

Original article

Pharmacokinetic profiles of marbofloxacin following single and repeated oral administration in broiler chickens

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Abstract

Marbofloxacin is a synthetic, 3rd generation fluoroquinolone compound, having concentration dependent bactericidal activity. After administration of drugs through oral route, first pass effect or pre-systemic elimination is one of the major factors which results in to reduced bioavailability. The present study was planned to investigate the pharmacokinetics of marbofloxacin, following single (5 mg/kg) and repeated dose (5 mg/kg) for 5 days oral administration in broiler chickens. Plasma samples were analyzed for marbofloxacin concentration by HPLC with UV detector. The mean values of absorption half-life ($t_{1/2ka}$) after single and repeated oral administration were 0.22 ± 0.04 and 0.34 ± 0.07 h, respectively and the area under curve (AUC) were 15.11 ± 2.19 and 16.49 ± 1.88 $\mu\text{g}\cdot\text{h}/\text{ml}$, respectively. The mean values of volume of distribution at pseudo equilibrium $V_{d(\text{area})}$ were 1.32 ± 0.10 and 1.61 ± 0.21 l/kg, respectively after single and repeated oral administration whereas elimination half-life ($t_{1/2\beta}$) were 4.62 ± 0.42 and 5.63 ± 0.60 h, respectively. The total body clearance (Cl_b) and mean residence time (MRT) of drug were not significantly differ after repeated dose oral administration as compared to single dose. The plasma concentrations of $\geq 0.38 \pm 0.06$ and $\geq 0.43 \pm 0.07$ $\mu\text{g}/\text{ml}$, were maintained up to 12 h after single and repeated oral administration, respectively which were found to produce sufficient $\text{AUC}/\text{MIC}_{90}$ and $C_{\text{max}}/\text{MIC}_{90}$ of 151.10 h and 20.50, respectively at MIC_{90} value of 0.10 $\mu\text{g}/\text{ml}$. Thus, marbofloxacin following single and repeated dose oral administration at 5 mg/kg for 5 days may be effective to eliminate susceptible bacteria in broiler chickens.

Key words: Marbofloxacin, single and repeated oral administration, pharmacokinetics, broiler chickens

1. Introduction

Development of antimicrobial resistance is an important global concern and there is an utmost requirement of new antimicrobial agent which has diverse chemical properties and mechanism of action (Jinukuti and Giri, 2013). Marbofloxacin, a third generation, fluorinated quinolone compound which is developed for exclusive use against animal bacterial infections (Brown, 1996). Marbofloxacin differs from other fluoroquinolones in chemical structure as presence of an oxadiazine ring, which provides pharmacokinetic advantage such as long elimination half-life (Fitton, 1992). It exhibits bactericidal action by inhibiting bacterial DNA topoisomerases II (gyrase) and IV, and prevents supercoiling of DNA (Drlica and Zhao, 1997). 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 (Plumb, 2015). Important pharmacokinetic parameters of marbofloxacin 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 (Brown, 1996; Ihrke *et al.*, 1999). Along with higher efficacy, marbofloxacin is one of the safer fluoroquinolone compound as it did not produce any adverse reactions and significant alterations in biochemical and hematological parameters in rats after repeated intramuscular administration (Chauhan *et al.*, 2017).

Pharmacokinetics of marbofloxacin after single oral administration in various animal species and birds revealed its poor oral bioavailability, which limits its therapeutic effectiveness. Pharmacokinetics of marbofloxacin following repeated oral administration have been conducted in cats (Albarellos *et al.*, 2005) and rabbits (Carpenter *et al.*, 2009). Pharmacokinetics of marbofloxacin after repeated oral administration in broiler chickens were not studied earlier. Hence, present study was planned to investigate the pharmacokinetics of marbofloxacin following single (5 mg/kg) and repeated dose (5 mg/kg, for 5 days) oral administration in broiler chickens to generate valuable information for designing effective dosage regimen for long term oral administration.

2. Materials and Methods

2.1 Approval of project by ethics committee

The study protocol was approved by Institutional Animal Ethics Committee (IAEC), College of Veterinary Science and A. H., JAU, Junagadh (Protocol No.: JAU/JVC/IAEC/SA/22/2017 dated: 26/05/2017).

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2.2 Experimental animals

The pharmacokinetics of the drug after single and repeated administration was carried out on six broiler chickens (same set of animals) of strain 'Cobb 400' which were obtained from Venky's India Ltd. (Division of Narmada Hatcheries), Anand, Gujarat. Birds were maintained as per CPCSEA guidelines for laboratory animal facility (CPCSEA, 2003). Initially, day old chicks were maintained with twenty four hour light with brooder for one week in broiler house and reared up to the age of 3 weeks and vaccination schedule was followed as per standard managemental practices to control common infectious diseases of birds. During entire study period, the broiler chickens were housed in the cool environment of winter season of 20 to 30°C temperature and with relative humidity ranged between 40 to 55%. Broiler starter and finisher feed of BIS (9862-1992) specification (Simran Feeds Pvt. Ltd, Indore, Madhya Pradesh, India) and reverse osmosis drinking water was provided *ad libitum* to chickens. All broiler chickens were randomly selected for the study.

2.3 Drugs and chemicals

Technical grade pure marbofloxacin powder was procured from Sigma Aldrich, Bangalore, India. Marbofloxacin tablet 50 mg (Marbomet®) (Intas Pharmaceuticals Ltd., Ahmedabad, India) was used for oral administration to broiler chickens. Water, acetonitrile, perchloric acid and formic acid of HPLC grade were purchased from Merck India Ltd., Mumbai.

2.4 Experimental design

Six broiler chickens of 3 weeks of age were administered with marbofloxacin (5 mg/kg) through oral gavaging needle (16 G x 4" bent feeding needles) for 5 consecutive days. Pharmacokinetic analysis was carried after first and fifth dose of marbofloxacin in six chickens only. Blood samples (approximately, 0.50 ml) were collected through IV catheter (26 G x 3/4; 0.6 x 0.19 mm; flow 15 ml/min) fixed in wing vein in heparinized centrifuge tubes. Following oral administration of drug, at day 1st and day 5th, blood samples were collected at 0 min (before drug administration) 5 (0.0833 h), 10 (0.1667 h), 15 (0.25 h) and 30 (0.5 h) min and at 1, 2, 4, 8, 12 and 24 h. Plasma was separated after centrifugation of each blood sample at 12000 rpm for 10 min at 4°C (Eppendorf 5430 R, Germany) and transferred to cryo-vial (2 ml capacity) and then stored at -85°C until assayed for marbofloxacin concentration using HPLC.

2.5 HPLC analysis

2.5.1 Chromatographic condition

The plasma samples were analyzed for marbofloxacin concentration with minor modifications in method described by Carpenter *et al.* (2006). The HPLC apparatus (LC-2010 CHT) of Shimadzu, Japan, comprising quaternary gradient delivery pump (LC-2010) with UV detector was used for assay. Chromatographic separation was carried out using reverse phase Zorbax XDB-C₁₈ analytical column (4.6 mm x 250 mm; ID 5 µ). The mobile phase was a mixture of 10 mM formic acid in HPLC water and acetonitrile (80:20) which was filtered by 0.45 µm 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 with column oven temperature of 30°C. The effluent was monitored at 295 nm wavelength.

2.5.2 Extraction of plasma samples

Deproteinization of each plasma sample (250 µl) was done by precipitation with addition of 250 µl of perchloric acid (0.8 M). Mixture was vortexed for 10 min, followed by centrifugation at 12000 rpm for 10 min. Clear supernatant was collected in to HPLC vials and 20 µl of sample was injected in to HPLC system through auto injector. The HPLC data integration was performed using LC solution software (Shimadzu).

2.5.3 Method validation

For standardization, initially stock solution of marbofloxacin was prepared by dissolving 1 mg pure form of marbofloxacin (Sigma Aldrich) in 1 ml HPLC water. The stock solution of drug was diluted with drug-free poultry plasma to prepare standard marbofloxacin concentrations of 0.049, 0.097, 0.195, 0.391, 0.781, 1.563, 3.125, 6.25, 12.5, 25.0 and 50.0 µg/ml. Quantification of marbofloxacin in plasma samples was done by reference to the resultant standard curve (Figure 1). Chromatographic separation of marbofloxacin from plasma standard (6.25 µg/ml) is shown in (Figure 2). The assay was sensitive and reproducible, and linearity was observed from 0.049 to 50 µg/ml with mean correlation coefficient (r) > 0.999. The lower limit of quantification of the drug was 0.049 µg/ml with a coefficient of variation of less than 9.43%.

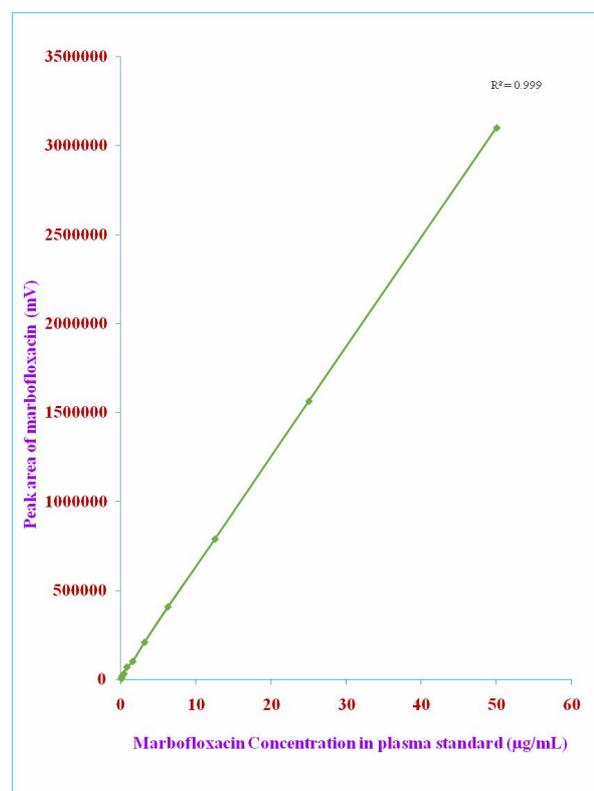


Figure 1: Standard curve of marbofloxacin in drug free plasma of broiler chickens.

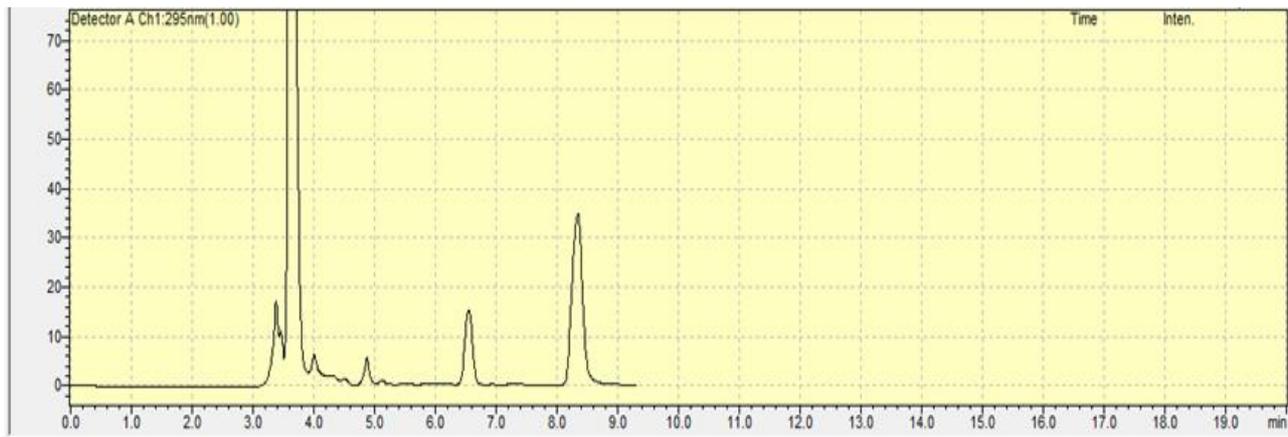


Figure 2: Chromatographic separation of marbofloxacin from plasma standard (6.25 µg/ml) with retention time of 8.0 ± 0.2 min.

2.6 Pharmacokinetic analysis

Pharmacokinetic parameters were calculated as per standard methods (Baggot, 1977; Gibaldi and Perrier, 1982). A': Zero-time intercept of absorption phase and B: Zero-time intercept of elimination phase were calculated by the method of residual yields, K_a : Absorption rate constant and β : Elimination rate constant were calculated by least square regression analysis method, $t_{1/2ka}$: Absorption half-life ($0.693/k_a$), $t_{1/2\beta}$: Elimination half-life ($0.693/\beta$), C_{max} : Maximum drug concentration in plasma and T_{max} : Time of maximum observed concentration in plasma were calculated from actual plasma concentrations of each broiler chicken, AUC: Area under the curve and AUMC: area under the first moment of curve were calculated by linear trapezoidal rule, $Vd_{(area)}$: Apparent volume of distribution ($Dose \times F/(\beta \times AUC)$), $Vd_{(ss)}$: Volume of distribution at steady state ($Dose \times AUMC/(AUC^2)$), Cl_b : Total body clearance ($\beta \times Vd_{(area)}$), MRT: Mean residence time ($AUMC/AUC$), F: Bioavailability ($Dose \text{ i.v.} \times AUC \text{ p.o.}/(Dose \text{ p.o.} \times AUC \text{ i.v.})$). were calculated as per standard formula.

2.7 Statistical analysis

The data obtained for pharmacokinetic parameters were presented as Mean ± S.E. and analyzed statistically using paired sample t-test. The levels of significance to observe difference were 0.05 and 0.01. The p values < 0.05 or < 0.01 were considered as statistically significant or highly significant, respectively.

3. Results and Discussion

The plasma concentrations (µg/ml) of marbofloxacin in relation to time in broiler chickens following single (5 mg/kg) and repeated dose oral administration (5 mg/kg, daily for 5 days) are presented in Table 1 and semilogarithmic plot of the same is shown in Figure 3. Following oral administration, the plasma concentrations at 0.0833 h (5 min) were 0.45 ± 0.08 and 0.50 ± 0.08 µg/ml after single and repeated administration, respectively. The plasma concentration at 30 min after single oral administration was 1.69 ± 0.20 µg/ml which was significantly ($p < 0.05$) higher than the respective value of 1.34 ± 0.23 µg/ml after repeated administration.

Following single and repeated oral administration of marbofloxacin, peak plasma concentrations (C_{max}) of 2.05 ± 0.23 and 1.81 ± 0.25 µg/ml, respectively were observed at (T_{max}) 0.83 ± 0.11 and 1.50 ± 0.22 h, respectively. The C_{max} and T_{max} values after single and repeated

oral administration of marbofloxacin were non-significantly different. Patel *et al.* (2011) reported lower C_{max} value of 1.74 ± 0.02 µg/ml at 2 h after single oral administration of gatifloxacin in white leg horn layer birds. Similarly, after single oral administration of ciprofloxacin (10 mg/kg), lower peak plasma drug concentration (C_{max}) of 1.12 ± 0.18 µg/ml was observed at 0.67 ± 0.12 h in rats (Devi *et al.*, 2016). However, after six days, repeated oral administration of marbofloxacin in cats, higher value of C_{max} (2.34 ± 0.98 µg/ml at 1.60 ± 1.20 h) was observed as compare to respective value of C_{max} (1.78 ± 0.53 µg/ml at 1.61 ± 1.80 h), following single dose of drug (Albarellos *et al.*, 2005). Carpenter *et al.* (2009) also reported higher C_{max} value of 2.56 ± 0.71 µg/ml at 1.40 ± 0.44 h in rabbits after repeated oral administration for 10 days as compare to respective value of 1.73 ± 0.35 µg/ml at 1.60 ± 0.94 h after single dose.

Table 1: Comparison of plasma concentrations of marbofloxacin following single (5 mg/kg) and repeated dose (5 mg/kg for 5 days) dose oral administration in broiler chickens (n = 6)

Time after drug administration (h)	Plasma concentrations (µg/ml)	
	Marbofloxacin single dose	Marbofloxacin repeated dose
0.0833	0.45 ± 0.08	0.50 ± 0.08
0.1667	1.13 ± 0.24	0.88 ± 0.20
0.25	1.45 ± 0.22	1.03 ± 0.23
0.5	1.69 ± 0.20	1.34 ± 0.23*
1	2.00 ± 0.23	1.65 ± 0.21
2	1.68 ± 0.18	1.68 ± 0.29
4	1.16 ± 0.17	1.29 ± 0.17
6	0.90 ± 0.18	0.96 ± 0.13
8	0.67 ± 0.18	0.68 ± 0.08
12	0.38 ± 0.06	0.43 ± 0.07
24	0.08 ± 0.01	0.14 ± 0.03

Values are expressed as Mean ± SEM

* Significant ($p < 0.05$); ** highly significant ($p < 0.01$) difference between single and repeated administration

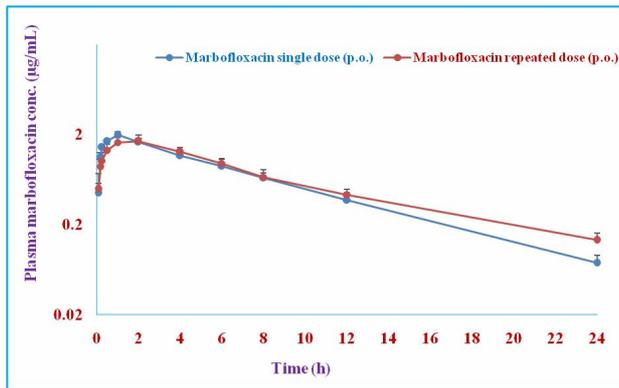


Figure 3: Semilogarithmic plot of marbofloxacin concentration in plasma versus time following single (5 mg/kg) and repeated dose (5 mg/kg, for 5 days) oral administration in broiler chickens.

The plasma concentrations of marbofloxacin of $\geq 0.38 \pm 0.06$ (after single dose) and $\geq 0.43 \pm 0.07$ $\mu\text{g/ml}$ (after repeated dose) were maintained up to 12 h after drug administration. The plasma concentrations at 12 h in both cases were found higher than reported range of minimum inhibitory concentration (MIC_{90}) value of 0.125-0.20 $\mu\text{g/ml}$ against *E. coli* and other Gram-negative bacterial infections in chickens and turkeys (Spreng *et al.*, 1995; Haritova *et al.*, 2006).

Table 2: Comparison of pharmacokinetic parameters of marbofloxacin following single (5 mg/kg) and repeated dose (5 mg/kg for 5 days) dose oral administration in broiler chickens (n=6)

Pharmacokinetic parameters	Unit	Marbofloxacin single dose	Marbofloxacin repeated dose
A'	$\mu\text{g/ml}$	2.07 ± 0.15	1.75 ± 0.29
B	$\mu\text{g/ml}$	2.22 ± 0.23	2.05 ± 0.30
K_a	h^{-1}	3.84 ± 0.80	2.29 ± 0.30
β	h^{-1}	0.16 ± 0.01	0.13 ± 0.01
$t_{1/2ka}$	h	0.22 ± 0.04	0.34 ± 0.07
$t_{1/2\beta}$	h	4.62 ± 0.42	5.63 ± 0.60
C_{\max}	$\mu\text{g/ml}$	2.05 ± 0.23	1.81 ± 0.25
T_{\max}	h	0.83 ± 0.11	1.50 ± 0.22
$\text{AUC}_{(0-\infty)}$	$\mu\text{g}\cdot\text{h/ml}$	15.11 ± 2.19	16.49 ± 1.88
AUMC	$\mu\text{g}\cdot\text{h}^2/\text{ml}$	106.00 ± 17.21	143.92 ± 22.30
$\text{Vd}_{(\text{area})}$	l/kg	1.32 ± 0.10	1.61 ± 0.21
$\text{Vd}_{(\text{ss})}$	l/kg	2.62 ± 0.50	2.95 ± 0.58
$\text{Cl}_{(\text{B})}$	l/h/kg	0.20 ± 0.02	0.20 ± 0.02
MRT	h	7.03 ± 0.33	8.80 ± 0.81
F	%	60.22 ± 8.07	64.55 ± 7.95

Values are expressed as Mean \pm SEM

* Significant ($p < 0.05$); ** highly significant ($p < 0.01$) difference between single and repeated administration

The pharmacokinetic parameters of marbofloxacin after its single and repeated dose oral administration (5 mg/kg, daily for 5 days) in broiler chickens are presented in Table 2. Following oral

administration of the drug, mean absorption rate constants (K_a) after single and repeated doses were 3.84 ± 0.80 and 2.29 ± 0.30 h^{-1} , respectively whereas mean absorption half-life ($t_{1/2ka}$) were 0.22 ± 0.04 and 0.34 ± 0.07 h, respectively. After repeated oral administration of marbofloxacin, mean value of $t_{1/2ka}$ of 0.39 ± 0.38 h was reported in cats (Albarellos *et al.*, 2005). In present study, lower $t_{1/2ka}$ value of marbofloxacin was observed which suggested that drug has rapid absorption rate after repeated oral administration in broiler chickens as compared to cats.

In present study, mean values of elimination half-lives ($t_{1/2\beta}$) were 4.62 ± 0.42 and 5.63 ± 0.60 h after single and repeated dose, respectively. Carpenter *et al.* (2009) observed lower value of $t_{1/2\beta}$ of 3.90 ± 0.00 h in rabbits after repeated oral administration of marbofloxacin. Whereas, higher value of $t_{1/2\beta}$ of 7.77 ± 0.31 h was reported after repeated oral administration in cats (Albarellos *et al.*, 2005). After 3 days of repeated intramuscular administration of marbofloxacin, high value of $t_{1/2\beta}$ of 6.27 ± 2.80 h was also found in lactating cows (Schneider *et al.*, 2004). Such lower $t_{1/2\beta}$ values in broiler chickens might be due to comparatively high clearance rate as compared to cows and cats. Lower elimination half-life in birds also might be due to anatomical and functional differences of kidneys between birds and mammals, as in birds tubular reabsorption is very low or absent (Landoni and Albarellos, 2015). Other reasons may be variation in dose, duration of marbofloxacin treatment and blood collection time intervals.

The area under the plasma concentration time curve (AUC) is a basic and important pharmacokinetic parameter which is proportionate to systemic exposure to a drug and is used to calculate bioavailability, volume of distribution and clearance of drug. The mean area under curve (AUC), following single and repeated administration in broiler chickens were 15.11 ± 2.19 and 16.49 ± 1.88 $\mu\text{g}\cdot\text{h/ml}$, respectively. In contrast to this, higher values of AUC of 29.19 ± 9.12 $\mu\text{g}\cdot\text{h/ml}$ in cats were found (Albarellos *et al.*, 2005). AUC has been found lower after repeated oral administration in broiler chickens as compared to cats, may be related to substantial first pass effect (Adams, 2001).

Volumes of distribution are proportionality constants between total amount of drug in the body and plasma concentrations. Volume of distribution $\text{Vd}_{(\text{area})}$ after single and repeated administration were 1.32 ± 0.10 and 1.61 ± 0.21 l/kg, respectively in broiler chickens. Mean values of $\text{Vd}_{(\text{area})}$ were non-significantly different after single and repeated administration. However, earlier study reported low value of $\text{Vd}_{(\text{area})}$ of 0.96 ± 0.24 l/kg in cats (Albarellos *et al.*, 2005) as compared to the present study. The marbofloxacin has large volume of distribution in chickens compared to cats, which indicates extensive penetration of the drug in the body of broiler chickens after repeated oral administration.

Fluoroquinolones are excreted by renal, biliary or hepatic metabolic pathways. Renal tubular secretion is the major process involved in urinary excretion of drugs (Neuman, 1988). Marbofloxacin is excreted as unchanged form in the urine up to 40 % of total administered drug in dogs (Schneider *et al.*, 1996) and 30 % in broiler chickens (Anadon *et al.*, 2002). Following single and repeated oral administration of marbofloxacin, the total body clearance ($\text{Cl}_{(\text{B})}$) values were similar. The mean residence time (MRT) after single and repeated administrations were 7.03 ± 0.33 and 8.80 ± 0.81 h, respectively. We also evaluated pharmacokinetic profile of

marbofloxacin in broiler chickens following single and repeated intravenous administration (Patel *et al.*, 2018). The values of AUC of the drug following i.v. administration were used to calculate bioavailability, following single and repeated oral administration of marbofloxacin in broiler chickens. The mean calculated bioavailabilities after single and repeated oral administration were 60.22 ± 8.07 and 64.55 ± 7.95 %, respectively. However, after repeated oral administration, higher value of bioavailability (106.0 ± 37.0 %) was observed in cats (Albarellos *et al.*, 2005). The MRT and bioavailability values were non-significantly increased after repeated oral administration which might be due to entero-hepatic recycling of marbofloxacin in broiler chickens.

It has been recognized that for concentration-dependent antibacterial agents, such as fluoroquinolones, the C_{max}/MIC and AUC/MIC ratio are the most important efficacy predictors. The ratio of AUC/MIC₉₀ should at least 100-125 h and C_{max}/MIC_{90} should be at least 8-10 for achieving maximum clinical cure, bactericidal effect and to prevent emergence of resistant organisms (Craig, 1998; Turnidge, 1999). Single dose oral administration of marbofloxacin (5 mg/kg) in broiler chickens have shown AUC/MIC₉₀ ratio of 302.20, 151.10 and 75.55 h and C_{max}/MIC_{90} ratio of 41.00, 20.50 and 10.25 at MIC values of 0.05, 0.10 and 0.20 µg/ml, respectively. Similar to this, C_{max}/MIC_{90} and AUC/MIC₉₀ ratio were of 8.00 and 99.00 h, respectively, observed at MIC level of 0.25 µg/ml after oral administration of marbofloxacin in cats (Albarellos *et al.*, 2005).

4. Conclusion

After single and repeated dose oral administration of marbofloxacin (5 mg/kg) in broiler chickens, therapeutic effective concentrations were maintained up to 12 h post drug administration, which were larger than the reported concentration range of 0.125-0.20 µg/ml (MIC₉₀) against *E. coli* and other Gram-negative bacteria isolated from birds. This suggested longer duration of action of marbofloxacin against susceptible bacterial infections in broiler chickens.

In present study, long elimination half-life, large volume of distribution and area under curve were observed after single and repeated oral administration of marbofloxacin in broiler chickens. These favorable pharmacokinetic profile suggested that drug has capacity to clear the deep seated bacterial infections in broiler chickens. After single oral administration of marbofloxacin, higher C_{max}/MIC_{90} and AUC/MIC₉₀ values were observed which indicates drug's efficacy for treatment of susceptible bacterial infections with maximum clinical cure in broiler chickens.

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Conflict of interest

We declare that we have no conflict of interest.

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