doi.org/10.36721/PJPS.2025.38.2.REG.13117.1

Preclinical pharmacokinetic profile of ciprofloxacin analogues in rabbits after oral administration

Sumbul Shamim[1], Mahwish Akhtar[2], Javeria Choudhuri[3], Khurrum Fareed[4], Afrina Raza[5] and Mohammad Arshad[6]

[1]Department of Pharmacology, Dow College of Pharmacy, Dow University of Health Sciences,
[2]Department of Pharmaceutical Chemistry, Dow College of Pharmacy, Dow University of Health Sciences,
[3]Institute of Biological Biochemical and Pharmaceutical Sciences, Dow University of Health Sciences,
[4]Institute of Life Sciences, Dow University of Health Sciences,
[5]Department of Pharmacology, Dow Medical College, Dow University of Health Sciences,
[6]Department of Pharmaceutics, Dow College of Pharmacy, Dow University of Health Sciences,

Abstract: Ciprofloxacin (CFX) belongs to the second-generation broad-spectrum fluoroquinolone antibiotic and it has been targeted for the development of new moiety against resistant microbes by the alteration at position C3 (carboxylic group) and C7 (piperazine moiety). Seven ciprofloxacin derivatives were developed, out of them three were found to be potent against resistant microbes. In current research study, we present the pharmacokinetics parameters of CFX and derivatives using animal model. Fifteen rabbits were fasted for 12 h before given single oral dose of 40mg/kg CFX and analogues. The blood sample of rabbits were collected over the period of 0 to 24 h. The parameters of pharmacokinetics of CFX and analogues were evaluated by validated high performance liquid chromatography (HPLC) method. The results unveiled that, the CFX and analogues were quickly absorbed, distributed, and moderately eliminated for the animal body. The volume of distribution was large with (Vdss) value of 263.51-1068.89 (mg)/(µg/ml). The total body clearance (CL) of ciprofloxacin and its 3 mentioned analogues were in the range of 42.35 to 200.16 mg/(µg/ml) in each hour. The peak plasma concentration (Cmax) of 1.04-5.66 µg/mL was attained at 0.5 h which is showing its time for achieving maximum plasma concentration (Tmax). The elimination half-life (T1/2) was 4.055-10.14 h. The preclinical pharmacokinetics study revealed that all analogues of CFX indicates that the analogues have better pharmacokinetics than the parent compound, Ciprofloxacin, after oral administration.

Keywords: ciprofloxacin; derivatives, Pharmacokinetics; oral administration; Rabbits.

Submitted on --------- – Revised on ---------- – Accepted on ----------

INTRODUCTION

Fluoroquinolones (FQs) belongs to the family of gyrase inhibitor shows a wide spectrum of activity against gram negative, gram positive and mycobacterial organisms (Casal and Asís, 2017). This class of antibiotics inhibits topoisomerases II and IV DNA gyrase. Fluoroquinolones majorly target DNA gyrase of tuberculosis bacteria. In 1996 WHO recommended Ciprofloxacin, Ofloxacin and Sparfloxacin as second line treatment for TB, mainly in patients who are resistant to first line anti-TB therapy. According to recent WHO guidelines, Levofloxacin and Moxifloxacin gives promising results in MDR-TB. Ciprofloxacin is no longer used (Chang and Yew, 2013).

FQs are derived from quinolones by the addition of fluoride atom at 6th position. It is the class of broad-spectrum synthetic compounds. The FQs are responsible for the inhibition of the bacterial cell division by targeting the enzyme, topoisomerase II and IV. The Ciprofloxacin (CFX) belongs to the 2nd generation of FQs with excellent activity against Gram-positive and Gram-negative microbe as well as *Mycobacterium tuberculosis*. The Ciprofloxacin has been targeted for the development of new moiety against resistant microbes by the alteration at position C3 (carboxylic group) and C7 (piperazine moiety) (Barathe *et al*., 2022, Shee *et al*., 2022).

In recent year, bacterial resistances are the alarming situation and to solve this problem; series of derivative of fluoroquinolones have been synthesized and screened against their antibacterial activities (Towle *et al*., 2018, Mansha *et al*., 2021, Faidallah *et al*., 2018, Mohammed *et al*., 2020).

The study of structure activity relationship (SAR) revealed that the C3 and C7 position of fluoroquinolones are important for their antimicrobial activities and the derivatives of almost all fluoroquinolones are synthesized by the alteration at the 7th position by a nitrogen heterocycle and some are substituted at 3rd position that is carboxylic group and by this modification the antimicrobial activities were also increased (Garza *et al*., 2017, Salunke *et al*., 2019, Akhtar *et al*., 2019a, Akhtar *et al*., 2019b). Similarly, Ciprofloxacin belongings to the second-generation broad-spectrum fluoroquinolone antibiotic hydrochloride. The Ciprofloxacin has been targeted for the development of new moiety against

*Corresponding author: e-mail: ----------

resistant microbes by the alteration at position C3 (carboxylic group) and C7 (piperazine moiety) (Akhtar *et al*., 2019a, Dileep *et al*., 2018).

Low potency and toxicity are two main causes of drug failures, and the pharmacokinetics heavily influences both factors. The compounds having good pharmacokinetics are also consider as effective and safe. Therefore, the preclinical pharmacokinetic assessment is considered enough to give a clue that drugs will be successful in the clinic trials (Yuan *et al*., 2022). The absorption CFX has been reported by many scientists after oral administration (van Rhee *et al*., 2022, Vance-Bryan *et al*., 1990).

The present study illustrates the preclinical pharmacokinetic studies of selected analogues of CFX in the rabbit model after the single oral administration. This study was performed with 13 healthy male rabbits with body weight in the range of 1 to 1.5 kg.
The aims of present study were:
(a) To established the method for the determination of pharmacokinetics parameters of newly synthesized compounds.
(b) To propose a limited sampling strategy for estimation of total clearances (CL) and the elimination half-life ($T1/2$) of compounds from the body.
(c) To calculate the concentration of compounds in blood of rabbits after oral administration.

Structures of CFX and analogues (CIN, CN, CSA) are shown in fig. 1. The outline of synthesis of derivatives was compiled in scheme 1.

Methodology

Chemical reagents

All reagents used in this study were of analytical grade and were purchased from Sigma Pakistan. The derivatives of ciprofloxacin were freshly prepared and store in cool and dry place to maintain their stability.

Study design

The present study was designed to evaluate the preclinical pharmacokinetics of novel synthesized derivatives of CFX after oral dose administration in rabbits. The washout period between two compounds was 15 days. In this study, CFX and three derivatives of CFX were studied. The compounds were CIN, CSA and CN (fig. 1).

The drug and dose

The analogues of CFX were freshly re-synthesized using previous selected method (Scheme1) (Akhtar *et al*., 2019a, Akhtar *et al*., 2019b). The novel derivatives and ciprofloxacin were administered orally for once a day at 40 mg/kg/day which are found effective after the literature search of ciprofloxacin (Al-Ghazawi *et al*., 2012). Plasma concentrations of derivatives were measured using a HPLC-UV (Sultana *et al*., 2010).

Dose preparation

The dose of each compound was calculated according to the body weight of individual rabbit. The samples were freshly prepared in water at the time of dosing. Calculated dose of CFX and analogues were dissolved in 5ml of distilled water individually using 5ml volumetric flask.

Experimental animals

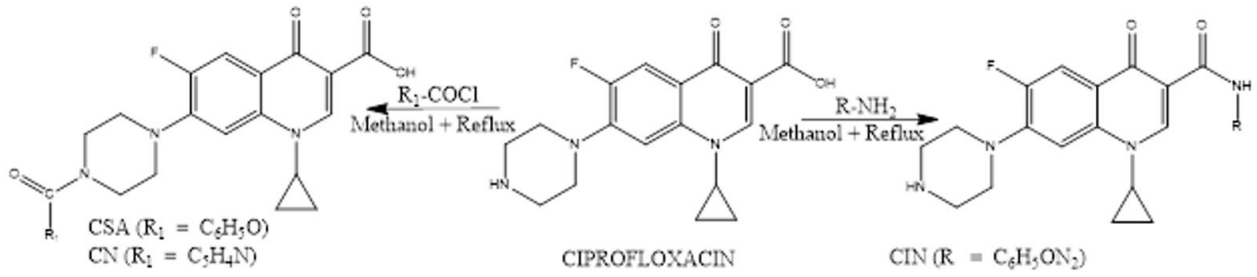
Fifteen rabbits of weight 1 kg approximately were taken from animal house of Dow University of Health Sciences (DUHS). This study was approved by animal IRB of DUHS (IRB-473/DUHS/-14).

The animals were cared for and used in accordance with the Institute of Laboratory Animal Research (ILAR) guidelines in experimental studies (Festing and Altman, 2002). The animals were allowed to acclimatize for 21 days during which they had free access to commercial pellet diet.

HPLC instrumentation and chromatographic Conditions

The HPLC system used was (SHIMADZU 20AT) attached with UV detector. The degasser was used to remove gas in solvent system. The chromatographic responses were recorded using Lab solution CFR 21 software compatible with computer system (HP i7). the chromatographic separation was achieved at ambient temperature. The C18 silica column (PHENOMENEX), 5 µm particle size, 25cm x 4.6 mm, attached with the guard column. The pH meter was belonged to Hanna Instruments (Model H12550).

The mobile phase was water and Acetonitrile (ACN) in the ratio of 87:13 (v/v) with pH 3.2. The sample was extracted from plasma with ACN. The ratio of ACN and plasma was 500:500 and 500:700 respectively. Flow rate was 1.0



Scheme 1: Synthetic scheme of C3 and C7 derivatives of CFX derivatives (CIN, CSA, and CN)

Table 1: Absorption of compounds with and without plasma

Concentration (µg/ml)		Absorption (nm)			
		CFX	CIN	CN	CSA
Without spiking with plasma	20	2021041	755927	931817	393970
	10	985803	405424	431618	141871
	5	491017	181871	171594	88443
	2.5	185727	91932	84201	40273
	1.25	89103	43929	35214	17231
	0.625	43960	2870	14717	7614
Spiking with plasma	20	1324031	1516226	757404	426973
	10	652908	691895	348516	197097
	5	347589	364309	162239	91408
	2.5	133125	172450	64198	49869
	1.25	68886	85047	35643	23052
	0.625	33829	46115	13551	11976

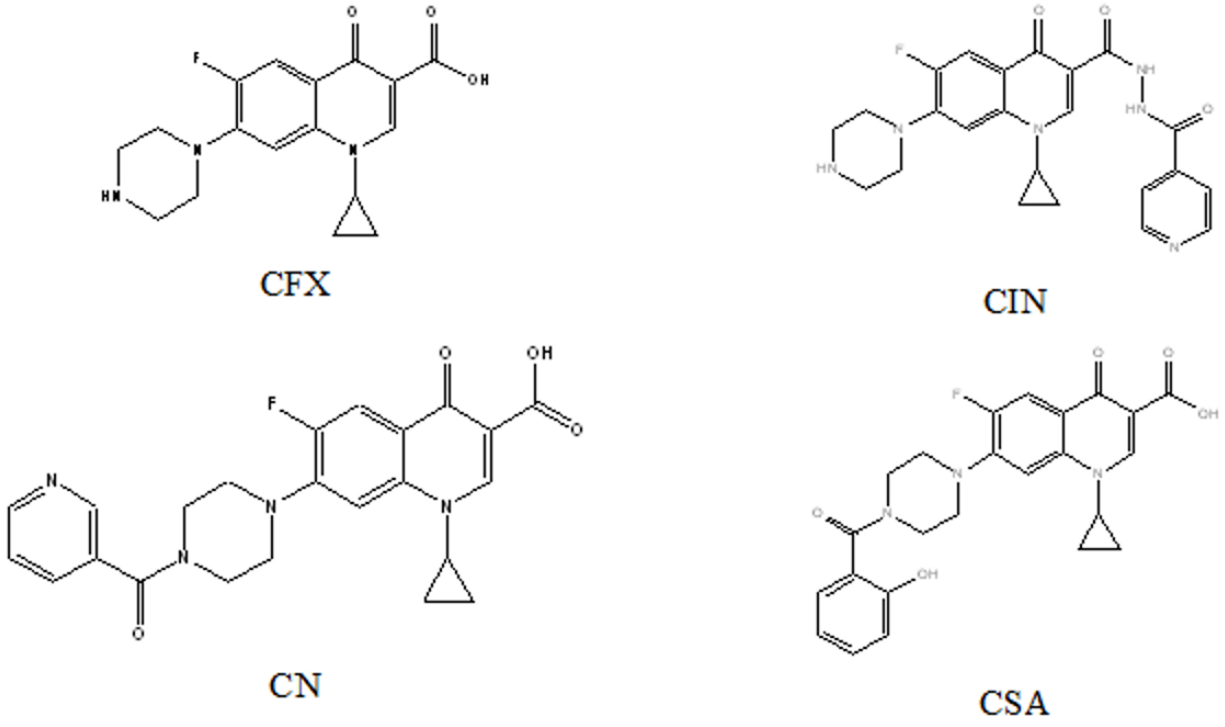


Fig. 1: The chemical structures of CFX, C3 analogue (CIN), and C7 analogues (CSA and CN)

ml/min. The effluent was monitored by UV detector at 278 nm.

Drug dosing and sample collection

Before dosing, the rabbits were fasted for 12 hours. The dose of 40mg/kg of CFX and derivatives were given to each rabbit on the day of study by oral tube. Each compound was given to 3 individual rabbits and 3 rabbit was used as reference. The blood of quantity 5ml was withdrawn from the ear vein of each rabbit at 0, 0.25, 0.5, 1, 2, 4, 6, 8, 12 and 24 hours post dosing into heparinized bottles and centrifuged at 3000 rpm for 15 min to separate plasma. The plasma was collected and stored at -80˚C (Ukpo *et al*., 2017).

Assay of compounds

The concentration of ciprofloxacin and analogues were analyzed by the previously developed and validated method with slight modification (Ukpo *et al*., 2017). The 10 replicates of each compound were used to determine the concentration of samples in plasma.

Table 2: Values of regression, slope, and intercept of studied compounds

Compounds	Stock solution			Spiking with Plasma		
	Regression value	Slope	Intercept	Regression value	Slope	Intercept
CFX	0.9994	102947	-39482	0.9991	66903	-12324
CIN	0.9976	38731	-7177.5	0.9981	75535	-16355
CN	0.9971	47744	-35128	0.9983	38542	-22673
CSA	0.9808	19443	-12696	0.9979	21382	-6926.1

Table 3a: Calculated plasma concentration of CFX in rabbits after a single oral administration.

Time	Conc	ln(C)	AUC	AUMC	R	R_adj
0	0		0	0		
0.25	0.353227807	-1.040642083	0.044153476	0.011038369		
0.5	2.577627311	0.946869329	0.410510366	0.183178445	-0.871857326	0.700168997
1	1.10102686	0.096243253	1.330173908	0.780638574	-0.914169306	0.780940692
2	0.563457543	-0.573663293	2.16241611	1.894609547	-0.963598683	0.892783633
4	0.362390326	-1.015033399	3.088263979	4.471085938	-0.969742795	0.880802175
6	0.33	-1.108662625	3.780654305	7.900647243		
8	0.26	-1.347073648	4.370654305	11.96064724		

Table 3b: Calculated plasma concentration of CIN in rabbit after a single oral administration.

Time	Conc	ln(C)	AUC	AUMC	R	R_adj
0	0		0	0		
0.5	1.04290726	0.04201226	0.26072682	0.13036341	-0.9079966	0.76594371
1	0.6341034	-0.4555433	0.67997948	0.41925266	-0.9416546	0.83007017
2	0.40025154	-0.9156621	1.19715695	1.1365559	-0.9393113	0.7646113
4	0.36710134	-1.0021173	1.96450983	3.40546435		
6	0.25	-1.3862944	2.58161117	6.37386973		

Table 3C: Calculated plasma concentration of CN in rabbit after a single oral administration.

Time	Conc	ln(C)	AUC	AUMC	R	R_adj
0	0		0	0		
0.25	0.91603965	-0.0876956	0.11450496	0.02862624		
0.5	1.23530175	0.21131527	0.38342263	0.13445884	-0.978454	0.9467152
1	1.08844896	0.08475371	0.96436031	0.5609838	-0.9709445	0.92364432
2	1.06885994	0.06659261	2.04301476	2.17406822	-0.9801965	0.94117763
4	0.95	-0.0512933	4.06187471	8.11178811	-0.9895759	0.95852079
6	0.8	-0.2231436	5.81187471	16.7117881		
8	0.6	-0.5108256	7.21187471	26.3117881		

Table 3d: Calculated plasma concentration of CSA in rabbit after a single oral administration.

Time	Conc	ln(C)	AUC	AUMC	R	R_adj
0	0		0	0		
0.25	3.58446824	1.27661014	0.44805853	0.11201463		
0.5	5.66883828	1.73498421	1.60472185	0.57833166	-0.913055	0.79208675
1	2.40529885	0.87767416	3.62325613	1.88826115	-0.961832	0.90016107
2	1.24778318	0.22136852	5.44979714	4.33869376	-0.9923602	0.97716819
4	0.90660836	-0.0980447	7.60418869	10.4606936	-0.9807967	0.92392452
6	0.57792068	-0.5483186	9.08871773	17.5546511		
8	0.46399308	-0.7678856	10.1306315	24.7341198		

Table 4: Pharmacokinetic parameters of ciprofloxacin and analogues after a single 40 mg/kg oral dose administration in rabbit.

Parameter	Unit	CFX	CIN	CN	CSA	P-value (between groups)
Lambda_z	1/h	0.120693	0.162329	0.068348	0.170902	< 0.001
$t_{1/2}$	h	5.74306	4.270024	10.1414	4.055821	< 0.001
T_{max}	h	0.5	0.5	0.5	0.5	< 0.001
C_{max}	µg/ml	2.577627	1.042907	1.235302	5.668838	< 0.001
T_infusion	h	1.5	1.5	1.5	1.5	< 0.001
Clast_obs/Cmax		0.100868	0.239715	0.640293	0.08185	< 0.001
AUC 0-t	µg/ml*h	4.370654	2.581611	7.905684	10.13063	< 0.001
AUC 0-inf_obs	µg/ml*h	6.52488	4.121697	19.47811	12.8456	< 0.001
AUC 0-t/0-inf_obs		0.669844	0.626347	0.405875	0.788646	< 0.001
AUMC 0-inf_obs	µg/ml*h^2	47.04326	25.10184	292.3928	62.34	< 0.001
MRT 0-inf_obs	h	6.459827	5.340171	14.26136	4.103023	< 0.001
Vz_obs	(mg)/(µg/ml)	1047.609	1233.056	619.6972	375.7966	< 0.001
Cl_obs	(mg)/(µg/ml)/h	126.4391	200.1603	42.35525	64.22433	< 0.001
Vss_obs	(mg)/(µg/ml)	816.7747	1068.89	604.0433	263.5139	< 0.001

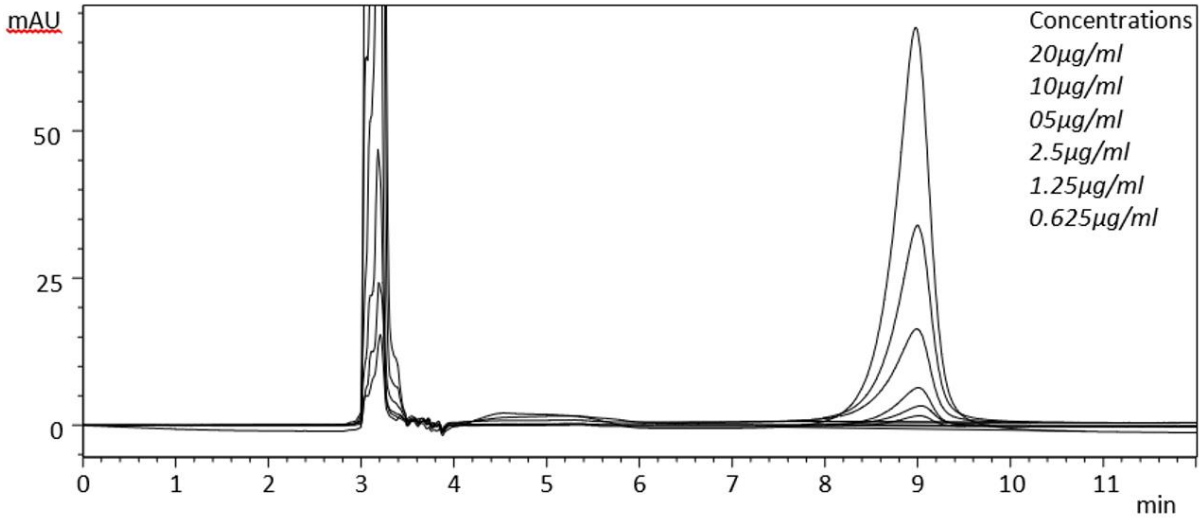


Fig. 2a: Chromatograms representation linear curve analysis of Ciprofloxacin (without Plasma).

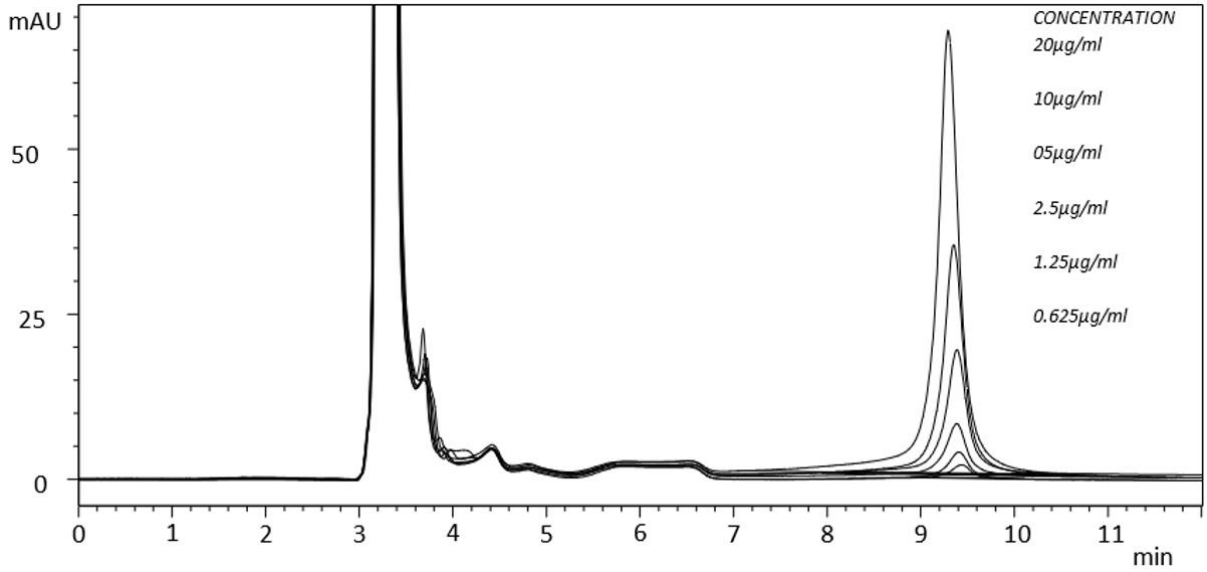


Fig. 2b: Chromatograms representation linear curve analysis of Ciprofloxacin (Plasma).

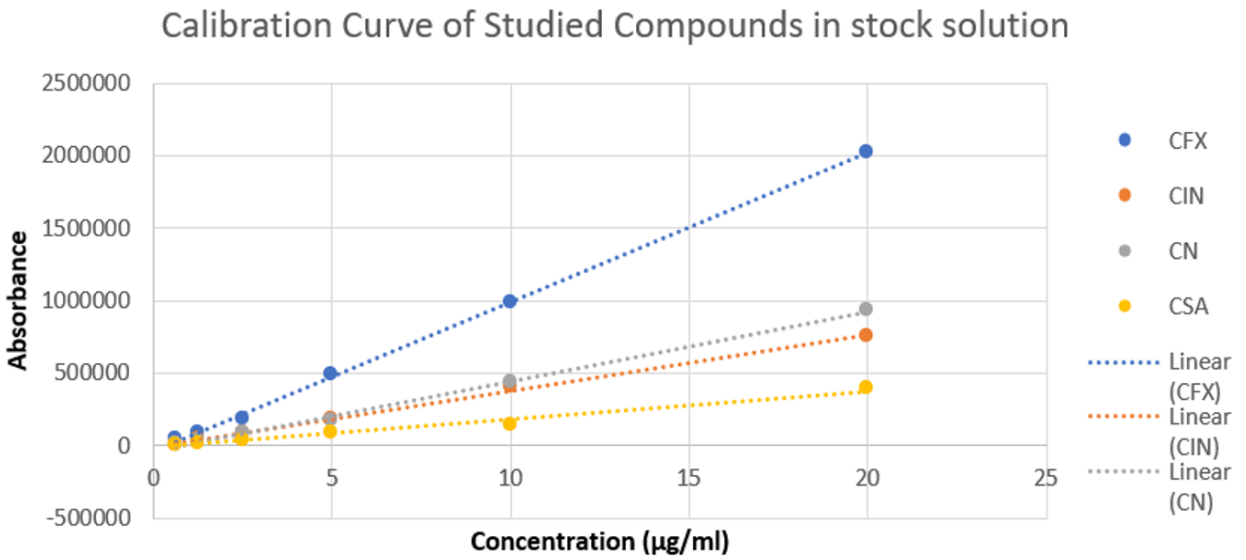


Fig. 3a: Graphical representation of calibration curve of CFX, CIN, CN, and CSA in selected concentration (20- 6.25 µg/ml) without plasma

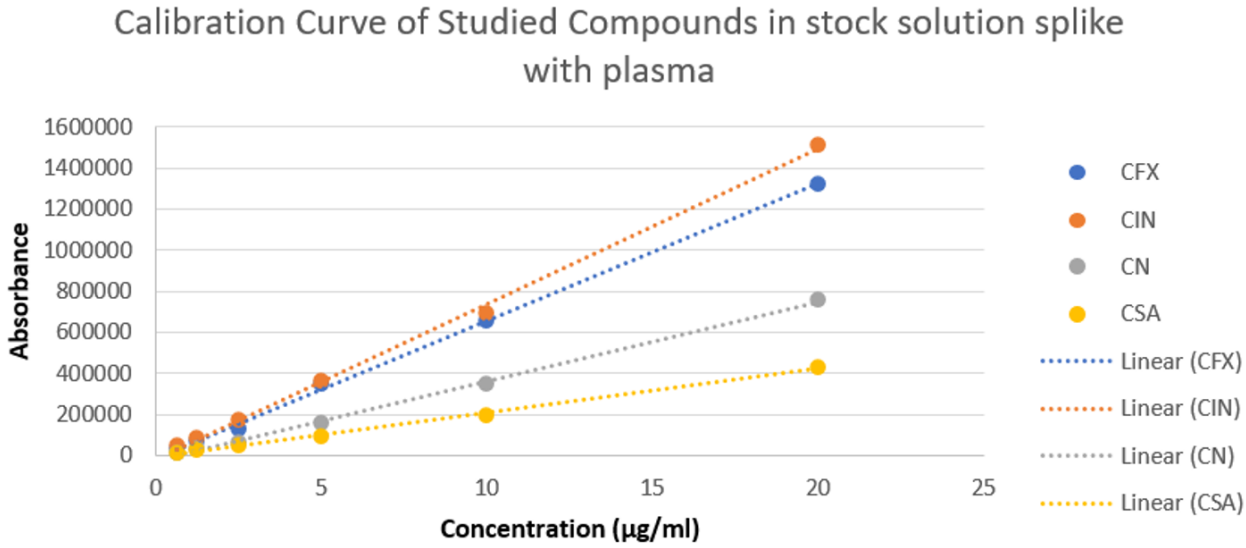


Fig. 3b: graphical representation of calibration curve of CFX, CIN, CN, and CSA by spike with plasma at concentration of 20 – 6.25 µg/ml

Preparation of stock solutions

10 mg of CFX and analogues were dissolved water individually and water to final volume of 100 ml in volumetric flask to get concentration of 100µg/ml. The stock solutions of CFX and analogues were serially diluted to obtained 20, 10, 5, 2.5, 1.25, 0.625 µg/ml concentrations. The prepared solutions were filtered into auto-sampler vials using 0.45µm syringe filters. Auto-sample volume to be injected into HPLC system was adjusted at 50µL.

Preparation of plasma sample solutions

1 ml of acetonitrile was added in 0.5 ml of plasma sample. Then the sample was centrifuged at 3000 rpm for 15 min. the supernatant solution was collected for the analysis. The prepared solutions were filtered into auto-sampler vials using 0.45 µm syringe filters. Auto-sample volume to be injected into HPLC system was adjusted at 50 µL. The amount of CFX and analogues in plasma were estimated by the calibration curve using line equation that is y = mx + C (m = slope, C = y -intercept).

Preparation of Calibration curve

The plasma sample was spiked with standard drug (CFX) and analogues solution to obtained 20- 0.625 µg/ml concentrations. The UV-absorbance of drug was plotted against concentration to obtain calibration curve and linear

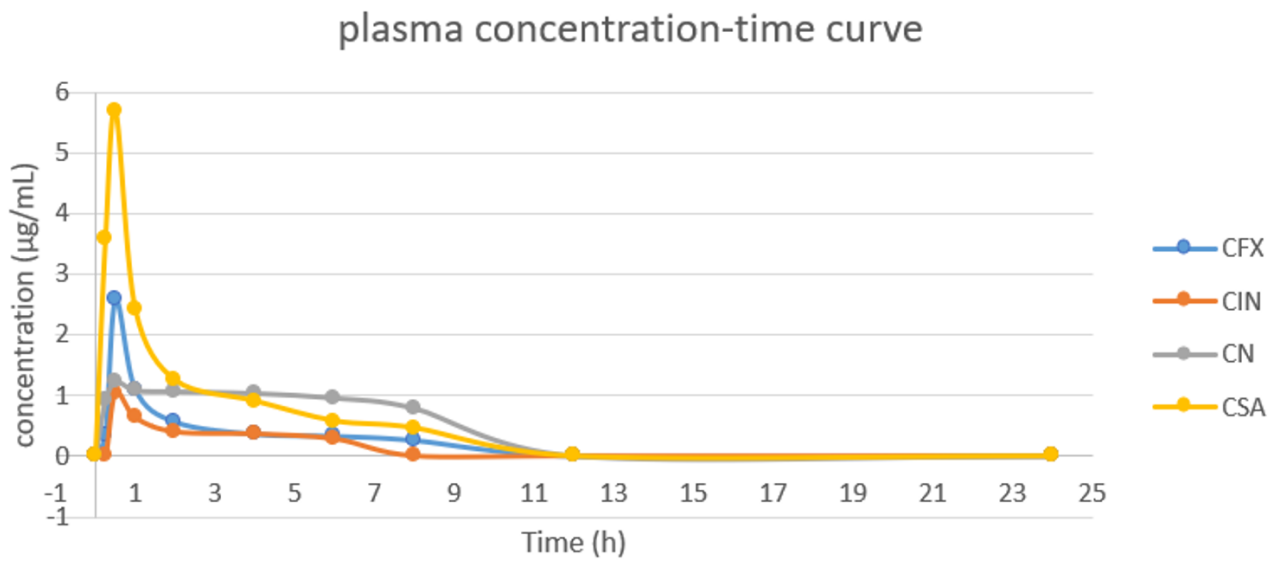


Fig. 4: Cumulative graph of mean plasma concentration-time curve of oral administration of CFX and derivatives (40mg/kg) in rabbit model by HPLC

regression. The linear relationships were observed between relative peak area and mentioned concentration ranges. The values of slope, intercept and correlation (r) are compiled in table 1. This calibration curve was used for the calculation of amount drug in plasma. The calibration study was conducted in 3 replicates.

Pharmacokinetic analysis of data

The one compartment analysis was used to determine the plasma concentration time data and area under curve (AUC) was obtained by trapezoidal rule method. The PK-Solver was used to estimate the pharmacokinetics parameter includes terminal rate constant of the concentration-time curve (lambda_z), maximum time of plasma peak concentration (T_{max}), maximum peak plasma concentration (C_{max}), volume of distribution (V_d), half-life ($T_{1/2}$), clearance (Cl), last measured concentration time point / maximum plasma concentration (Clast/Cmax), area under curve at 0 time to maximum time (AUC 0-t), Area under first moment curves (AUMC), mean residence time (MRT), volume of distribution based on the terminal slope (Vz), Steady-State Volume of Distribution (Vss). The "inf" and "obs" mean infinity and observe value respectively.

Safety of compounds

The calculated dose of analogues was administered orally to the healthy rabbits individually. The behavioral changes, clinical signs and body weight was monitored during the study period.

STATISTICAL ANALYSIS

The CFX and derivative were analysed by using IBM SPSS Statistics 27. The analysis was carried out by one-way ANOVA with the 95% level of confidence interval. Significant differences between individual means were identified using LSD test.

RESULTS

The *in-vivo* pharmacokinetics studies of CFX and the calibration curve was created in concentration range between 20 to 0.625µg/ml for all studied compounds without plasma and spike with plasma (fig. 2a and 2b). All samples were analyzed e times and mean values of absorbance of studied compounds against concentration are presented in table 1 and the graph was built between concentration and absorbance with plasma and without plasma (fig. 3a and 3b). The values of linear regression, slope and intercept of studies compounds are measured by the help of constructed graph and are compiled in table 2.

Pharmacokinetics study of compounds has been performed in rabbit model. 3 rabbits were taken for one compound and the mean values were calculated for final result. The duration of study was 24 hours and the oral dose of compounds was 40mg/kg. The blood samples were collected in the time duration of 0.0, 0.25, 0.5, 1, 2, 4, 6, 8, 10, 12 and 24 hours. The concentration (conc), log of concentration (ln (C)), area under curve (AUC), under first moment curves (AUMC), correlation coefficient (R) and adjusted R-squared value (R_adj) of CFX and analogues were compiled in table 3a -3d. Pharmacokinetic parameters of compounds were calculated by PK-Solver and presented in table 4. Mean plasma concentration-time curves of oral administration of studied compounds were calculated and cumulative graph of mean plasma concentration with time was presented in fig. 4.

DISCUSSION

Pharmacokinetic studies are representation of the time course of drug absorption, distribution, biotransformation, and excretion. The drug must achieve its acquired concentration at site of action to produce its therapeutics

effect. Our study was investigated the preclinical pharmacokinetics of ciprofloxacin analogues. The pharmacokinetics parameters were compared with the reference drug. In this study all compounds' samples were injected 3 times and mean of samples presented as results
.

Safety of compounds

After the administration of CFX analogues, there are no toxicity symptoms observed in rabbits, neither locally nor systemically. All rabbits were active and live during the period of study and there are no changes in the behavior of rabbits. It is concluded that the studies analogues were non-toxic and save for administration.

Calibration curve

The calibration curve was constructed in range of 20 to 0.625 µg/ml for ciprofloxacin and all selected analogues using stock solution and spiking with plasma. The calibration study was conducted in 10 replicates. The graphs were constructed between selected concentrations and absorbance of solution with and without plasma separately for calculation of linear regression. The values of slope and intercept were calculation by using line equation and compiled in table 2. The calibration curve of all compounds was linear with correlation coefficient (r^2) were in the range of 0.9808 to 0.9994 and 0.9979 to 0.9991 without plasma and with plasma respectively (fig. 3).

Pharmacokinetics of ciprofloxacin and derivatives

The pharmacokinetics study of CFX has been published by many scientists in human (van Rhee *et al*., 2022, Vance-Bryan *et al*., 1990, Lebel and Bergeron, 1987, Campoli-Richards *et al*., 1988) and in animal model (Manceau *et al*., 1999, Turnidge, 1999, Papich, 2012). The 40mg/kg/day was the selected dose of CFX which was reported in literature (Manceau *et al*., 1999, Hanan *et al*., 2000, Rootman *et al*., 1992, Fernandez *et al*., 1999, Bashir *et al*., 2008, Al-Ghazawi *et al*., 2012). The structures of analogues were related to the CFX and therefore, same dose as CFX was assumed for analogues. Because of the molecular weight of all compounds <500 Da, the oral route of administration was selected. The duration of study was 24 h after the single dose administration. After 8h the trace of compounds in blood was not observed. The plasma concentration-time curve of CFX and analogues (40mg/kg), after oral administration, is represented in fig. 4 and 5. The plasma concentration of compounds and *in-vivo* pharmacokinetics parameters of all compounds were summarized in table 2 and table 3 respectively. The one-way ANOVA results revealed that the pharmacokinetics results of all derivatives were significantly different from the standard drug (CFX). The absorption time of CFX and analogues were same as 30 min. The C_{max} of CFX was 2.578 µg/ml which was higher than the analogue CIN (1.043 µg/ml) and CN (1.235µg/ml). However, the value of C_{max} of CSA was 5.668 µg/ml which was higher than the standard drug (CFX). According to the fig. 4a-d and fig. 5, the C_{max} of all given drugs was followed by the concentration decreased by time and showing straight line in concentration-time plot indicating the first order mode of elimination. Furthermore, the half-life of reference drug and analogues was calculated as $T_{1/2}$. It was observed that the half-life of CFX was 5.74 h. Whereas, the values of half-life of CIN and CN were 8.07 and 10.14h respectively. Among all studied compounds the CSA showed minimum half-life that was 4.05 h. the CSA was removed from the animal body quickly and it was supposed as less toxic as compared to the other derivatives. The analogues CN showed the maximum $T_{1/2}$ values as mentioned above and the $T_{1/2}$ values of CIN was also greater than the CFX. Similarly, the AUC of CSA was higher among all derivatives as well as standard (CFX). The volume of distribution of CFX and analogues were 816, 1422, 604, 263 mg.ml/µg for CFX, CIN, CN and CSA respectively. The total clearance (CL) of CFX and derivatives were in the range of 42 to 139 mg/(µg/ml)/h. The faster a drug is absorbed, the greater the peak plasma concentration and shorter the time to peak plasma concentration (Jambhekar, 2002).

CIN has greater $T_{1/2}$ with high volume of distribution and high drug clearance rate as compared to the CFX. Large volume of distribution indicated that the high amount of compound distributed into the body cells and the molecules of CIN was not deposited into the cell as disclosed by calculated value of drug clearance (CL). The 2nd studied of compound CN showed very high half-life with low volume of distribution and low drug clearance. According to the calculated data, the onset of action of CN may be slower than the control (CFX). The C_{max} value of 3rd compound, CSA, was higher than the control means the absorption of CSA was 2 times greater than the control (CFX). The half-life was 4.05 h which was also better than the control, but the volume of distribution and drug clearance was lower than the control. This result indicated rapid onset of drug action with quick drug elimination from the body.

CONCLUSION

In this study, we performed *in-vivo* pharmacokinetics study of freshly synthesized compounds through HPLC-UV on rabbit model. It is concluded that in this analysis, preclinical pharmacokinetic parameters of CFX and its analogues were estimated using collective data after oral administration. The pharmacokinetics model was computed after oral administration using a compartment-model dependent analysis directly. The pharmacokinetics was evaluated using area under curve, the zero and first moment curves from 0 to last time, distribution half-life, and MRT. The data demonstrates that the newly synthesized derivatives of CFX were safe in animal model and show good pharmacokinetics. In future, these compounds could be the candidates for clinical trial.

REFERENCES

Akhtar M, Sultana N, Arayne MS, Siddiqi TA and Khan A (2019a). Moxifloxacin-ester derivatives: Synthesis, characterization and pharmacological evaluation. *Pak. J. Pharm. Sci.*, **32**: 1301-1316.

Akhtar M, Sultana N, Arayne MS, Siddiqi TA and Khan A (2019b). Synthesis, characterization, antimicrobial and enzyme inhibitory studies of moxifloxacin with aromatic carboxylic acids. *Pakistan Journal Of Pharmaceutical Sciences,* **32**: 1201-1206.

Al-Ghazawi M, Aburjai T, Shraim N, Bani-Jaber A and Aburuz S (2012). Effect of licorice extract on the pharmacokinetics of ciprofloxacin in rabbits after oral administration using an improved high-performance liquid chromatography assay. *Jordan Journal Of Pharmaceutical Sciences,* **5**: 120-30.

Barathe P, Reddy S, Kaur K, Shriram V, Bhagwat R, Dey A, Verma SK and Kumar V (2022). Nanomaterial-mediated delivery of antimicrobial agents:'the nanocarriers. *nano-strategies for addressing antimicrobial resistance: nano-diagnostics, nano-carriers, and nano-antimicrobials.* Springer. pp---?

Bashir S, Jamshaid M, Ahmad B and Iqbal J (2008). Pharmacokinetics of ciprofloxacin in normal rabbits and changes observed in induced dehydrated state. *Pakistan Journal Of Pharmaceutical Sciences,* **21**: 225-230.

Campoli-Richards DM, Monk JP, Price A, Benfield P, Todd PA and Ward A (1988). Ciprofloxacin: A review of its antibacterial activity, pharmacokinetic properties and therapeutic Use. *Drugs*, **35**: 373-447.

Casal J and Asis S (2017). Natural and synthetic quinoline derivatives as anti-tuberculosis agents. *Austin Tuberc. Res. Treat*, **2**:1007-1010.

Chang KC and Yew WW (2013). Management of difficult multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis: update 2012. *Respirology*, **18**: 8-21.

Dileep K, Polepalli S, Jain N, Buddana SK, Prakasham R and Murty M (2018). Synthesis of novel tetrazole containing hybrid ciprofloxacin and pipemidic acid analogues and preliminary biological evaluation of their antibacterial and antiproliferative activity. *Molecular Diversity,* **22**: 83-93.

Faidallah HM, Girgis AS, Tiwari AD, Honkanadavar HH, Thomas SJ, Samir A, Kalmouch A, Alamry KA, Khan KA and Ibrahim TS (2018). Synthesis, antibacterial properties and 2d-qsar studies of quinolone-triazole conjugates. *European Journal Of Medicinal Chemistry,* **143**: 1524-1534.

Fernandez J, Barrett JF, Licata L, Amaratunga D and Frosco M (1999). Comparison of efficacies of oral levofloxacin and oral ciprofloxacin in a rabbit model of a staphylococcal abscess. *Antimicrobial Agents And Chemotherapy,* **43**: 667-671.

Festing MF and Altman DG (2002). Guidelines for the design and statistical analysis of experiments using laboratory animals. *Ilar Journal,* **43**: 244-258.

Garza I, Wallace MJ, Fernando D, Singh A, Lee RE, Gerding JS, Franklin C and Yendapally R (2017). Synthesis and evaluation of thiazolidine amide and n-thiazolyl amide fluoroquinolone derivatives. *Archiv Der Pharmazie,* **350**: E201700029.

Hanan M, Riad E and El-Khouly N (2000). Antibacterial efficacy and pharmacokinetic studies of ciprofloxacin on pasteurella multocida infected rabbits. *Dtw. Deutsche Tierarztliche Wochenschrift,* **107**: 151-155.

Jambhekar SS (2002). Physicochemical and biopharmaceutical properties of drug substnaces and pharmacokinetics. *Faye's Principles Of Medicinal Chemistry*, pp.61-105.

Lebel M and Bergeron M (1987). Pharmacokinetics in the elderly. studies on ciprofloxacin. *The American Journal Of Medicine,* **82**: 108-114.

Manceau J, Gicquel M, Laurentie M and Sanders P (1999). Simultaneous determination of enrofloxacin and ciprofloxacin in animal biological fluids by high-performance liquid chromatography: application in pharmacokinetic studies in pig and rabbit. *Journal Of Chromatography B: Biomedical Sciences And Applications,* **726**: 175-184.

Mansha M, Taha M and Ullah N (2021). The design of fluoroquinolone-based cholinesterase inhibitors: synthesis, biological evaluation and in silico docking studies. *Arabian Journal Of Chemistry,* **14**: 103211.

Mohammed AA, Suaifan GA, Shehadeh MB and Okechukwu PN (2020). Design, synthesis and antimicrobial evaluation of novel glycosylated-fluoroquinolones derivatives. *European Journal Of Medicinal Chemistry,* **202**: 112513.

Papich MG (2012). Ciprofloxacin pharmacokinetics and oral absorption of generic ciprofloxacin tablets in dogs. *American Journal Of Veterinary Research,* **73**: 1085-1091.

Rootman D, Savage P, Hasany S, Chisholm L and Basu P (1992). Toxicity and pharmacokinetics of intravitreally injected ciprofloxacin in rabbit eyes. *Canadian Journal Of Ophthalmology. Journal Canadien D'ophtalmologie,* **27**: 277-282.

Salunke RA, Shukla M, Kaul G, Bansal BR, Chopra S and Chhibber M (2019). New fluoroquinolone compounds with endo-nortropine derivatives at c-7 position show antibacterial activity against fluoroquinolone-resistant strains of staphylococcus aureus. *Chemical Biology & Drug Design,* **94**: 1626-1633.

Shee S, Singh S, Tripathi A, Thakur C, Kumar TA, Das M, Yadav V, Kohli S, Rajmani RS and Chandra N (2022). Moxifloxacin-mediated killing of mycobacterium tuberculosis involves respiratory downshift, reductive stress, and accumulation of reactive oxygen species. *Antimicrobial Agents And Chemotherapy,* **66**: E00592-22.

Sultana N, Arayne MS, Akhtar M, Shamim S, Gul S and Khan MM (2010). High-Performance liquid chromatography assay for moxifloxacin in bulk, pharmaceutical formulations and serum: application to in-vitro metal interactions. *Journal Of The Chinese Chemical Society,* **57**: 708-717.

Towle TR, Kulkarni CA, Oppegard LM, Williams BP, Picha TA, Hiasa H and Kerns RJ (2018). Design, synthesis, and evaluation of novel n-1 fluoroquinolone derivatives: probing for binding contact with the active site tyrosine of gyrase. *Bioorganic & Medicinal Chemistry Letters,* **28**: 1903-1910.

Turnidge J (1999). Pharmacokinetics and pharmacodynamics of fluoroquinolones. *Drugs*, **58**: 29-36.

Ukpo GE, Owolabi MA, Imaga NO, Oribayo OO and Ejiroghene AJ (2017). Effect of carica papaya (linn) aqueous leaf extract on pharmacokinetic profile of ciprofloxacin in rabbits. *Tropical Journal Of Pharmaceutical Research,* **16**: 127-134.

Van Rhee KP, Smit C, Wasmann RE, Van Der Linden P D, Wiezer R, Van Dongen EP, Krekels EH, Brüggemann RJ and Knibbe CA (2022). Ciprofloxacin pharmacokinetics after oral and intravenous administration in (morbidly) obese and non-obese individuals: a prospective clinical study. *Clinical Pharmacokinetics,* **61**: 1167-1175.

Vance-Bryan K, Guay DR and Rotschafer JC (1990). Clinical pharmacokinetics of ciprofloxacin. *Clinical Pharmacokinetics,* **19**: 434-461.

Yuan Y, He Q, Zhang S, Li M, Tang Z, Zhu X, Jiao Z, Cai W and Xiang X (2022). Application of physiologically based pharmacokinetic modeling in preclinical studies: a feasible strategy to practice the principles of 3rs. *Frontiers In Pharmacology,* **13**: 895556.