \pm 1.03 \text{ h}^{-1}$ and $0.11 \pm 0.01 \text{ h}^{-1}$, respectively. The elimination half-lives ($t_{1/2\beta}$) of $6.40 \pm 0.47 \text{ h}$ was found in the present study. After single i.v. administration, proximate values of $t_{1/2\beta}$ of $5.26 \pm 0.66 \text{ h}$ has been reported in broiler chickens [31] and $6.4 \pm 0.08 \text{ h}$ in foals [32]. Whereas, lower values of $t_{1/2\beta}$ were found ($1.47 \pm 0.31 \text{ h}$) in ostriches [33], ($2.83 \pm 0.28 \text{ h}$) Muscovy ducks [34], and ($4.03 \pm 0.08 \text{ h}$) Japanese quails [35]. In contrast to this, Schneider *et al.*, (2004) [35] observed little high value of $t_{1/2\beta}$ of $6.27 \pm 2.80 \text{ h}$, after repeated i.m. administration of marbofloxacin (2 mg/kg, for 3 days) in lactating cows. Lower elimination half-life in broiler chickens as compare to cows, might be due to difference in route of drug administration, pH of urine and inter-species differences.

Following single dose subcutaneous administration of marbofloxacin alone in the present study, the mean value of absorption half-life ($t_{1/2k(a)}$) and the volume of distribution Vd (area) were $0.13 \pm 0.02 \text{ h}$ and $4.79 \pm 0.36 \text{ L/kg}$, respectively and AUC were $9.35 \pm 0.43 \mu\text{g.h/mL}$. The marbofloxacin has large volume of distribution owing to its high lipid solubility and low plasma protein bindings which results in extensive penetration of the drug in the body of rats. The total body clearance of marbofloxacin in rats following single dose subcutaneous administration was $0.52 \pm 0.02 \text{ L/h/kg}$ with the MRT values of 5.21 ± 0.54 . In the present study, after subcutaneous administration low MRT value indicates that marbofloxacin remains for shorter span of time in rats due to relatively faster elimination of the drug compared to that in other animal species.

Findings of present study, indicate that the drug was absorbed fast after subcutaneous administration by low mean value of absorption half-life and high value of absorption rate constant. After absorption, the drug was rapidly distributed in the body fluids which is clearly indicated by high mean value of $V_{d\text{area}}$ and then relatively slowly eliminated from the body in rats. The value of elimination half-life of the drug can be considered quite long which may lead to good therapeutic effect for longer time with single dose drug administration.

P-glycoprotein (P-gp) as the drug efflux pump, is important for the absorption, distribution and excretion of drug [37]. Moreover, piperine can modulate the activity of P-gp and drug metabolizing enzymes, which may alter the pharmacokinetics. In the present study, possible pharmacokinetic interaction was comparatively investigated following single dose subcutaneous administration of marbofloxacin with piperine pre-conditioning, the mean values of absorption (K_a), elimination (β) rate constants, absorption half-life ($t_{1/2k(a)}$), elimination half-life ($t_{1/2\beta}$), area under curve (AUC), apparent volume of distribution ($V_{d(\text{area})/F}$) and total body clearance were $6.15 \pm 2.28 \text{ h}^{-1}$, $0.10 \pm 0.02 \text{ h}^{-1}$, $0.29 \pm 0.14 \text{ h}$, $7.48 \pm 0.97 \text{ h}$, $8.68 \pm 1.30 \mu\text{g.h/mL}$, $6.80 \pm 1.34 \text{ L/kg}$ and $0.60 \pm 0.06 \text{ L/h/kg}$, respectively in rats. Following single subcutaneous administration of marbofloxacin in piperine pre-conditioning in rats, significant changes in pharmacokinetic parameters were not observed compared to those parameters following single subcutaneous administration of marbofloxacin alone. Studies have shown that piperine inhibited P-gp mediated drug efflux during

intestinal absorption to increase the plasma concentrations of some drugs [38]. Such drug interaction has not been seen with subcutaneously administered drug.

Table 2: Comparison of pharmacokinetic parameters (Mean \pm S.E.) of marbofloxacin after subcutaneous administration (5 mg/kg) alone and with piperine pre-conditioning (10 mg/kg orally for 5 days) in rats (n = 6)

Pharmacokinetic Parameter	Unit	Marbofloxacin alone (Group I)	Piperine pre-treatment+ Marbofloxacin (Group II)
B	$\mu\text{g/mL}$	0.51 ± 0.06	0.45 ± 0.16
B	h^{-1}	0.11 ± 0.01	0.10 ± 0.02
A	$\mu\text{g/mL}$	3.65 ± 0.76	5.25 ± 2.52
A	h^{-1}	0.62 ± 0.08	0.75 ± 0.15
A'	$\mu\text{g/mL}$	5.61 ± 1.90	6.28 ± 2.19
Ka	h^{-1}	6.11 ± 1.03	6.15 ± 2.28
$t_{1/2Ka}$	h	0.13 ± 0.02	0.29 ± 0.14
$t_{1/2\alpha}$	h	1.23 ± 0.21	1.09 ± 0.19
$t_{1/2\beta}$	h	6.40 ± 0.47	7.48 ± 0.97
C_{max}	$\mu\text{g/mL}$	2.89 ± 0.28	3.58 ± 0.75
T_{max}	h	0.50 ± 0.00	0.50 ± 0.00
AUC(0-t)	$\mu\text{g.h/mL}$	9.35 ± 0.43	8.68 ± 1.30
AUMC	$\mu\text{g.h}^2/\text{mL}$	51.31 ± 5.93	46.57 ± 3.31
MRT	h	5.21 ± 0.54	5.33 ± 0.51
Vd(area)/F	L/kg	4.79 ± 0.36	6.80 ± 1.34
Cl(B)	L/h/kg	0.52 ± 0.02	0.60 ± 0.06

(B: intercept of elimination phase; β :elimination rate constant; A:intercept of distribution phase; α :distribution rate constant; A': intercept of absorption phase; K_a : absorption rate constant; $t_{1/2ka}$, absorption half-life; $t_{1/2\alpha}$: distribution half-life; $t_{1/2\beta}$, elimination half-life; C_{max} , the peak or maximum plasma concentration; T_{max} , the time to reach peak or maximum plasma concentration; AUC: area under plasma concentration - time curve; AUMC: area under moment curve; MRT, mean resident time; Vd(area)/F: volume of distribution where bioavailability is not known; Cl(B): total body clearance of drug)

Pharmacokinetic/Pharmacodynamic integration

It has been established that for concentration-dependent antibacterial agents, such as fluoroquinolones, a better predictor of efficacy is the $C_{\text{max}}/\text{MIC}$ ratio, considering that values above 8–10 would lead to better clinical results [39]. A second predictor of efficacy is the AUC/MIC ratio which should be 100–125 [40]. It is now accepted that high $C_{\text{max}}/\text{MIC}$ values are necessary to avoid bacterial resistance emergence [39].

The PK-PD efficacy predictors of marbofloxacin were determined by calculating the $C_{\text{max}}/\text{MIC}_{90}$ and $\text{AUC}/\text{MIC}_{90}$ ratios following subcutaneous administration alone and along with piperine pre-conditioning in rats (Table 3). To cover most of the susceptible organisms, the MIC_{90} of 0.02, 0.08 and $0.12 \mu\text{g/mL}$ of marbofloxacin have been taken into consideration. These values were derived from those determined in the studies involving antibacterial activity of marbofloxacin against different bacterial strains [41, 42, 43]. Based on the data, subcutaneous administration of marbofloxacin (5 mg/kg) alone and with piperine pre-treatment in rats resulted in AUC/MIC ratio (MIC: 0.12 $\mu\text{g/ml}$) of 77.91 and 72.33, respectively. Similarly, $C_{\text{max}}/\text{MIC}$ determined after subcutaneous administration of

marbofloxacin (5 mg/kg) alone and with piperine pre-treatment in rats were 24.08 and 29.83, respectively. C_{max}/MIC ratios at MIC of 0.12 $\mu\text{g}/\text{mL}$ after subcutaneous administration of the marbofloxacin (5 mg/kg) alone and with

piperine pre-treatment in rats were greater than 10 which indicate that administration of the drug would be effective against bacteria with $MIC \leq 0.12 \mu\text{g}/\text{mL}$.

Table 3: Efficacy predictors of marbofloxacin calculated using different MIC values

MIC ($\mu\text{g}/\text{mL}$)	Marbofloxacin alone (Group I)		Piperine pre-treatment + Marbofloxacin (Group II)	
	C_{max}/MIC	AUC/MIC	C_{max}/MIC	AUC/MIC
0.02	144.50	467.50	179.00	434.00
0.08	36.12	116.87	44.75	108.50
0.12	24.08	77.91	29.83	72.33

Conclusion

After single dose subcutaneous administration of marbofloxacin (5 mg/kg) alone and with piperine pre-treatment in rats, therapeutic effective concentrations were maintained up to 12 h post drug administration, which is useful to treat diseases caused by susceptible bacteria with $MIC \leq 0.12 \mu\text{g}/\text{mL}$. This indicate that marbofloxacin having longer duration of action against susceptible bacterial infections in animals. In present study, long elimination half-life, large volume of distribution and area under curve were observed after single dose subcutaneous administration of marbofloxacin (5 mg/kg) alone and with piperine pre-treatment in rats. These favourable pharmacokinetic profile suggested that drug has capacity to clear the deep-seated bacterial infections. Higher C_{max}/MIC ratios at MIC of 0.12 $\mu\text{g}/\text{mL}$ after subcutaneous administration of the marbofloxacin (5 mg/kg) alone and with piperine pre-treatment in rats were observed, which indicate that administration of the drug would be effective against susceptible bacterial infections with maximum clinical cure.

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