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Single and Multiple Pharmacokinetics of Enrofloxacin and Ciprofloxacin in Pigs

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Abstract

Pharmacokinetics of Enrofloxacin (ENR) and Ciprofloxacin (CPX) in pig plasma was studied by HPLC-FL analysis using two injectable solutions, Enromic® 20% (single dose of 7.5 mg ENR Kg^{-1} body weight) and Enromic® 10% (multiple dose of 2.5 mg ENR Kg^{-1} body weight/day during 3 consecutive days). For the method validation, standard calibration curves were prepared between 0.025 and 0.5 µg mL^{-1}, with r^2>0.9998 for both analytes. Quantification limits were 0.0282 and 0.0289 µg mL^{-1} for ENR y CPX, respectively; recovery percentages vary between 90.09% and 104.84% for ENR, and 63.01% and 89.01% for CPX, and precision obtained for measurements made on different days, expressed as %RSD, varied between 2.70% and 15.26% for ENR, and between 6.58% and 13.31% for CPX. Pharmacokinetic parameters gave values for Enromic® 20% of 1.139 ± 0.320 µg mL^{-1} (C_{max}), 3.500 ± 1.581 h (T_{max}) and 17.821 ± 3.020 µg mL^{-1} h ($AUC_{0\rightarrow\infty}$) DU for ENR and 0.047 ± 0.010 µg mL^{-1} (C_{max}), 9.200 ± 1.932 h (T_{max}) and 1.027 ± 0.138 µg mL^{-1} h ($AUC_{0\rightarrow\infty}$) for CPX. For the product Enromic® 10% (multiple doses), values were 0.428 ± 0.119 µg mL^{-1} (C_{max}), 5.000 ± 0 h (T_{max}) and 4.616 ± 1.138 µg mL^{-1} h ($AUC_{0\rightarrow\infty}$) for ENR and for CPX were 0.023 ± 0.006 µg mL^{-1} (C_{max}), 6.000 ± 2.108 h (T_{max}) and 0.424 ± 0.129 µg mL^{-1} h ($AUC_{0\rightarrow\infty}$). We conclude that the most analyzed parameters are similar for both products, regardless of their different administration regime.

Keywords: Pharmacokinetics; Pig plasma; Enrofloxacin; Ciprofloxacin; Liquid chromatography

Introduction

Enrofloxacin (ENR) is an antimicrobial agent belonging to the group of third-generation fluoroquinolones (FQs) [1,2]. ENR has been historically used as veterinary medicine for treatment of gastrointestinal and respiratory infections in several animal species, including pigs cursing diseases caused by gram-positive and negative bacteria. In animals, ENR is de-ethylated to its primary metabolite ciprofloxacin (CPX), and both molecules are effective against microorganisms which are resistant to other antimicrobial agents, such as aminoglycosides, tetracyclines, macrolides and β-lactams [3-9].

The chemical extraction of ENR and its metabolite CPX in biological samples is a major challenge due to the presence of two ionisable functional groups in their molecules: carboxylic acid and basic piperazine, which are directly involved in the pH-dependent interactions between fluoroquinolones and its biological matrix. Liquid chromatography provides a sensitive technique to detect ENR and CPX, and there are several validated methods for determining the analytes in different biological matrixes [8].

Pharmacokinetics of ENR has been studied in several animal species, such as buffalos [10,11], goats [4,5], sheep [12] and rabbits [13,14]. The aim of the study was to investigate the pharmacokinetics of ENR and its metabolite CPX in pig plasma after the administration of two injectable solutions of ENR: Enromic® 20% DU (single dose) and Enromic® 10% (multiple doses).

Materials and Methods

Chemicals and reagents

Standards of Enrofloxacin ($C_{19}H_{22}FN_3O_3$) and Ciprofloxacin ($C_{17}H_{18}FN_3O_3$) were obtained from USP (Rockville, USA) with purities of 99.64% and 99.80%, respectively. Enrofloxacin-based products including Enromic® 20% DU SAG Reg. Nº 2151, and Enromic® 10% SAG Reg. Nº 1443, were obtained from Centrovet Ltda. (Santiago, Chile). HPLC grade acetonitrile, methanol and dichloromethane, as well as disodium hydrogen phosphate anhydrous (99.40%) were obtained from J.T. Baker (Edo. de Mexico, Mexico). Chemical reagents used including 85% phosphoric acid, potassium di-hydrogen phosphate and sodium hydroxide were obtained from Merck (Darmstadt, Germany) and triethylamine was obtained from Merck (Hohenbrunn, Germany). The water used for all the experiments was purified using a Milli-Q system, giving HPLC grade water (Young Lin, Republic of Korea).

Animals

Pigs (average weight 16 Kg) were obtained from healthy sows and grown at Centrovet's animal facilities (Santiago, Chile). Animals were maintained at 21°C, 60% Relative Humidity and air circulation of 10 cycles/ hour, with water and feed *ad libitum*. A Veterinarian supervised all animal management, as stated by the protocol approved by the Institutional Committee for Care and Use of Laboratory Animals (ICCLA).

Standard solutions

ENR stock solution was prepared by dissolving 10 mg of standard in 10 mL of Methanol, and CPX stock solution was prepared by dissolving 15 mg of standard in 50 mL of mobile phase. For ENR, the working solution 1 (ST1) was prepared by diluting 1 mL of stock solution in 10 mL of dilution solution. Working solution 2 (ST2) was prepared by

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diluting 0.1 mL of ST1 in 10 mL of dilution solution; and the working solution 3 (ST3) was prepared by diluting 0.1 mL of (ST2) in 10 mL of dilution solution. The dilution solution was prepared dissolving 3.54 g of potassium di-hydrogen phosphate and 5.82 g of hydrogen phosphate anhydrous in 1000 mL of Milli-Q water, and adjusting to pH 7 with sodium hydroxide solution [8].

For CPX, the working solution 1 (ST1) was prepared diluting 1 mL of stock solution in 10 mL of mobile phase. The working solution 2 (ST2) was prepared diluting 0.5 of stock solution in 100 mL of mobile phase; and the working solution 3 (ST3) was prepared diluting 1 mL of stock solution in 100 mL of mobile phase.

Mixtures of working standards of ENR and CPX were prepared for the calibration curve at 0.025, 0.05, 0.1, 0.2, 0.35 and 0.5 μg mL^{-1} with appropriate volumes of individual working solutions.

HPLC method

Concentrations of ENR and CPX in pig plasma were simultaneously determined by HPLC-FL detection. The analysis was conducted with a High Performance Liquid Chromatography HITACHI, model ELITE LaChrome, which has pump, automatic injector, oven for column, and Fluorescence detector, in which a C18, 120Å, 5 μm (250 mm × 4.6 mm) column was used. The mobile phase contain 16% acetonitrile: methanol (13:1 v/v) and 84% water with 0.4% triethylamine and 0.4% phosphoric acid (85%) adjusted to pH 2.5 with triethylamine [8]. 90 μL of the sample was injected into the HPLC column with a flow rate of 1.2 mL min^{-1}. The oven temperature is 30°C. Excitation and emission wavelengths were 294 nm and 500 nm, respectively.

Sample preparation and extraction method

Pig blood was collected in tubes containing EDTA as anticoagulant. Plasma was prepared from the collected blood by centrifugation at 4000 rpm for 10 min, and samples were stored at -18°C until use. Plasma samples were subjected to liquid phase extraction adding 1 ml of methanol to 1 mL of plasma, vortexed for 60 sec, and incubated on ice for 15 min. After this time, samples were centrifuged at 4000 rpm for 10 min. The supernatant was transferred to a test tube, where 6 mL of dichloromethane was added and vortexed for 60 sec. After homogenization, samples were centrifuged at 4000 rpm for 10 min. The organic phase was transferred to a clean glass tube and evaporated to dryness at 40°C [15]. The solid residue was then reconstituted in 1 mL of mobile phase, filtered through a 0.45 μm filter and 90 μL injected in the chromatographic system.

Method of validation

Validation of the analytical method was conducted under the aforementioned Chromatographic conditions. Three standard curves and 4 curves with spiked plasma were prepared. These curves were made at six levels of concentration, in a range of 0.025 and 0.5 μg mL^{-1}. Limits of quantification for both analytes were determined from the aqueous average curves, as the average plus ten times the standard deviation of the measure from the blank samples.

From the curves with spiked plasma, accuracy was determined by the recovery percentage, taking the aqueous standard curves as references; and between-run precision by the %RSD obtained from measurements performed on different days.

Study design

For the pharmacokinetic study, 10 pigs were intramuscularly injected with a single dose of Enromic® 20% DU (7.5 mg Kg^{-1} body weight), and 10 pigs were daily injected with a dose of Enromic® 10% 2.5 mg Kg^{-1} body weight during 3 consecutive days. Serial blood samples were collected for a period of 77 hours. Plasma containing drug was extracted by liquid extraction procedure.

Pharmacokinetic analysis

The sample concentration was plotted versus elution time for both analytes and products. These are shown in Figures 2A and 2B. Data for both products was adjusted to a non-compartmental model based on the Statistical Moments theory [15-20], using the semi logarithmic curves of ENR and CPX.

Calculated pharmacokinetic parameters of absorption were: maximum concentration (C_{max}); time of maximum plasma concentration (T_{max}); other parameters such as slope of the final part of the curve (λ_z) (which indicates speed of elimination of the drug); elimination half-life ($t_{1/2,z}$); mean residence time (MRT) (which gives a quantitative estimation of the persistence time of the drug in the organism); area under the curve from zero to t ($AUC_{0\to77}$); area under the curve from zero to infinite ($AUC_{0\to\infty}$); area under the first moment curve (AUMC) (which corresponds to the area of plasmatic concentration times time); apparent volume of distribution (V_d/F) and total body clearance (CL_s/F), dependent on the bioavailability (F) of the drug for extravasal administrations. These parameters were calculated by using the Origin 8 (OriginLab Corporation, Massachusetts, USA) computer program.

Results and Discussion

Method validation

Figure 1 shows the HPLC profile of blank plasma, standard solutions and plasma from ENR- and CPX-treated pigs. The profile demonstrates the selectivity of the analytical method, since standard peaks were consistent with the profiles observed in the antibiotic-treated pigs. Standard calibration curves showed a linear relationship between area and concentration, varying between 0.025 and 0.5 μg mL^{-1} for both analytes. The correlation coefficient r^2 was equal to 0.9998 for ENR, and 0.9999 for CPX. Spiked curves from the same animal tissue matrix also demonstrated the linear relationship between area and concentration, with variation between 0.025 and 0.5 μg mL^{-1}, with an r^2 value of 0.9995 for ENR and 0.9996 for CPX. Detection limits were 0.0029 and 0.0104 μg mL^{-1}, and quantification limits were 0.0282 and 0.0289 μg mL^{-1} for ENR and CPX, respectively (Table 1).

The % of recovery was obtained from five levels of fortification varying between 90.09% and 104.84% for ENR, and 63.01% and 89.01% for CPX, shown in (Table 2). Values for ENR are consistent to those reported in the literature for cattle and swine [21,22]; similarly, obtained CPX values were similar to those reported for mares [8]. Between-run precision obtained for measures made in different days, expressed as %RSD, varied from 2.70% to 15.26% for ENR, and from 6.58% to 13.31% for CPX, as indicated in (Table 2), values were also comparable to those previously reported for cattle either for ENR or CPX [21].

Pharmacokinetic analysis

Calculated pharmacokinetic parameters are shown in (Tables 3 and 4) for single and multiple doses of ENR, respectively. For single dose of 7.5 mg kg^{-1}, C_{max} value obtained for ENR was 1.319 ± 0.320 μg mL^{-1} at 3.5 hours of analysis. C_{max} value for multiple doses was 0.428 ± 0.119 μg mL^{-1} at 5 hours of analysis (third dose). Multiplying this concentration by the three days of dosing, gives us a C_{max} value of 1.284

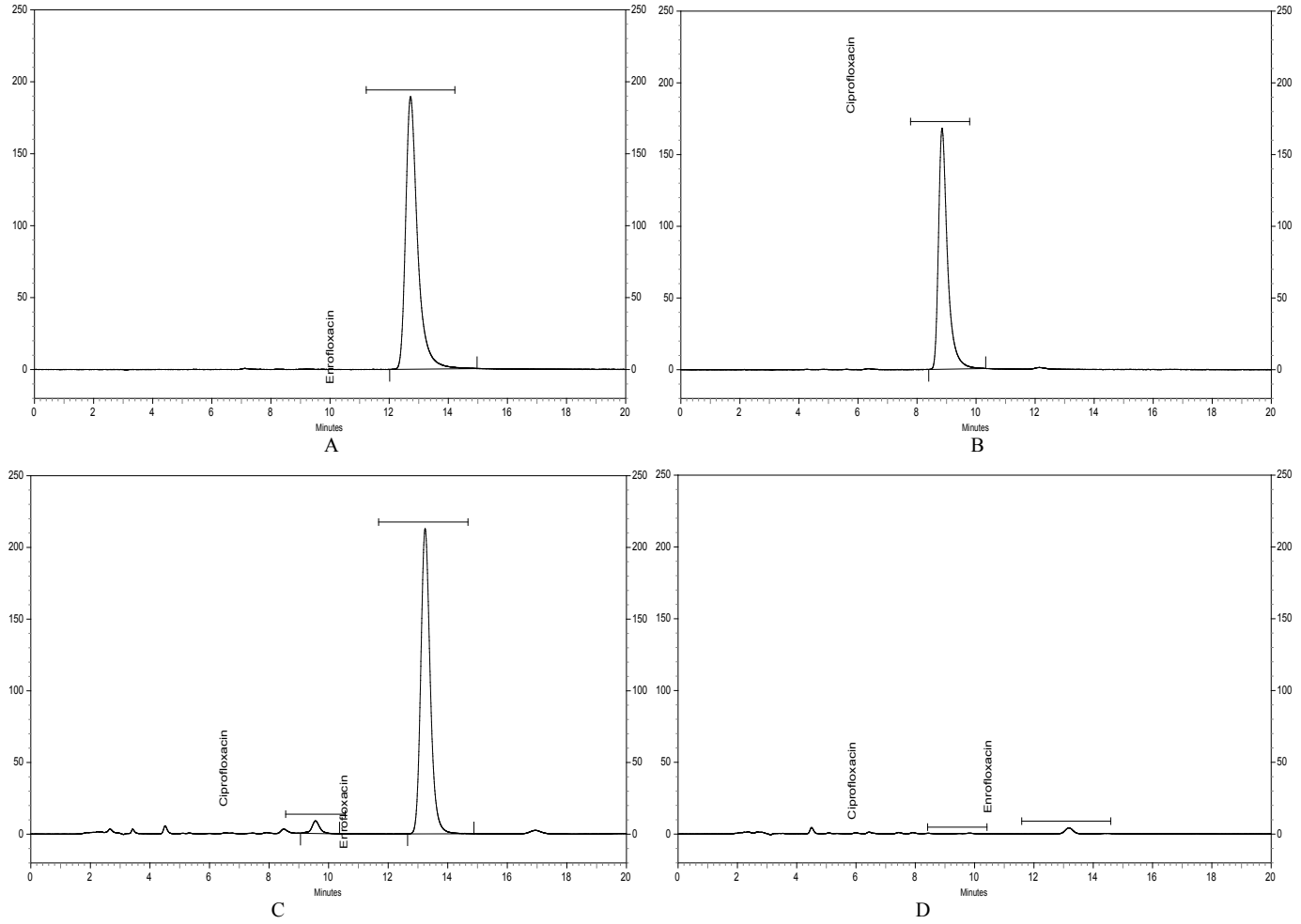

Figure 1: Representative HPLC chromatogram for a standard solution of (A) Enrofloxacin and (B) Ciprofloxacin at 0.2 µg mL-1. (C) Pig plasma sample 24 hours after intramuscular injection of the product Enromic® 20% DU, and blank plasma (D).

µg mL^{-1}. These values indicated that the achieved concentration in pig plasma is similar in both products, despite dosing 7.5 mg kg^{-1} as a single dose or injecting a dose of 2.5 mg kg^{-1} for 3 consecutive days. However, as absorption occurs in a higher time period when multiple doses are applied, antibiotic absorption rate is lower in this case. Additionally, data obtained for λ_Z of 0.077 ± 0.018 h^{-1} and half-life $t_{1/2,z}$ dose of 9.487 ± 2.118 h for single dose, compared to the data obtained for multiple doses λ_Z of 0.084 ± 0.029 h^{-1} and half-life $t_{1/2,z}$ of 8.939 ± 2.343 h, indicates that elimination occurred practically with the same rate for both dosages. This elimination was faster than that obtained in other species, such as rhea [18], yak [15] and sheep [23].

The apparent volume of distribution (V_d) of 5.601 ± 0.970 L kg^{-1} for single dose, compared to V_d for multiple doses of 7.465 ± 2.722 L kg^{-1}, indicates that the distribution of ENR in pig was higher for multiple dose than for single dose. These values were higher to those obtained in other species, such as crab and goats [5], and lower than in buffalo calves [10].

Clearance (CL_s) of 0.430 ± 0.063 L Kg^{-1} h^{-1} for single dose and of 0.569 ± 0.126 Kg^{-1} h^{-1} for multiple doses, was similar for both treatments and faster than in goats [5], yak [15] and buffalo calves [10].

Values of the statistical moments for the single dose were: $AUC_{0\to t}$ of 17.640 ± 3.041 µg mL^{-1} h, $AUC_{0\to\infty}$ of 17.821 ± 3.020 µg mL^{-1} h, AUMC of 235.005 ± 63.683 µg mL^{-1} h^2 and MRT of 13.087 ± 1.778 h. For multiple doses (third dose) were, $AUC_{0\to t}$ of 3.949 ± 0.879 µg mL^{-1} h, $AUC_{0\to\infty}$ of 4.616 ± 1.138 µg mL^{-1} h, AUMC of 58.035 ± 22.078 µg mL^{-1} h^2 and MRT of 13.275 ± 4.365 h. However, as these values are dose-dependent, they cannot be directly compared. To overcome this issue, AUC, AUMC and MRT parameters were calculated for dose, at times from zero to infinite. The new values for single dose were 2.376, 31.334 and 1.745 respectively, and for multiple doses were 1.846, 23.214 and 5.310, respectively. Differences in the three values can be observed from these data, indicating that, despite similar elimination rate for both dosages, drug residence time was longer for multiple doses due to a higher MRT/dose value. These parameters are higher to the values obtained in other species, such buffalo calves [10], goats [4,5] and yak [15]. Regarding the active metabolite, CPX, the C_{max} value for single dose was 0.047 ± 0.010 µg mL^{-1} at 92 hours of analysis; also values for λ_Z of 0.044 ± 0.005 h^{-1} and $t_{1/2,z}$ dose of 15.990 ± 1.856 h were obtained. For multiple doses (third dose), values were: C_{max} of 0.023 ± 0.006 µg mL^{-1} at 6 hours of analysis, λ_Z of 0.052 ± 0.016 h^{-1} and $t_{1/2,z}$ of 14.303 ± 3.761 h. In this case, similar values were observed for elimination of CPX, but times when maximum concentrations were reached were different, what could be explained as when injecting more ENR in the single dose, the pig takes more time to metabolize it to CPX.

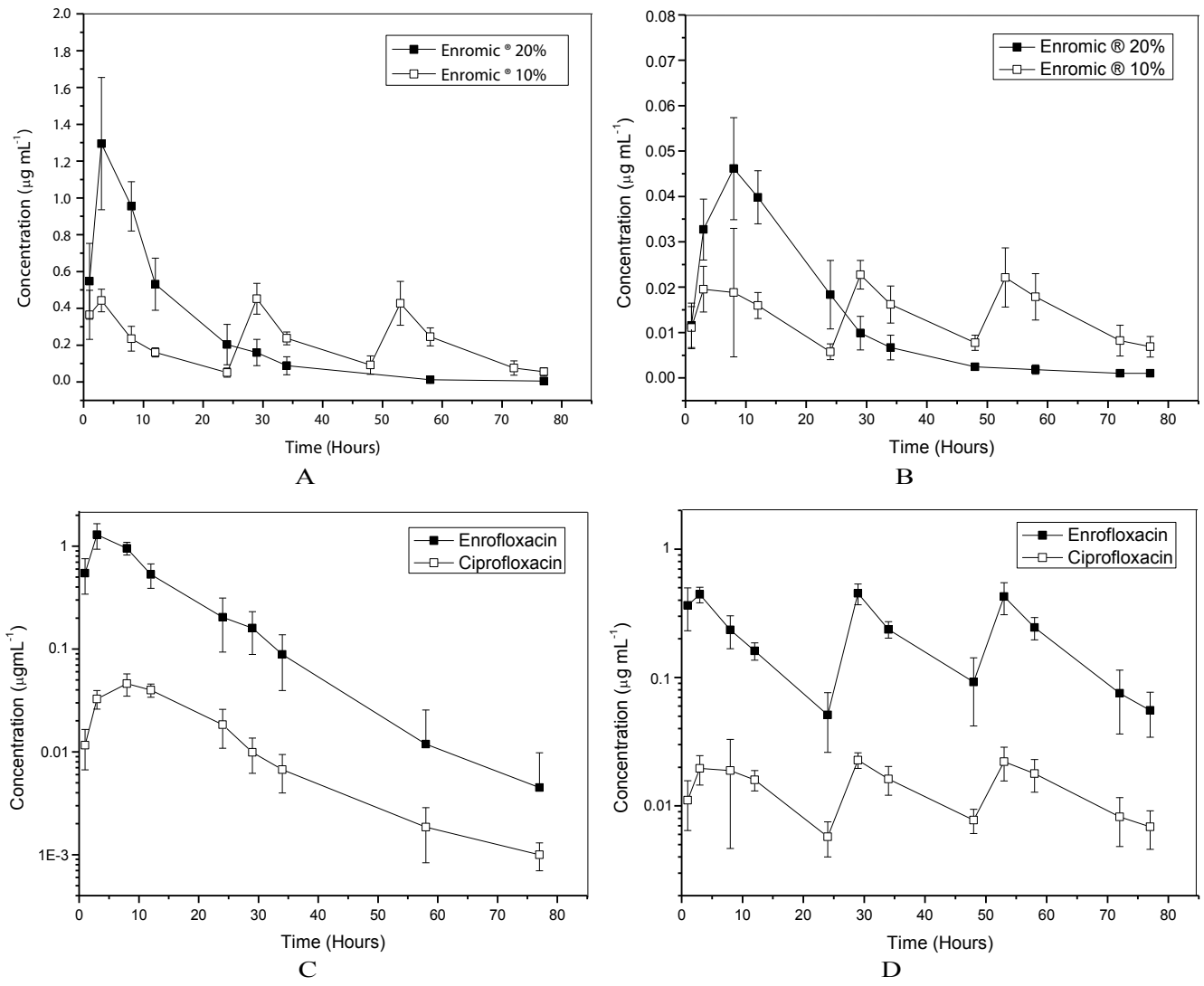

Figure 2: Concentration-time curves in pig plasma (n=10) for Enrofloxacin (A) and Ciprofloxacin (B) following intramuscular injection of Enromic® 20% DU (7.5 mg kg^{-1} of ENR, single dose, filled squares) and Enromic®10% (2.5 mg Kg^{-1} per day of ENR, three consecutive days-dose, empty squares). Semi-logarithmic concentration-time curves for Enrofloxacin (filled squares) and Ciprofloxacin (empty squares) in pig plasma after treatment with Enromic® 20% (single dose, C) and Enromic® 10% (three consecutive days-doses, D).

	Regression equation	r^2	LOD	LOQ
			[μg mL^{-1}]	[μg mL^{-1}]
Enrofloxacin	y=107973.40 x+473847.57	0.9998	-	-
Ciprofloxacin	y=72830.93 x+85180.81	0.9999	-	-
*Enrofloxacin	y=96593.73 x+1412731.28	0.9995	0.0029	0.0282
*Ciprofloxacin	y=48968.34 x+60102.99	0.9996	0.0104	0.0289

*Curves in spiked plasma samples

Table 1: Mean calibration curves of Enrofloxacin and Ciprofloxacin for the range of 0.025 and 0.5 μg mL^{-1} -in standard and spiked plasma samples.

Values of the statistical moments for single dose were: $AUC_{0\to t}$ of 1.004 ± 0.137 μg mL^{-1} h, $AUC_{0\to\infty}$ of 1.027 ± 0.138 μg mL^{-1} h, AUMC of 19.665 ± 3.402 μg mL^{-1} h^2 and MRT of 17.283 ± 1.785 h; and for the third dose of the multiple doses were: $AUC_{0\to t}$ of 0.278 ± 0.068 μg mL^{-1} h, $AUC_{0\to\infty}$ of 0.424 ± 0.129 μg mL^{-1} h, AUMC of 8.598 ± 3.927 μg mL^{-1} h^2 and MRT of 19.623 ± 4.283 h. Parameters such as AUC, AUMC and MRT were also calculated per dose, for times from zero to infinite. For single dose, the new values were 0.137, 2.622 and 2.304, respectively; and for multiple doses the new values were 0.170, 3.439 and 7.849, respectively. These values also differed regarding the time area of plasmatic concentration, and the mean residence time previously observed for ENR, which proves that the residence time of the drug was longer for multiple doses.

Conclusions

Enrofloxacin and its metabolite Ciprofloxacin have been used as

	Enrofloxacin		Ciprofloxacin	
Concentration (μg mL^{-1})	Recovery (%)	Between-run precision (RSD, %)	Recovery (%)	Between-run precision (RSD, %)
0.025	104.80	2.70	89.01	10.69
0.050	104.84	10.82	64.87	10.34
0.100	97.38	15.26	63.01	9.52
0.200	95.84	10.22	65.14	6.58
0.350	90.09	10.60	66.88	13.31
0.500	91.10	15.13	70.53	12.45

Table 2: Recovery and precision studies for the determination of Enrofloxacin and Ciprofloxacin in pig plasma.

Parameters	Units	Enromic® 20%	
		Enrofloxacin	Ciprofloxacin
C_{max}	μg mL^{-1}	1.319 ± 0.320	0.047 ± 0.010
T_{max}	h	3.500 ± 1.581	9.200 ± 1.932
λ_Z	h^{-1}	0.077 ± 0.018	0.044 ± 0.005
$AUC_{0\rightarrow t}$	μg h mL^{-1}	17.640 ± 3.041	1.004 ± 0.137
$AUC_{0\rightarrow \infty}$	μg h mL^{-1}	17.821 ± 3.020	1.027 ± 0.138
AUMC	μg h^2 mL^{-1}	235.005 ± 63.683	19.665 ± 3.402
MRT	h	13.087 ± 1.778	17.283 ± 1.785
$t_{1/2,z}$	h	9.487 ± 2.118	15.990 ± 1.856
V_d/F	L Kg^{-1}	5.601 ± 0.970	
CL_S/F	L Kg^{-1} h^{-1}	0.430 ± 0.063	

C_{max}: Maximum concentration in pigs plasma; T_{max}: Time when maximum concentration was obtained. $AUC_{0\rightarrow t}$: Area under the concentration-time curve from the time zero to 77 h; $AUC_{0\rightarrow \infty}$: Area under the concentration-time curve from the time zero to infinity in pigs plasma; AUMC: Area under the first moment concentration-time curve; MRT: Mean residue time of drug in body; λ_Z : Terminal slope of the drug concentration-time curve; $t_{1/2,z}$: Half-life of the drug; CL_s/F : Total body clearance; V_d/F: Apparent volume of distribution.

Table 3: Pharmacokinetic parameters that describe the disposition of Enrofloxacin and its metabolite Ciprofloxacin in pigs plasma (n=10) after single intramuscular injection of Enromic® 20% DU (7.5 mg kg^{-1} of ENR).

Parameters	Units	Enromic® 10%			
		Enrofloxacin		Ciprofloxacin	
		1st Dose	3rd Dose	1st Dose	3rd Dose
C_{max}	μg mL^{-1}	0.450 ± 0.076	0.428 ± 0.119	0.023 ± 0.012	0.023 ± 0.006
T_{max}	h	2.800 ± 0.633	5.000 ± 0.000	4.300 ± 2.627	6.000 ± 2.108
λ_Z	h^{-1}	0.102 ± 0.046	0.084 ± 0.029	0.073 ± 0.030	0.052 ± 0.016
$AUC_{0\rightarrow t}$	μg h mL^{-1}	4.568 ± 0.645	3.949 ± 0.879	0.332 ± 0.085	0.278 ± 0.068
$AUC_{0\rightarrow \infty}$	μg h mL^{-1}	5.236 ± 0.194	4.616 ± 1.138	0.428 ± 0.083	0.424 ± 0.129
AUMC	μg h^2 mL^{-1}	62.033 ± 27.480	58.035 ± 22.078	7.354 ± 2.834	8.598 ± 3.927
MRT	h	11.522 ± 3.506	13.275 ± 4.365	17.098 ± 5.697	19.623 ± 4.283
$t_{1/2,z}$	h	7.909 ± 3.305	8.939 ± 2.343	10.891 ± 4.169	14.303 ± 3.761
V_d/F	L Kg^{-1}	5.545 ± 1.440	7.465 ± 2.722		
CL_S/F	L Kg^{-1} h^{-1}	0.491 ± 0.088	0.569 ± 0.126		

C_{max}: Maximum concentration in pigs plasma; T_{max}: Time when maximum concentration was obtained. $AUC_{0\rightarrow t}$: Area under the concentration-time curve from the time zero to t; $AUC_{0\rightarrow \infty}$: Area under the concentration-time curve from the time zero to infinity in pigs plasma; AUMC: Area under the first moment concentration-time curve; MRT: Mean residue time of drug in body; λ_Z : Terminal slope of the drug concentration-time curve; $t_{1/2,z}$: Half-life of the drug; CL_s/F: Total body clearance; V_d/F: Apparent volume of distribution.

Table 4: Pharmacokinetic parameters that describe the disposition of Enrofloxacin and its metabolite Ciprofloxacin in pigs plasma (n=10) after multiple intramuscular injection of Enromic® 10% (2.5 mg kg^{-1} per day of ENR).

veterinary medicine for the treatment of several microbial affections. The distribution and effect of the drug in pig plasma were carried out by the pharmacokinetic study of the drug using a validated HPLC method. Quantifications limits for ENR and CPX obtained from the results were 0.282 and 0.0289 μg mL^{-1}, respectively. Recovery percentages for the five spiked-plasma levels varied between 90.09% and 104.84% for ENR, and from 63.01% and 89.01% for CPX; and the between-run precision values, expressed as %RSD, varied between 2.70%–15.26% for ENR, and 6.58%–13.31% for CPX.

For the pharmacokinetic study, a non-compartmental analysis was conducted, where data obtained for ENR in single dose are: 0.077 ± 0.018 h^{-1}, 9.487 ± 2.118 h, 5.601 ± 0.970 L Kg^{-1} and 0.430 ± 0.063 L Kg^{-1} h^{-1}, for λ_Z, $t_{1/2,z}$, V_d, and CL_S, respectively. Also, the most important statistical moments were: 17.821 ± 3.020 μg mL^{-1} h, 235.005 ± 63.683 μg mL^{-1} h^2 and 13.087 ± 1.778 h for $AUC_{0\rightarrow\infty}$, AUMC and MRT, respectively. In the case of multiple dose (third dose) were: 0.084 ± 0.029 h^{-1}, 8.939 ± 2.343 h, 7.465 ± 2.722 L Kg^{-1} and 0.569 ± 0.126 L Kg^{-1} h^{-1}, for λ_Z, $t_{1/2,z}$, V_d, CL_S, respectively, and the statistical moments were: 4.616 ± 1.138 μg mL^{-1} h, 58.035 ± 22.078 μg mL^{-1} h^2 and 13.275 ± 4.365 h for $AUC_{0\rightarrow\infty}$, AUMC and MR, respectively.

We conclude that the most of the analyzed parameters are similar for the two enrofloxacin formulations studied, regardless of their concentration and different administration program, indicating an effective absorption of the active ingredient for both products.

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