Curcumin ameliorates the absolute and relative bioavailabilities of marbofloxacin after oral administrations in broiler chickens

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Abstract
This investigation was carried out to elucidate the influence of curcumin pre-treatment on bioavailability of marbofloxacin following single oral administration in broiler chickens. Chickens were divided into four groups of seven each. Group-I and II were administered marbofloxacin (5 mg/kg body weight {b.w.}) intravenously and orally, while animals in group-III and IV received similar dose of marbofloxacin (5 mg/kg b.w.) intravenously and orally, after oral pre-treatment with curcumin (100 mg/kg b. w. per day, 10 days). Blood samples were collected from the right wing vein at 0 (blank sample), 0.166, 0.25, 0.33, 0.5, 0.75, 1, 2, 4, 6, 8, 10, 12, 18, 24 and 48 hr in all groups. The Serum concentrations of marbofloxacin were determined by a reverse phase high-performance liquid chromatography (HPLC) with UV detection at 295 nm. The serum concentrations were significantly higher in curcumin treated chickens following oral and intravenous routes. The pharmacokinetic data revealed that curcumin treated chickens had significantly higher area under curve (AUC), volume of distribution (Vc) and mean residential time (MRT). After oral dosing the absorption rate constant (kab) is significantly higher than the elimination rate constant (kel). This could result in the presence of in vivo flip-flop pharmacokinetics. The delayed absorption was evident following oral administration, which limited the elimination and demonstrated sustained release from entero-hepatic circulation. Curcumin ameliorates the systemic and relative bioavailabilities of marbofloxacin after oral administrations in broiler chickens.

Keywords: Bioavailability, Chickens, Curcumin, Marbofloxacin, Pharmacokinetics,
1. Introduction

Augmenting the bioavailability of poorly absorbed antibacterial molecules has always been a vital aspect of drug development plans, as it reduces the drug dosage and frequency resulting in reduced toxicity and bacterial resistance (Dudhatra et al., 2012). Marbofloxacin is a fluoroquinolone member developed solely for animals. It has an additional oxadiazine ring, which may delay the elimination pattern and indeed increases its bioavailability after extravascular routes, (Heinen, 2002). Marbofloxacin exhibits high bactericidal activity against a broad spectrum of aerobic Gram-negative and some Gram-positive bacteria, and also against Mycoplasma spp. (Drugeon et al., 1997). The pharmacokinetics of marbofloxacin has been extensively investigated in rabbits (Abo-El-Sooud and Goudah, 2010); turkeys (Haritova et al., 2006); ostriches (De Lucas et al., 2005); Muscovy ducks (Yuan et al., 2011) and broiler chickens (Ding et al., 2013). Orally administered marbofloxacin is not as commonly used in poultry as other fluoroquinolones, because of its lower bioavailability after gastrointestinal absorption (Anadon et al., 2002).

Zhang et al., 2010 found that marbofloxacin and other fluoroquinolones inhibit the enzyme activity, protein levels and mRNA expression of liver cytochrome P450 (CYP) 1A and 3A in male broiler chicks raising the possibility of drug–drug interaction when using these compounds.

Bioenhancers are chemical units that augment the bioavailability of the drugs when are given concurrently and they do not exhibit synergistic effect with the drug. The need for bioenhancers arises due to drugs which are poorly available and administered for long periods (Tatiraju et al., 2013).

Curcumin (Curcuma longa) is a common food flavor item used as ethno-therapy for a variety of diseases. It is a flavonoid in nature had the ability to suppress drug metabolizing enzymes especially CYP3A4 in liver and is also capable of inducing change in drug transporter P-glycoprotein (P-gp) and thus increased the absolute bioavailability of concomitant drugs via increasing the maximum absorption concentration (C$_{\text{max}}$) and area under the serum concentration-time curve (AUC) (Zhang et al., 2007). Moreover, Basu (2004) found that curcumin suppresses UDP-glucuronyl transferase level in intestine and hepatic tissues. It also modifies the physiological activity in the gastrointestinal tract leading to better absorption of drugs. With this background, the aim of the present study was to access
curcumin pre-treatment for improving the gastrointestinal absorption patterns and bioavailability of marbofloxacin after oral administrations in broiler chickens.

2. Materials and methods

2.1. Drugs

Marbofloxacin raw material (99.8%) was kindly provided by Pharma Sewed (Jordan). 0.1% marbofloxacin solution (prepared by dissolving 0.250 g of marbofloxacin raw material in 0.1 mol/L NaOH solution and then diluting to 2500 ml with water) was orally administrated into the crop by stomach tube and injected intravenously via left wing vein. Standard curcumin was obtained from Sigma Chemicals, Cairo branch, Egypt

2.2. Chickens

Thirty female broiler chickens (Hubbard breed), 40–45 days old, weighing between 2 and 2.5 kg, were obtained. During acclimatization (at least 2 weeks before starting the experiment to ensure the complete withdrawal of any residual drugs) and subsequent treatment periods, all chickens had free access to water and antibacterial-free food. The animal house temperature was maintained at 22±2°C and humidity at 40–55%. The study was approved by the Animal Care and Use Committee at the Faculty of Veterinary Medicine, Cairo University.

The animals were allowed to acclimatize and did not receive any drug treatment for at least 15 days preceding the study.

2.3. Experimental design

Twenty eight broiler chickens were divided into four groups of seven each. Chickens in group-I and II were administered marbofloxacin (5 mg/kg body weight) intravenously and orally, while animals in group-III and IV received similar dose of marbofloxacin (5 mg/kg body weight) intravenously in left wing vein and orally via stomach tube, after pre-treatment with curcumin (100 mg/kg body weight per day, 10 days, orally into the crop using thin plastic tube attached to a syringe). Blood samples (0.5 ml each) were taken via indwelling catheter into Vacutainers (Becton Dickinson vacutainer Systems, Rutherford, NJ, USA), from the right wing vein at 0 (blank sample), 0.166, 0.25, 0.33, 0.5, 0.75, 1, 2, 4, 6, 8, 10, 12, 18, 24 and 48 h in all groups. Serum was separated by centrifugation at 2000g for 10
min and stored at -20 °C until assayed. The remaining two birds were used for obtaining antibacterial free serum that is necessary for standard curve.

2.4. Analysis for marbofloxacin

The Serum concentrations of marbofloxacin were determined by a reverse phase high-performance liquid chromatography (HPLC) using the method described by Ding et al. (2013), briefly. 50 µL supernatant was injected into the HPLC system for analysis. Chromatography was carried out using a HYPERSIL BDS C18 column (5 µm, 4.6 mm × 250 mm); the mobile phase consisted of 12% acetonitrile, 0.75% formic acid, and 0.4% triethylamine, while the UV detector was operated at a wavelength of 295 nm. The analytical method was validated by limit of quantification, linearity for a range of concentrations, accuracy, precision, and susceptibility to interferences.

2.5. Calibration curve

The calibration curve of serum was prepared with seven different concentrations between 0.001 and 10 µg/ml using blank chicken serum. A calibration curve was obtained by plotting the peak area versus the nominal concentrations. The equation was calculated by the least-squares method using linear regression. The standard curve of marbofloxacin in chicken serum was linear, lying between 0.001 and 5 µg/ml ($r^2 > 0.99$). The peak area of unknown specimen was compared with that of the standard marbofloxacin.

2.6. Validation of the assay method

The precision and accuracy of the method were evaluated by repetitive analysis of the serum samples (n=6) spiked with different known concentrations of marbofloxacin. Intra-assay variations were determined by measuring six replicates (n = 6) of three standard samples used for calibration curves. The intra-assay variation coefficients was <5% for serum. An inter-assay precision was determined by assaying the three standard samples on three separate days. The inter-assay variation coefficients was <5% for serum. Recovery of marbofloxacin from serum was found to be 97%. The limit of quantification (LOQ) of marbofloxacin for serum was 0.001 µg/ml.

2.7. Sample preparation procedure

To a 200 µL aliquot of chicken serum, 100 µL of 20% perchloric acid (HClO4) was added. The mixture was vortexed, and then centrifuged at 4500 rpm for 10 min. A 100 µL aliquot of the supernatant solution was added to the auto-sampler vial for analysis (Ding et al. 2013).
2.8. Pharmacokinetic analysis

Serum concentrations of marbofloxacin after IV and oral administrations were subjected to a compartmental analysis using a nonlinear least-squares regression analysis with the help of a PK Solver, China Pharmaceutical University, Nanjing, Jiangsu, China (Zhang et al., 2010) a freely available menu-driven add-in program for Microsoft Excel written in Visual Basic for Applications (VBA), for solving basic problems in pharmacokinetic (PK) and pharmacodynamic (PD) data analysis. Maximum serum concentration (C\text{max}) in serum and the time required to reach C\text{max} (T\text{max}) were directly calculated from the data by the software program. The elimination rate constant (lambda-z) was estimated by log-linear regression of concentrations observed during the linear phase of elimination, using at least three data points automatically selected by the program and confirmed by visual examination of the plotted data. The area under the concentration vs. time curve (AUC\text{0–\infty}) was calculated using the linear trapezoidal rule and absolute and relative bioavailabilities (F) were calculated according to the following equations:

\[ F = \left[ \frac{\text{mean AUC}_{\text{oral}}}{\text{mean AUC}_{\text{IV}}} \right] \times 100. \]

\[ F_{\text{rel}} = \left[ \frac{\text{mean AUC}_{\text{oral with curcumin}}}{\text{mean AUC}_{\text{oral without curcumin}}} \right] \times 100. \]

2.9. Statistical analysis

The statistical analysis was performed using the SPSS® 10.0 software package (SAS, Cary, NC, USA). Results are presented as arithmetic mean ± standard deviation (SD). The nonparametric Wilcoxon test was used to compare the parameters obtained in normal and curcumin treated birds following each route of administration. Means were considered significantly different at p< 0.05 and P<0.01.

3. Results

Mean (±SD) marbofloxacin serum concentration–time curves in normal and curcumin pretreated chickens following IV injection are shown in Figure 1. The serum concentrations in curcumin pretreated chickens were greater than those registered in normal ones. Pharmacokinetic parameters following IV injection are presented in Table 1. As compared with normal chickens, the values of MRT, V\text{c}, T\text{1/2a} and AUC were significantly higher in curcumin pretreated chickens. Mean (±SD) marbofloxacin serum concentration–time curves chickens following oral dosing are illustrated in Figure 2. The serum concentrations in curcumin group were also significantly higher than those in
normal chickens. Pharmacokinetic parameters after oral administration are presented in Table 2. After single oral administration, mean residence time (MRT) and maximum serum concentration (C_{max}) were higher in curcumin pretreated chickens. The absorption rate constant (k_{ab}) is significantly higher than the elimination rate constant (k_{el}). This could result in the presence of in vivo flip-flop pharmacokinetics. The delayed absorption was evident following oral administration, which limited the elimination and demonstrated sustained release from entero-hepatic circulation. In curcumin pretreated chickens, both absolute and relative bioavailabilities were more than 100% indicating complete absorption of marbofloxacin after oral administrations in broiler chickens.

4. Discussion

Some drugs administered orally are poorly bioavailable as they readily undergo first pass metabolism and incomplete absorption. Thus, there is need of molecules which themselves have no same therapeutic activity but when combined with other drugs/molecules enhance their bioavailability. Many natural compounds from medicinal plants have capacity to augment the bioavailability when co-administered with another drug (Tatiraju et al., 2013). The increased serum levels of marbofloxacin observed in curcumin pretreated chickens may be due to the by-pass of glucuronidation process in the intestine since curcumin was reported to suppress UDP-glucuronyltransferase levels in intestine and hepatic tissue (Basu, 2004). Furthermore, the ability of curcumin to suppress CYP3A4 drug metabolizing enzymes (Zhang et al., 2007) might have delayed the excretion of marbofloxacin in chickens.

Elimination half-life and mean residence time of marbofloxacin in serum were 7.26 and 6.43 h 10.11 and 8.8 h after intravenous administration, in curcumin pretreated and normal chickens, respectively. These values were much longer than obtained in of marbofloxacin in ostriches (1.47 h); broilers (5.26 h) and Eurasian buzzards (4.11 h), after IV administration by De Lucas et al., 2005; Anadon et al., 2002 and García Montijano et al., 2001, respectively.

It is more likely that the increased absorption observed in the present study may have been due to the ability of curcumin to influence drug transporter protein (P-gp) in the intestine, as occurs with celiprolol. The bioenhancer nature of curcumin is similar to piperine (Singh et al., 2005). In this respect, Mekala and Arivuchelvan, (2012) found that natural bioenhancer may inhibit the renal clearance of co-administer drugs by preventing glomerular filtration and active tubular secretion.
Sometimes biliary clearance is also affected by inhibiting the UDP glucuronyl transferase enzyme which conjugates and inactivates the drug. Similarly, Liu et al., 2012 ascertained that curcumin (100 mg/kg, for 7 days) pretreatment is significantly increased the plasma concentrations of losartan and its metabolite EXP3174. They implicated the existence of herb-drug interaction between curcumin and losartan, and further evaluation of the possible interaction during curcumin administration needs to be considered. On contrary, Prasad et al., 2016 noticed a significantly lower plasma concentration of phenacetin in rats after curcumin pretreatment. This could be due to the use of a single high dose of this study 400 mg/kg that may reduce phenacetin absorption after curcumin pretreatment. Occurrence of physical or chemical interaction between drug and phytochemical in the intestine is one reason for decreased absorption of phenacetin from the intestine (Chen et al., 2002). Drug absorption is a complex process involving various physicochemical and physiological variables (Zhou, 2003). After oral dosing of marbofloxacin the absorption rate constant ($k_{ab}$) is significantly higher than the elimination rate constant ($k_{el}$). This could result in the presence of in vivo flip-flop pharmacokinetics. These factors can often be accompanied by the lack of intravenous (iv.) drug concentration–time data available to the pharmacokineticist, making it impossible to determine whether absorption rate constant ($ka$) > elimination rate constant ($kel$) or $ka$ > $kel$. This could result in not realizing the presence of in vivo flip-flop pharmacokinetics (Yáñez et al., 2011).

The maximal serum concentrations ($C_{max}$) of marbofloxacin after oral administrations were 1.92 and 1.32 µg/ml, with time to peak concentration ($T_{max}$) values of 0.39 and 1.11 h and absolute bioavailability were < 100 % and 71.10 %, in curcumin pretreated and normal chickens, respectively. In this respect, Anadon et al., 2002 found that Maximal plasma concentration was 1.05 µg/ml until maximum concentration was 1.48 hours and oral bioavailability of marbofloxacin was 56.82%. These differences may be attributed to dose difference as Anadon et al., 2002 used lower regimen 2 mg/kg b.w. The absorption phase in chickens after oral dosing was extremely rapid as reflected by the parameters describing this process ($k_{ab}$, $T_{1/2ab}$ and $T_{max}$). Curcumin was significantly enhanced and augment all the absorption parameters. Serum $C_{max}$ calculated in this study is near to those previously described in chickens (Ding et al., 2013; Anadon et al., 2002). The significantly higher values of AUC, AUMC and mean residence time (MRT) observed in curcumin pretreated birds might be attributable to the
enhanced absolute availability of marbofloxacin that were < 100%. These findings indicate complete absorption of the drug from gastrointestinal tract. Similar finding was recorded by Pavithra et al., 2009 who found that curcumin might have delayed the excretory mechanism of norfloxacin in rabbits, since P-gp protein also exists in the proximal convoluted tubules. It is more likely that the increased absorption observed in the present study may have been due to the ability of curcumin to influence drug transporter protein (P-gp) in the intestine. Furthermore, they proved the modification of physiological activity in the gastrointestinal tract by curcumin (Rao et al., 1982) in rabbits might have contributed to the improved absorption of norfloxacin. Another clarification is predominant mechanisms of action of natural bioenhancers are enhancing the absorption by increased blood supply of the GIT and reducing biotransformation and efflux by modulation of intestinal drug metabolizing enzymes and efflux drug transporters, respectively (Kesarwani et al., 2013).

Using the MIC breakpoint of 0.1 µg/ml (Garcia Montijano et al., 2003), the pharmacokinetic parameters determined in our study and the pharmacodynamic variables correlated to the outcome of infection, the optimal dosage regimen could be estimated. A single marbofloxacin 5 mg/kg dose gave a C\text{max}/MIC of 19.2 and AUC/MIC of 180 h values after oral administration with curcumin. Based on the available published reports on the value of surrogate markers to predict clinical success, a C\text{max}/MIC ratio of 10 or an AUC/MIC ratio of 125–250; have been associated with optimum bactericidal effect. High C\text{max}/MIC ratios also have been associated with a lower incidence of resistance development (Giguère et al., 2013).

Conclusion

The co-administration of natural bioenhancers to enhance the bioavailability of chemotherapeutic agents is a promising issue in the therapeutic plan to reduce dose and cost coupled with decrease the incidence of bacterial resistance. Further studies are necessary to establish the enhancing effect of curcumin with other poorly gastrointestinal-absorbed antibacterials.

5. References


Table 1: Mean ± SD serum pharmacokinetic parameters of marbofloxacin in chickens (n=7) following intravenous administrations at a dose rate of 5 mg/kg b.w.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>unit</th>
<th>With curcumin</th>
<th>Without curcumin</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>μg/ml</td>
<td>1.08 ± 0.22</td>
<td>5.22 ± 1.51</td>
</tr>
<tr>
<td>α</td>
<td>h⁻¹</td>
<td>2.15 ± 0.36</td>
<td>9.20 ± 1.74</td>
</tr>
<tr>
<td>B</td>
<td>μg/ml</td>
<td>1.31 ± 0.78</td>
<td>1.15 ± 0.49</td>
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<tr>
<td>β</td>
<td>h⁻¹</td>
<td>0.096 ± 0.03</td>
<td>0.108 ± 0.04</td>
</tr>
<tr>
<td>k_{el}</td>
<td>h⁻¹</td>
<td>0.17 ± 0.08</td>
<td>0.57 ± 0.09</td>
</tr>
<tr>
<td>k_{12}</td>
<td>h⁻¹</td>
<td>0.86 ± 0.28</td>
<td>6.99 ± 1.12</td>
</tr>
<tr>
<td>k_{21}</td>
<td>h⁻¹</td>
<td>1.22 ± 0.35</td>
<td>1.75 ± 0.62</td>
</tr>
<tr>
<td>T_{1/2α}</td>
<td>h</td>
<td>0.32 ± 0.09</td>
<td>0.08 ± 0.01</td>
</tr>
<tr>
<td>T_{1/2β}</td>
<td>h</td>
<td>7.26 ± 0.64</td>
<td>6.43 ± 0.52</td>
</tr>
<tr>
<td>C⁰</td>
<td>μg/ml</td>
<td>2.38 ± 0.94</td>
<td>6.37 ± 1.20</td>
</tr>
<tr>
<td>V_{c}</td>
<td>L/kg</td>
<td>2.10 ± 0.53</td>
<td>0.785 ± 0.24</td>
</tr>
<tr>
<td>Cl_{tot}</td>
<td>L/h/kg</td>
<td>0.35 ± 0.12</td>
<td>0.45 ± 0.16</td>
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<tr>
<td>AUC_{0-∞}</td>
<td>μg•h/ml</td>
<td>16.16 ± 2.10</td>
<td>15.24 ± 1.50</td>
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<tr>
<td>AUMC</td>
<td>μg•h²/ml</td>
<td>143.23 ± 22.50</td>
<td>98.93 ± 17.45</td>
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<tr>
<td>MRT</td>
<td>h</td>
<td>10.11 ± 0.72</td>
<td>8.82 ± 0.84</td>
</tr>
<tr>
<td>V_{dss}</td>
<td>L/kg</td>
<td>3.57 ± 0.41</td>
<td>3.92 ± 0.33</td>
</tr>
</tbody>
</table>

A: Intercept of the distribution line with the concentration axis; B: Intercept of the straight line of elimination phase with the concentration α: distribution rate constant; t_{1/2α}: distribution half-life; β: Elimination rate constant; T_{1/2β}: elimination half-life; k_{el}: Elimination rate constant; C⁰ = The concentration of drug in serum at time zero time; K_{12}: First order transfer rate constant for drug distribution from central to peripheral compartment; K_{21}: First order transfer rate constant for drug distribution from peripheral to central compartment; V_{c}: Volume of distribution of central compartment; V_{dss}: volume of distribution; Cl_{tot}: total body clearance; AUC: area under the curve by the trapezoidal integral; AUMC: area under moment curve by the trapezoidal integral; MRT: V_{dss} volume of distribution at steady state. Values of curcumin treated chickens were significantly different from corresponding normal chickens at *P<0.05, **P<0.01.
Table 2: Mean ± SD serum pharmacokinetic parameters of marbofloxacin chickens (n=7) following oral administrations at a dose rate of 5 mg/kg bw.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>unit</th>
<th>With curcumin</th>
<th>Without curcumin</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>µg/ml</td>
<td>0.012 ± 0.01</td>
<td>0.011 ± 0.02</td>
</tr>
<tr>
<td>B</td>
<td>µg/ml</td>
<td>1.85 ± 0.41</td>
<td>1.52 ± 0.65</td>
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<tr>
<td>$k_{ab}$</td>
<td>h$^{-1}$</td>
<td>39.22 ± 5.30**</td>
<td>3.402 ± 1.12</td>
</tr>
<tr>
<td>$T_{lag}$</td>
<td>h</td>
<td>0.24 ± 0.06</td>
<td>0.06 ± 0.02</td>
</tr>
<tr>
<td>$k_{el}$</td>
<td>h$^{-1}$</td>
<td>0.09 ± 0.05</td>
<td>0.10 ± 0.07</td>
</tr>
<tr>
<td>$T_{1/2ab}$</td>
<td>h</td>
<td>7.51 ± 0.52</td>
<td>6.71 ± 0.61</td>
</tr>
<tr>
<td>$T_{1/2el}$</td>
<td>h</td>
<td>0.018 ± 0.02*</td>
<td>0.20 ± 0.08</td>
</tr>
<tr>
<td>V/F</td>
<td>L/kg</td>
<td>2.71 ± 0.84*</td>
<td>0.25 ± 0.17</td>
</tr>
<tr>
<td>Cl/F</td>
<td>L/h/kg</td>
<td>3.38 ± 0.77**</td>
<td>0.35 ± 0.11</td>
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<tr>
<td>$C_{max}$</td>
<td>µg/ml</td>
<td>1.92 ± 0.12</td>
<td>1.32 ± 0.14</td>
</tr>
<tr>
<td>AUC$_{0-\infty}$</td>
<td>µg•h/ml</td>
<td>18.02 ± 2.71</td>
<td>13.22 ± 1.87</td>
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<tr>
<td>AUMC</td>
<td>µg•h$^2$/ml</td>
<td>217.47 ± 12.47</td>
<td>142.08 ± 10.24</td>
</tr>
<tr>
<td>MRT</td>
<td>h</td>
<td>10.63 ± 1.40</td>
<td>9.92 ± 1.21</td>
</tr>
<tr>
<td>F</td>
<td>%</td>
<td>&lt; 100</td>
<td>86.70 ± 4.22</td>
</tr>
<tr>
<td>F$_{Rel}$</td>
<td>%</td>
<td>&lt; 100</td>
<td>71.10 ± 3.50</td>
</tr>
</tbody>
</table>

A: Intercept of the distribution line with the concentration axis; B: Intercept of the straight line of elimination phase with the concentration $k_{ab}$; absorption rate constant; $t_{lag}$: absorption half-life; $T_{1/2ab}$: elimination half-life; $k_{el}$: Elimination rate constant; Cl/F = apparent clearance; V/F = apparent volume of distribution; AUC: area under the curve by the trapezoidal integral; AUMC: area under moment curve by the trapezoidal integral; MRT: mean residence time; $C_{max}$: maximum serum concentration; $T_{max}$: time to peak concentration; F%: bioavailability F$_{Rel}$ %: relative bioavailability. Values of curcumin treated chickens were significantly different from corresponding normal chickens at *P<0.05, **P<0.01.
Fig. 1: Mean ± SD serum concentrations of marbofloxacin in broiler chickens in normal and with curcumin pretreated after single intravenous injection of 5 mg/kg b.w. (n=7)
Fig. 2: Mean ± SD serum concentrations of marbofloxacin in broiler chickens in normal and with curcumin pretreated after single oral dose of 5 mg/kg bw (n=7)