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THE EFFECT OF BINDERS ON THE BIO-AVAILABILITY OF OFLOXACIN TABLETS IN HUMAN VOLUNTEERS

Naveed Akhtar[1], Muhammad Shoaib Khan[1], Mahmood Ahmad[1], Gulzeb Aziz[1] and Mohammad Aleem[2]

[1]*Department of Pharmacy, Faculty of Pharmacy and Alternative Medicine, The Islamia University of Bahawalpur, Pakistan*
[2]*Department of Statistics, Faculty of Science, The Islamia University of Bahawalpur, Pakistan*

إن الإتاحة الحيوية لعقار أوفلوكساسين الذى يستخدم فى علاج العدوى البكتيرية تختلف بإختلاف اللاصق الذى يستخدم فى صياغة الأقراص وذلك مرجعه إختلاف فى خواص اللصق وكذلك فى إنطلاق الدواء من الأقراص. ولقد تم فى هذا البحث تحضير صياغتين من أوفلوكساسين وكان الفرق الوحيد بينهما هو نوع اللاصق حيث تم إختيار الجيلاتين والنشا كالاصق. تم تقييم هذه الأقراص معمليا وحيويا. تم إجراء الدراسة الحيوية على مجموعتين كل منهما يحتوى على أربعة متطوعين ، ولقد تناول كل فرد من المجموعة الأولى قرص يحتوى على ٢٠٠ مجم أوفلوكساسين واستخدم فى تحضيره الجيلاتين كمادة لاصقة. أما الصياغة الثانية والتى استخدم فيها النشا كمادة لاصقة فقد تم إعطاء كل متطوع قرص يحتوى على نفس كمية الدواء التى تم إعطائها للمجموعة الأولى (قرص يحتوى على ٢٠٠ حجم دواء). وبعد مضى حوالى أسبوع دون إعطاء الدواء للمتطوعين حتى يحدث تخلص كامل من الدواء ثم إعطاء متطوعى المجموعة الأولى الصياغة الثانية وتم إعطاء متطوعى المجموعة الثانية الصياغة الأولى. تم تجميع عينات من دم المتطوعين على فترات متتابعة وتم تعيين تركيز الدواء عند هذه الأوقات بإستخدام جهاز كروماتوجرافيا الضغط العالى. وتم تقدير العوامل الآتية لكل من الصياغتين ١ ، ٢. أعلى تركيز فى الدم (C_{max}) ، الوقت اللازم للوصول إلى أعلى تركيز (t_{max}) ، فترة نصف العمر ($t_{½}$) ، حجم التوزيع (Vd). تم عمل تحليل إحصائى للنتائج التى تم الحصول عليها من الصياغتين الأولى والثانية ووجد أن الصياغة الأولى التى أستخدم فيها الجيلاتين كمادة لاصقة تساعد على إنطلاق الدواء أكبر من الصياغة الثانية التى استخدم فيها النشا كمادة لاصقة وذلك خلال ساعتين من التعاطى. أيضا وجد هناك اختلاف بين العوامل

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الفارماكوكينتيكية مثل معدل التخلص ، حجم التوزيع ، مدة نصف العمر وهذا يرجع إلى نوعية المادة اللاصقة المستعملة.

The bioavailability of ofloxacin, a fluoroquinolone widely used in the treatment of bacterial infection varies different with different binders used in the formulation of tablets due to different binding properties and variable release characteristics.

In this study, two formulations of ofloxacin were prepared. The only difference between them was of binder. The two binders used were gelatin and starch. In-vitro and in-vivo evaluation of tablets was performed. Eight healthy human volunteers were selected for this study, and were divided into two groups each consisting of 4 volunteers. First group was given formulation 1 with gelatin as binder. Each volunteer received 200 mg ofloxacin tablet. Volunteers of the second group were given formulation 2 with starch as binder. After one week wash out period, volunteers of the first group received formulation 2 and volunteers of second group received formulation 1. Blood samples were collected at different time intervals. The drug concentrations in plasma were assayed by High Performance Liquid Chromatography.

Pharmacokinetic parameters of formulation 1 were C_{max} *1.4412 ± 1.8367 µg/ml,* t_{max} *was 1.00 ± 0.00 hours, AUC 8.6804 ± 0.8346 µg.h/ml, AUMC 43.017 ± 0.2893 µg.*h^2*/ml, MRT 4.8869±1.3587 hours, Ke 0.2067 ± 6.9207, T½ 3.3886 ± 1.6321 hours, Vd 113.826±0.2983 L/Kg, Vss 4.833 ± 0.9138 L/Kg, Cl 23.595 ± 0.5070 ml/h/Kg. For Formulation 2 these values were 1.515 ± 1.5898 µg/ml, 0.5 ± 0.00 hours, 9.0317 ± 0.8805 µg.h/ml, 35.4486±0.3337 µg.*h^2*/ml, 3.8798 ±1.4668 hours, 0.2606 ± 6.0291, 2.68 ± 1.76 hours, 86.609 ± 0.3354 L/Kg, 5.94 ± 0.84L/Kg, 22.580 ± 0.5333 ml/h/Kg respectively.*

Statistical analysis was performed and it was found that the formulation 1 (formulated with gelatin) released the drug slightly greater than the formulation 2 within two hours after its administration. There was highly significant difference between mean residence time, elimination rate constant, half life and volume of distribution between both of the formulations. Therefore, formulation 2 has greater bioavailability than the formulation 1. Thus it can be concluded that the binder can affect the bioavailability and pharmacokinetic parameters of a drug.

INTRODUCTION

Effects of ofloxacin

Ofloxacin is a new fluoroquinolone with a spectrum of activity similar to other fluoroquionolones with activity which includes *Chlamydia trachomatis*, *Mycobacterium* spp., *Mycoplasma* spp. and *Legionella pneumophila*. Through its additional mechanisms of action, ofloxacin may be less susceptible to the development of resistance from *Staphylococcus aureus* commonly seen with currently available flouroquinolones. The impact of these findings cannot be evaluated without further clinical experience. The pharmacokinetics of ofloxacin are characterized by almost complete bioavailability (95 to 100%), peak serum concentrations in the range of 2 to 3 mg /L after a 400mg oral dose and an average half life of 5 to 8 h. In comparison with other available quinolones, elimination is more highly dependent on renal clearance, which may lead to more frequent dosage adjustments in patients with impaired renal function.

Pharmacokinatics

Ofloxacin appears less likely to affect the pharmacokinetics of drugs (e.g. theophylline) which commonly interact with fluoroquinolones such as ciprofloxacin and enoxacin. The properties of ofloxacin make it a therapeutic alternative to currently available flouroquinolones.

Clinical usefulness of nalidicix acid is limited by the rapid emergence of resistant strain. Most of the absorbed drug i.e., 90% is protein bound and levels of the free drug are therefore inadequate for the treatment of systemic infection.[1] Fluoro-quinolones are highly effective against gram positive and gram negative bacteria both in vino and *in-vitro* with few of the problems of their predecessors.[2] The spectra of activity of the fluoroquinolones against these organisms appear comparable; however, differences emerge against other microorganisms, such as *Chlamydia trachomatis*, *Mycobacterium* spp. and *Mycoplasma pneumoniae*

Ofloxacin is a broad spectrum antibiotic with poor activity against anaerobes.[3-8] The ofloxacin minimum inhibitory concentration (MIC) for 90% (MIC_{90}) of Enterobacteriaceae isolates (range 0.6 to 4mg /L) would indicate inferior activity compared with ciprofloxacin.[9] This may not be clinically significant since ofloxacin achieves higher serum concentrations. Gram- positive bacteria are similarly sensitive to ofloxacin and ciprofloxacin, with *Staphylococci* spp. more sensitve than *Streptococci* spp. As with other available fluoroquinolones, Streptoccoci are only moderately sensitive to ofloxacin with MIC values ranging from 1 to 4 mg/L.[10] *Pseudomonas* spp. exhibit differing susceptibilities. *Pseudomonas aeruginosa* and non-aeruginosa species are less susceptible to ofloxacin than to ciprofloxacin, however, ofloxacin is at least as active against *Xanthomonas maltophilia*.[3] Ofloxacin is active against *Clostridium perfringens* but few other anaerobes are inhibited at obtainable serum concentrations. *Legionella pneumophila* and *Mycobacterium tuberculosis* are also susceptible to ofloxacin. *C. trachomatis* is very sensitive to ofloxacin with *Ureaplasma urealyticum* and *Mycoplasma hominis* only moderately susceptible. In situations of comparable serum concentration to MIC ratios and efficacy, the choice of quinolone may be more influenced by dosag intervals and drug interactions than minor differences in *in-vitro* activity.

The aim of the work

Excepients are added to the formulations to produce certain properties to the drug and dosage form. Some of these properties of the excepients are used to improve the compatibility of the active drug. Stabilize the drug against, degradation, gastric irritation; control the rate of drug absorption increase drug bioavailability etc. Excepients in a drug product may also affect the dissolution kinetics of the drug. Excepients may be added intentionally to the formulation to enhance the rate and extent of drug absorption or to delay or slow the rate of drug absorption. Excepients in formulation may interact directly with the drug to form a water soluble or water insoluble complex, e.g., if tetracycline is formulated with calcium carbonate, an insoluble complex of calcium tetracycline is formed that has a slow rate of dissolution and poor absorption. Several studies show that changing the excepients in a formulation changes the bioavailability and pharmacokinetics of the active drug.

Binding material can also affect the release of active drug material from formulation which also affects bioavailability of active drug. So different binders affect the pharmacokinetics of drug.

MATERIALS AND METHODS

Chemicals

Ofloxacin (Aventis Pharma Karachi), Gelatin (Merck, Germany),Lactose (Riedel, Holland), Carboxymethyl cellulose (BDH, Germany), Starch (Merck, Germany), Magnesium Stearate (Merck, Germany), Talc (Merck, Germany), Cellulose Acetate Phthalate (Fluka, Switzerland), Propylene Glycol (Merck, Germany), Methylene Chloride (BDH, England), Alcohol (Merck, Germany), Hydroxypropyl Methyl Cellulose (BDH, England), Propylene Glycol, USP (Merck, Germany), Ethyl Alcohol, 200 proof (Merck, Germany), Acetonitrile (Merck, Germany), Disodium Hydrogen Phosphate (Sigma, Germany), Triethylamine (Merck, Germany), Double Distilled Water (Islamia University Bahawalpur).

Methods

Preparation of tablets

Ofloxacin	60 g
starch	19.5 g
Lactose	36.15 g

Gelatin for paste	8.1 g
Magnesium Stearate	2.25 g
Carboxy methyl cellulose	13.5 g
Talc	1.5 g
Corn starch	9 g

Two batches of Ofloxacin 200 mg tablets (400 tablets each) were prepared by using two different binders i.e. gelatin and starch by wet granulation method with single punch machine (Local made).

Determination of drug content

Tablets of each formulation were triturated in a mortar to fine powder form. 100 mg of the powder was then dissolved in 100 ml 0.1 N HCl. The solution in the flask was filtered and 1ml of this solution pipetted out in 100 ml volumetric flask. Volume was made upto 100 ml with 0.1 N HCl and the contents of Ofloxacin were determined using spectrophotometer at a wavelength of 294 nm. The analysis was conducted in sets of six and the average was then calculated.

***In-vitro* disintegration studies**

The *in-vitro* disintegration time of both formulations was determined using USP disintegration apparatus six vessel appartus (local made) using water as disintegration medium. Temperature was adjusted 37±2°. The disintegration time of two formulations was compared.

***In-vitro* dissolution studies**

The *in-vitro* ofloxacin release was determined using USP 2 dissolution apparatus (Curio, Pakistan) for both formulations using 0.1 N HCI (900 ml) as dissolution medium and at temperature 37±0.2° and paddle speed was set at 100 rpm.

***In-vivo* study protocol**

In-vivo study was conducted according to the randomized two way crossover design. Eight healthy, non smoking adult male volunteers with ages between 22 and 24 years old (mean = 22.62 years) their heights range from 154 cm to 169 cm (mean = 159.5 cm), and weighing from 56 kg to 61 kg (mean = 59.5 kg) participated in the study. The volunteers were divided into two groups, four volunteers in each group. Written informed consent was obtained from each volunteer after explaining the nature and the purpose of the study. All were found healthy after performing their complete blood and urine analysis and were not receiving any medication prior two weeks and during the study period.

All the four volunteers of group 1 each was administered one tablet (200 mg) of formulation 1 in random and all the volunteers of group 2 were administered one tablet of formulation two individually. After a washout period of one week, each volunteer of group 1 was given one tablet (200 mg) of formulation 2 and each volunteer of group 2 was given one tablet of formulation one. Both the formulations were administered with 240 ml of water after an overnight fasting. After 2 hours of dosing each subject was provided with breakfast consisted of 2 scrambled eggs, four pieces of toast and one glass of milk. Blood samples of 5 ml volume were collected in preheparinized syringes at 0 (before dosing), 0.5, 1.0, 2.0, 4.0, 6.0, 8.0, 10.0, 12.0 and 24.0 hours after dosing via an in-dwelling cannula placed in the forearm. The plasma was harvested and frozen at -15° until assayed.

Assessment of ofloxacin concentration in plasma

The plasma samples were analysed using reversed phase high performance liquid chromatography (HPLC) method. A Hypersil ODS reversed phase column (5 µm, 250 mm X 4.6 mm ID) was used for the separation. The detector was operated at 294 nm. The mobile phase consisted of distilled water, Acetonitrile and triethylamine (700:300:1.4). Adjusted the pH at 2.4 with orthophosphoric acid. Filtered the mobile phase by passing through filtration assembly under vacuum pressure of 150-200 torr using 0.45 µm membrane filter (sartorius). Now degassed the mobile phase by flushing it with nitrogen for 2-3 min. until complete degassing of the mobile phase was ensured. Analysis was run at a flow rate of 1.0 ml/min and quantified with peak height.

Prior to injection, ofloxacin was extracted from the plasma samples according to the following procedure: Extraction procedure was simply based on liquid-liquid extraction method.[11] In the extraction procedure 0.5 ml of the drug solution was spiked with 0.5 ml of the blank plasma in the 2 ml of the centrifuge tube and mixed well, then centrifuged for 10 min. Separated the organic layer by micropipette, filtered by using of the filtration syringe. And the filtrate was taken in polypropylene tubes. 20 µl was injected in to the HPLC injection port by injection syringe. Standard curve was prepared to encompass the anticipated range of plasma ofloxacin concentration found in healthy subjects taking ofloxacin. Blank plasma was spiked with ofloxacin drug solution to give the concentrations of 0.5, 1.0, 2.0, 4.0, 8.0 µg/ml. The extraction procedure was same as described earlier. Injections of 20 µl were injected and spectra were taken of each concentration. The peak areas were noted for each concentration. The absolute recovery of ofloxacin from the extraction procedure was determined at different plasma concentrations (0.5 to 8 µg/ml) by comparing the peak heights of the drug obtained from extracted plasma samples with those obtained from direct injections of the pure ofloxacin standards in water of equivalent amounts.

Data analysis

Pharmacokinetic analysis was performed by using MS Excel Windows Professional XP. PK analysis was performed by using non-compartmental model. Maximum concentration of Ofloxacin in serum (C_{max}) and times to these concentrations (T_{max}) were determined by visual inspection of plasma concentration time profiles. At each time points (t), (Ct/C_{max}) X 100% / individual was calculated, and the maximum, median and minimum values across all subjects were determined. These % ages can provide some guidance regarding sampling times that can be used clinically. The area under the concentration time curve from 0 hour - infinity ($AUC_{0-\infty}$) was calculated by the linear trapezoidal rule using the AUC from 0 hour to last measure concentration (C last) plus C last/K_{el} where t last is the time of the last measured concentration and Ke is the terminal elimination rate constant.

Statistical analysis

Statistical analysis was performed by using SPSS 7. Paired t-test was used to check the differences between the parameters of two formulations. For this purpose average concentration of the two formulations were taken and analyzed by the SPSS 7.

RESULTS AND DISCUSSION

***In-vitro* evaluation**

Percentages of active ingredients of both the formulations were noted and have been presented in the Table 1. Both formulations of ofloxacin tablets were analyzed by UV spectrophotomertric method. The percentage of active ingredients in both the formulations was found to be 101.22% in formulation 1 and 102.15 in formulation 2. This is in accordance with B.P.

Disintegration time for both the formulations was noted and has been presented in the Table 1. Disintegration test was performed on both the formulations. Mean disintegration time for formulation 1 was found to be 8 minutes and mean disintegration time for formulation 2 was 11 minutes. The difference in the mean disintegration time of two formulations may be due to difference in the binders. Hardness test was performed on both the formulations. The hardness of the formulation 1 was 7 Kg/cm^2 and the hardness of formulation 2 was 5 Kg/cm^2. Hardness of formulation 1 was found to be more than the formulation 2 as gelatin has more binding properties than starch.

Dissolution behaviour of both formulations have been shown in the Table 2 and presented in Figure 1.

Table 1: Assay, disintegration time and hardness test values of formulation 1 and 2.

In vitro parameter	Formulation 1	Formulation 2
Assay of Active Drug (%)	101.22	102.15
Disintegration Time (Minutes)	8	11
Hardness (kg/cm^2)	7	5

Table 2: Dissolution rate study of formulations 1 and 2.

Time (minutes)	Percent dissolved	
	Formulation 1	Formulation 2
15	32.39	28.36
30	53.46	45.03
45	68.27	62.03
60	90.68	85.49
90	96.89	90.68
120	100.09	100.01

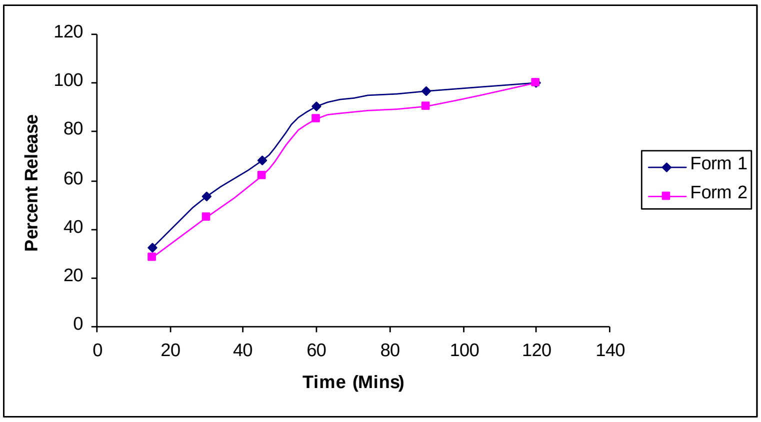

Fig. 1: Dissolution vs time profile of formulations 1 and 2.

Dissolution test was performed on both formulations. In the second formulation ofloxacin was released in a slower pattern in comparison with the first formulation. After first 15 minutes formulation 1 was released up to 32.39% while formulation 2 was released up to 28.36%. After 30 minutes formulation 1 was released up to 53.46% and the formulation 2 was released up to 45.03%. After 45 minutes formulation 1 was released up to 68.27% and formulation 2 was released up to 62.03%. After 60 minutes formulation 1 was released up to 90.68% and formulation 2 was released with a faster rate, which was up to 85.49%. Dissolution tests were continued until complete drug was released from the tablets. After 90 minutes the active ingredient in formulation 1 was released up to 96.89% and the active ingredient in formulation 2 was released about

90.68%. After 120 minutes formulation 1 was released up to 100.09% and the formulation 2 was released up to 100.01%.

On the basis of this comparison it can be concluded that formulation 1 released the ofloxacin in a slightly rapid pattern. In formulation 1 drug was released more quickly which might be due to presence of gelatin. Inspite of the fact that gelatin has more binding power as compared to starch, it liberated drug more quickly than starch. Perhaps gelatin helped in liberation of drug into water.

***In-vivo* evaluation**

The mean ofloxacin plasma concentration versus time profile for the formulation 1 has been represented in Figures 2 and 3 and the mean ofloxacin plasma concentration versus time profile for formulation 2 has been represented in Figures 4 and 5. Average plasma concentrations versus time for both formulations have been represented in Figure 6. Both the formulations show fluctuations at certain points. On the average formulation 2 is more bioavailable than formulation 1.

Pharmacokinetic parameters for formulations 1 and 2 of all the eight healthy subjects have been shown in Tables 3 and 4 respectively.

Pharmacokinetic parameters along with statistical analysis for formulation 1 and 2 have been presented in the Table 5.

Several pharmacokinetic parameters observed in our study were comparable to values previously reported[3-6] in studies of adult subjects. The peak plasma drug concentration, C_{max}, represents the maximum plasma drug concentration obtained after oral administration of drug. For many drugs, a relationship is found between the pharmacodynamic drug effects and the plasma concentration. C_{max} provides indications that the drug is sufficiently systemically absorbed to provide therapeutic response. In addition C_{max} provides warning of possibly toxic levels of drug.[12] In a pervious study conducted on human beings maximum plasma concentration (C_{max}) was found to be 1.6-2.2 mg/L with the dose of 200mg, 3.2-4.3 mg/L after the dose of 400 mg and 6.7-8.1 mg/L with the dose of 600 mg of ofloxacin.[13]

In this study maximum plasma concentrations (C_{max}) for formulation 1 were found to be ranging from 0.98-1.84 μg/ml with mean 1.44125 ± 1.8367μg/ml and for the formulation 2 maximum plasma concentrations (C_{max}) were ranging from 0.86-1.9 μg/ml with the mean value 1.5 ± 1.5898 μg/ml. These values were found to be almost closer to the values which have already been reported in the literature. The slight difference might be due to differences in body composition of different persons. The mean maximum plasma concentration values are consistent

Table 3: Pharmacokinetic parameters of all subjects after administering formulation 1.

Subject No.	AUMC (0-∞) (μg.h²/ml)	AUC (0-∞) (μg.h/ml)	C_{max} (μg/ml)	T_{max} (h)	MRT (h)	Ke (Hr^{-1})	$T_{1/2}$ (el) (h)	Vd (L/Kg)	(VSS) (L/Kg)	CL(ml/min)
1	34.410	7.577	1.23	1.0	4.5411	0.2202	3.1470	119.86	5.812	26.394
2	63.576	10.980	1.84	1.0	5.7899	0.1727	4.0124	105.46	3.146	18.214
3	37.892	8.555	1.64	1.0	4.4293	0.2258	3.0695	103.55	5.278	23.378
4	40.180	8.281	1.16	1.0	4.8527	0.2061	3.3629	117.21	4.978	24.155
5	29.425	6.555	0.98	1.0	4.4889	0.2228	3.1108	136.96	6.797	30.511
6	59.104	10.395	1.68	1.0	5.6858	0.1759	3.9403	109.40	3.384	19.240
7	38.450	8.1925	1.41	1.0	4.6933	0.2131	3.2525	114.58	5.202	24.413
8	41.097	8.907	1.59	1.0	4.6138	0.2167	3.1974	103.59	4.866	22.453
SUM	344.136	69.443	11.53	8.0	39.0948	1.6532	27.0927	910.60	39.463	188.757
MEAN	43.0170	8.6804	1.44125	1.000	4.8869	0.2067	3.3866	113.826	4.933	23.595
±SEM	0.2893	0.8346	1.8367	0.000	1.3587	6.9207	1.6321	0.2983	0.9138	0.5070

Table 4: Pharmacokinetic parameters of all subjects after administering formulation 2.

Subject No.	AUMC (0-∞) (μg.h^2/ml)	AUC (0-∞) (μg.h/ml)	Cmax (μg/ml)	Tmax (h)	MRT (h)	Ke (Hr^{-1})	$T_{1/2}$ (el) (h)	Vd (L/Kg)	(VSS) (L/Kg)	CL(ml /min)
1	40.1747	10.036	1.17	0.5	4.0031	0.2498	2.7741	79.77	4.978	19.928
2	28.2362	8.2578	1.78	0.5	3.4193	0.2925	2.3696	82.81	7.083	24.220
3	33.4325	9.2312	1.95	0.5	3.6217	0.2761	2.5098	78.47	5.982	21.666
4	24.446	6.8337	0.86	0.5	3.5773	0.2795	2.4791	104.70	8.181	29.267
5	28.4112	7.8462	1.19	0.5	3.6210	0.2762	2.5094	92.30	7.039	25.490
6	52.8183	10.771	1.91	0.5	4.9038	0.2039	3.3983	91.06	3.787	18.569
7	37.8012	9.6637	1.62	0.5	3.9117	0.2556	2.7108	80.96	5.291	20.696
8	38.2687	9.6137	1.64	0.5	3.9806	0.2512	2.7586	82.81	5.226	20.804
SUM	283.589	72.2532	12.12	4.0	31.0385	2.0849	21.5097	692.87	47.568	180.638
MEAN	35.4486	9.0317	1.515	0.500	3.8798	0.2606	2.6887	86.609	5.946	22.580
±SEM	0.3337	0.8805	1.5898	0.000	1.4668	6.0291	1.7620	0.3354	0.8404	0.5333

Table 5: Statistical analysis of pharmacokinetic parameters for formulation 1 and 2.

Parameters	Formulation 1	Formulation 2
C_{max} (µg/ml)	1.4412 ± 1.8367	1.515±1.5898 ^{ns}
T_{max} (Hrs)	1.00 ± 0.00	0.5 ± 0.00
AUC (µg.h/ml)	8.6804 ± 0.8346	9.0317 ± 0.8805 ^{ns}
AUMC (µg.h^2/ml)	43.017 ± 0.2893	35.4486 ±0.3337 ^{ns}
MRT (Hrs)	4.8869 ± 1.3587	3.8798 ±1.4668 **
Ke (hr^{-1})	0.2067 ± 6.9207	0.2606 ±6.0291**
$t_{1/2}$ (Hrs)	3.3886 ± 1.6321	2.68 ± 1.76 **
VD (L/Kg)	113.826 ± 0.2983	86.609 ± 0.3354 **
Vss (L/Kg)	4.833 ± 0.9138	5.94 ± 0.84^{ns}
Cl (ml/min)	23.595 ± 0.5070	22.580 ± 0.5333^{ns}

ns = non-significant difference ($p>0.05$)
* = significant difference ($p<0.05$)
** = highly significant difference ($p<0.01$)

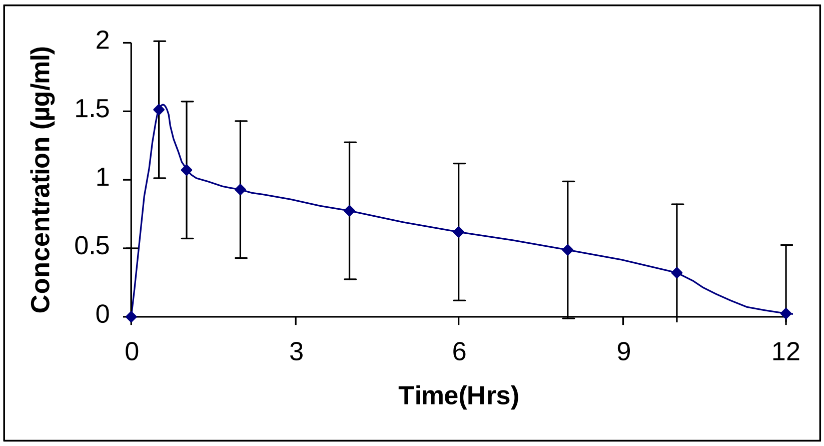

Fig. 2: Mean ± SEM plasma concentration vs time profile after administering formulation 1 in eight subjects

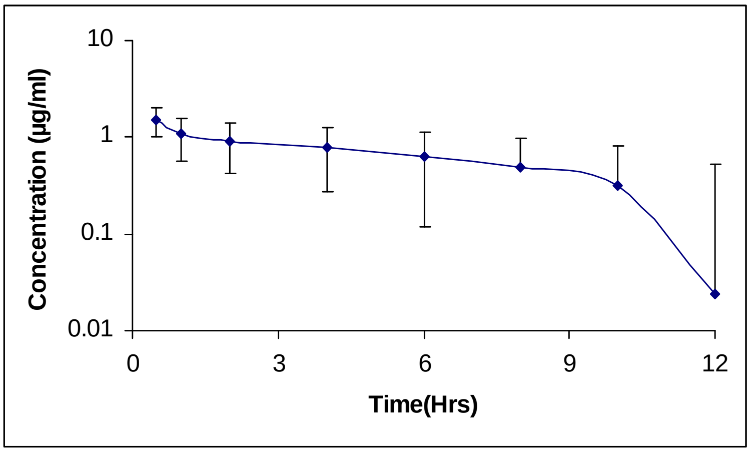

Fig. 3: Mean ± semi-log plot of plasma concentrations vs time of ofloxacin after administering of formulation 1.

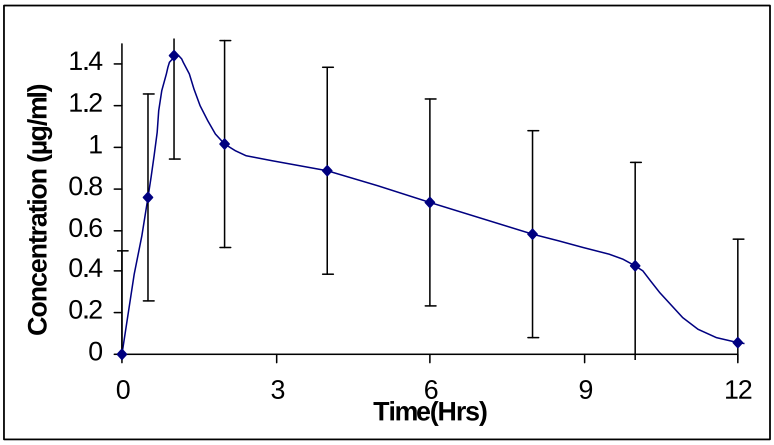

Fig. 4: Mean ± SEM plasma concentrations vs time profile after administering formulation 2 in eight subjects.

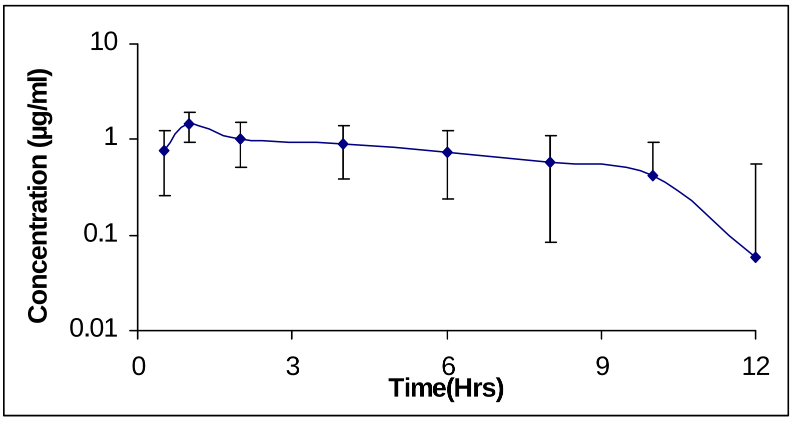

Fig. 5: Mean ± semi-log plot of plasma concentrations vs time of ofloxacin after administering of formulation 2.

in both these formulations. Paired t-test was performed on the average C_{max} values for two formulations. There was no significant difference between the two formulations at 95% confidence interval.

The time of peak plasma concentration, T_{max}, corresponds to the time required to reach maximum drug concentration after drug administration. At T_{max}, peak drug absorption occurs and the rate of drug absorption exactly equals to the rate of drug elimination.[12]

In a pervious study conducted on human volunteers ofloxacin has T_{max} 0.5 to 3 h.[14] In another study conducted on healthy young volunteers, T_{max} were repoted to be 1.6 ± 1.2 hours after the dose of 100 mg, 1.2 ± 0.4 hours with the dose of 300 mg and 1.2 ± 0.6 with the dose of 600 mg of ofloxacin.[15] In this study T_{max} of the formulation 1 was 1.0 hour in all volunteers and T_{max} of formulation 2 was 0.5 hours in all subjects. These two values were found in the range of values in pervious study.

In a pervious study conducted on human volunteers apparent volume of distribution of the drug was reported to be 1.0-1.5 L/kg with the dose of 200mg of ofloxacin.[13] In this study the volume of distribution (VD) for formulation 1 was ranging from 103.55-136.96-L/Kg with mean 113.826 ± 0.2983 L/Kg and for the formulation 2 was ranging from 79.77-104.70 L/Kg with mean 86.609 ± 0.3354 L/Kg. These values are very greater than reported in the pervious studies of healthy human volunteers. This difference may be due to alteration of body composition of different individuals and also due to different binding properties used in this study that's gelatin and starch.

Volume of steady state (Vss) of the formulation 1 was ranging from

3.146-6.797 L/Kg with mean 4.933 ± 0.9138L/Kg and of formulation 2 was ranging from 4.978-8.181L/Kg with mean 5.946 ± 0.8404 L/Kg. Elimination rate constant i.e. Ke of the formulation 1 was ranging from 0.1727-0.2258 with mean 0.2067 ± 6.9207 and for the formulation 2 was ranging from 0.2039-0.2925 with mean 0.2602 ± 6.0291. These values are constant in both formulations.

Conclusion

There is no big difference in the pharmacokinetic parameters of two formulations. As formulation 2 has greater AUC than formulation 1, on the basis of this it can be concluded that formulation 2 is slightly more better than formulation 1.

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