Available online on www.ijcpr.com
International Journal of Current Pharmaceutical Review and Research, 3(4), 91-98

ISSN: 0976-822X

Research Article

Pharmacokinetics of Diclofenac and Its Interaction with Cefotaxime in Female Goats after Intravenous Administration

Thakur Balwant Singh, *Nitesh Kumar, Chellappa Jayachandran

**Department of Veterinary Pharmacology & Toxicology, College of Veterinary Science & A. H., Rewa (M.P.), India*

Department of Veterinary Pharmacology & Toxicology, Bihar Veterinary College, Patna Rajendra Agricultural University, Pusa, Bihar, India.

ABSTRACT

A comparative pharmacokinetic study of diclofenac (2 mg/kg, i.v.) when given alone or in combination with cefotaxime (50 mg/kg, i.v.) in five female goats was carried out by using HPLC. The study revealed that the plasma concentrations of diclofenac were significantly lower ($p < 0.05$) in combined administration of diclofenac with cefotaxime (0.042, 0.083 and 0.25 h) whereas non-significant difference in plasma drug concentrations in later period upto 12 h. In urine, significantly higher ($p < 0.001$) drug concentration of diclofenac were observed from 0.042 to 4 h whereas significantly lower ($p < 0.001$) urine drug concentration were observed in later period (6 to 30 h) when diclofenac was given in combination with cefotaxime as compared to when diclofenac was given alone. Various kinetic parameters like A, C_p^0, β and K_{21} were significantly lower ($p < 0.001$) whereas $t_{1/2}$ β and MRT were significantly higher ($p < 0.05$ and $p < 0.001$, respectively) and rest other did not differ significantly in combined administration of diclofenac with cefotaxime as compared to its alone administration.

Key Words: Kinetics, diclofenac, interaction, cefotaxime and goat.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are usually combined with antimicrobial agents to treat various systemic infections associated with fever, pain and other inflammatory conditions.

Diclofenac is a potent NSAID that exhibits good analgesic, antipyretic, uricosuric and anti-inflammatory properties. It produces its effects by irreversibly inhibiting the cyclooxygenase pathway of prostaglandin synthesis which is the most common mediator of pain, inflammation and pyrexia. It is used in degenerative diseases, rheumatoid arthritis, ankolysing spondylitis and allied conditions [1].

Cefotaxime is a third generation semisynthetic cephalosporin with excellent bactericidal activity against a wide variety of gram-negative and most of the gram positive microorganisms, particularly β-lactamase producing

Author for correspondence: E-mail: niteshprof@gmail.com

strains [2]. It has a very important place in antimicrobial therapy because of its relatively expanded spectrum of antimicrobial activity, greater resistance to β-lactamase [3], low renal toxicity [4], excellent disposition kinetics characteristics and least problem of bacterial resistance as well. It can be given in penicillin allergic patients as well as against the infection of penicillin resistant microbes. It has minimum therapeutic concentration around 0.5 µg/ml for most of the susceptible microorganisms [5, 6].

Pharmacokinetic interactions between NSAIDs and antimicrobials have been described by various workers [7, 8, 9, 10, 11, 12, 13, 14, 15]. Though, available literatures show no studies on kinetic interactions between diclofenac and cefotaxime in animals, particularly in goats. An attempt is made in the present study to investigate the interaction of diclofenac with cefotaxime and whether the use of diclofenac in conjunction with cefotaxime may be advised or not.

Objectives of present investigation were (i) to determine the concentrations of diclofenac at different time intervals in plasma and urine when it was alone or in combination with cefotaxime following i.v. administration, (ii) to determine the kinetic parameters of diclofenac between both groups and (iii) to compare the differences in concentrations of diclofenac in plasma and urine, and various kinetic parameters between both groups.

MATERIALS AND METHODS

Experimental animals and drugs: The study was conducted on five clinically healthy female goats (*Capra hircus*) of non-descript breed between 18 to 24 months of age and 20 to 22 kg body weight. The animals were housed in animals shed with concrete floor, provided with dry fodder, concentrate feed and greens apart from grazing for 5 to 6 hours. Water was provided *ad lib*.

Diclofenac and cefotaxime were used in the present experiment. Versatan®-an injectable commercial preparation containing diclofenac in concentration of 25 mg/ml marketed by Ranbaxy, India and Britax®, an injectable commercial preparation containing sterile cefotaxime sodium U.S.P. equivalent to 1 gm of anhydrous cefotaxime marketed by Brihans Pharma, India and were used in the present study. Diclofenac (2 mg/kg, i.v) was given in each of five goats and in the same animals the drug was again given in the same dose rate along with cefotaxime (50 mg/kg, i.v.) in two different syringes one after another immediately after an interval of three weeks.

Collection and storage of blood and urine samples: Diclofenac (2 mg/kg) was injected into the jugular vein in each goat and the samples of blood were collected from the contralateral jugular vein into centrifuge tubes containing appropriate amount of sodium oxalate before and at 0.042, 0.083, 0.167, 0.25, 0.333, 0.50, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 30, 36 and 48 h post administration. Similarly diclofenac (2 mg/kg) was given simultaneously with cefotaxime (50 mg/kg) into the jugular vein and the samples of blood were collected similarly in the same animals as noted above. Simultaneously samples of urine were also collected at the above noted times. For collection of urine samples, a Foley's balloon catheter was into the bladder through the urethra and kept in position by inflating the balloon by giving 25 to 30 ml of water. Plasma was separated after centrifugation at 3000 rpm for 10-15 minutes at room temperature and kept in refrigerator until analysed, usually within three days of collection. Plasma and urine collected prior to drug administration were used for preparing drug standards in the respective biological fluids.

METHOD OF ANALYSIS

Table 1: Comparison of plasma and urine concentration (µg/ml) of diclofenac (2 mg/kg) when it was given alone and together with cefotaxime (50 mg/kg) in healthy goats following intravenous administration.

Time (h)	Diclofenac (µg/ml)		Diclofenac + Cefotaxime (µg/ml)	
	Plasma	Urine	Plasma	Urine
0.042	56.35 ± 10.47	1.68 ± 0.24	11.37 ± 1.61*	8.61 ± 0.70***
0.083	36.64 ± 8.36	3.15 ± 0.50	9.51 ± 1.81*	38.40 ± 7.56**
0.167	28.80 ± 7.98	6.43 ± 0.57	8.21 ± 1.69	62.18 ± 19.80*
0.25	14.73 ± 2.75	27.19 ± 0.77	7.11 ± 1.53*	115.49 ± 6.03***
0.33	7.06 ± 1.32	29.64 ± 0.84	6.17 ± 1.55	192.84 ± 10.25***
0.50	5.28 ± 1.08	95.64 ± 15.33	4.70 ± 1.24	206.66 ± 21.46***
0.75	3.36 ± 0.80	53.46 ± 2.93	3.95 ± 1.01	177.14 ± 11.83***
1	2.41 ± 0.71	36.79 ± 1.55	2.88 ± 0.73	141.1 ± 12.94**
1.5	1.86 ± 0.29	34.45 ± 1.67	1.95 ± 0.57	116.62 ± 8.48***
2	1.49 ± 0.25	24.52 ± 1.16	1.19 ± 0.30	87.99 ± 2.18***
3	1.20 ± 0.26	21.39 ± 0.63	0.73 ± 0.17	63.24 ± 2.21***
4	1.01 ± 0.23	12.76 ± 0.61	0.61 ± 0.13	36.43 ± 2.24***
5	0.80 ± 0.14	10.22 ± 0.37	0.56 ± 0.12	12.48 ± 2.79 ^{NS}
6	0.49 ± 0.10	8.67 ± 0.28	0.47 ± 0.10	4.18 ± 0.50**
8	0.33 ± 0.13	7.15 ± 0.20	0.41 ± 0.08	2.47 ± 0.23***
10	0.21 ± 0.08	7.03 ± 0.35	0.31 ± 0.08	1.27 ± 0.23***
12	0.08 ± 0.03	5.34 ± 0.14	0.30 ± 0.04	1.04 ± 0.16***
24	ND	3.92 ± 0.22	ND	0.80 ± 0.06***
30		2.06 ± 0.32		0.53 ± 0.05**
36		0.86 ± 0.17		0.41 ± 0.03 ^{NS}
48		0.38 ± 0.08		0.16 ± 0.01 ^{NS}

ND = Non-detectable ^{NS} *= Non-significant*

** P < 0.05* *** P < 0.01* **** P < 0.001*

Concentrations of diclofenac in plasma and urine were estimated by reverse phase partition chromatography using High Performance Liquid Chromatography (HPLC) as described [16] with slight modifications. The limit of quantitation of the method is 0.01 µg/ml.

Calculation of kinetic parameters: Log plasma drug concentration versus time profile showed a biphasic curve and thus followed a two-compartment open model as described [17, 18, 19]. Various kinetic parameters were obtained by least square regression method [19, 20]. The drug concentrations in plasma can be expressed by the following bi-exponential mathematical expression as a function of time:

$$C_p = Ae^{-\alpha t} + Be^{-\beta t}$$

Where, C_p = concentration of the drug in plasma; α and β = distribution and elimination rate constants, respectively; A and B = zero time intercept of distribution and elimination phases, respectively; e = base of natural logarithm and t = time elapsed after drug administration.

Elimination rate constant (β) and zero time concentration during elimination phase (B) were obtained by the least square regression method from the terminal slope of the biphasic curve. The theoretical plasma concentration for the elimination phase can be calculated during distribution phase of various time intervals. Subtracting the theoretical values from the observed values during distribution phase, a series of residual concentrations were obtained. From these residual concentrations, distribution rate constant (α) and zero time concentration during distribution phase (A) were calculated as per the method adopted for calculation of β and B.

STATISTICAL ANALYSIS

Concentrations of diclofenac in plasma and urine at various time intervals and its kinetic parameters when diclofenac was given alone or in combination cefotaxime in goats were compared by using paired t-test [21].

RESULTS

Comparisons of plasma and urine concentrations of diclofenac when given alone (2 mg/kg) and when given together with cefotaxime (50 mg/kg) after i.v. administration in goats are given in Table 1. Initially concentrations of diclofenac in plasma were noted to be lower and the difference was found to be significant ($p< 0.05$) at 0.042, 0.083 and 0.25 h when diclofenac was given in combination with cefotaxime as compared to its single administration. In both the cases, the drug was present in plasma upto 12 h.

Urine levels were noted to be highly significantly ($p< 0.001$) higher for long period (0.042 to 4 h) and thereafter, highly significantly lower (6 to 30 h) in case of combined administration as compared to single i.v. administration of diclofenac. No significant difference was observed at 5, 36 and 48 h.

Kinetic parameters of diclofenac when given alone and when given together with cefotaxime after i.v. administration are given in Table 2. The value of extrapolated zero time concentration during distribution phase (A) and theoretical zero time concentration (C_p^o) were found to be significantly ($p< 0.01$) lower in combined administration of the drugs as compared to single administration of diclofenac. Elimination rate constant (β) was found to be significantly ($p< 0.05$) lower while elimination half life ($t_{1/2}\beta$) was noted to be significantly ($p< 0.05$) higher when diclofenac is given with cefotaxime as compared to its alone administration. The value of mean residential time (MRT) was noted to be significantly ($p< 0.01$) higher while rate constant of drug transfer from peripheral to central (K_{21}) compartment was found to be significantly ($p< 0.05$) lower in combined administration group. Rest of the kinetic parameters did not differ significantly between both the groups.

DISCUSSION

Kinetic studies of diclofenac in animals are very little while studies in man [22, 23], rat [24], pig [25], buffalo calves [12] and sheep [13].

Concentrations of diclofenac in plasma were found to be significantly lower only at 0.042, 0.083 and 0.25 h, non-significantly lower upto 6 h and non-significantly higher thereafter in goats when the drug (diclofenac) was

Table 2: Comparison of kinetic parameters of diclofenac (2 mg/kg) when it was given alone and together with cefotaxime (50 mg/kg) in goats following intravenous administration.

Kinetic parameters (Unit)	Diclofenac	Diclofenac + Cefotaxime
A ($\mu g.\ ml^{-1}$)	45.95 ± 21.13	9.27 ± 1.91**
B ($\mu g.\ ml^{-1}$)	2.69 ± 0.65	1.03 ± 0.24^{NS}
C_p^o ($\mu g.\ ml^{-1}$)	48.65 ± 21.24	10.30 ± 2.04**
α (h^{-1})	4.467 ± 0.827	1.891 ± 0.327^{NS}
$t_{1/2}\alpha$ (h)	0.17 ± 0.02	0.51 ± 0.12^{NS}
β (h^{-1})	0.262 ± 0.040	0.119 ± 0.016*
$t_{1/2}\beta$ (h)	2.97 ± 0.53	6.64 ± 1.50*
AUC ($mg.L^{-1}h$)	19.40 ± 2.98	15.27 ± 3.71^{NS}
AUMC ($mg.L^{-1}h^2$)	51.50 ± 17.56	101.22 ± 40.50^{NS}
MRT (h)	2.62 ± 0.61	6.01 ± 1.00**
K_{12} (h^{-1})	1.710 ± 0.141	0.957 ± 0.216^{NS}
K_{21} (h^{-1})	0.514 ± 0.041	0.298 ± 0.050*
Kel (h^{-1})	2.509 ± 0.884	0.755 ± 0.088^{NS}
Fc (Ratio)	0.13 ± 0.02	0.16 ± 0.02^{NS}
T ≈ P (Ratio)	8.16 ± 2.21	5.87 ± 1.12^{NS}
Vd_C ($L.kg^{-1}$)	0.06 ± 0.01	0.40 ± 0.15^{NS}
Vd_B ($L.kg^{-1}$)	0.90 ± 0.18	3.14 ± 1.41^{NS}
Vd_{area} ($L.kg^{-1}$)	0.49 ± 0.11	2.01 ± 0.97^{NS}
Vd_{SS} ($L.kg^{-1}$)	0.28 ± 0.06	1.78 ± 0.71^{NS}
Cl_B ($ml.kg^{-1}.min^{-1}$)	1.91 ± 0.33	4.10 ± 2.21^{NS}

^{NS} = Non-significant ** P < 0.05* *** P < 0.01*

given in combination with cefotaxime. Available literature shows that no kinetic interaction study with cefotaxime particularly plasma level of diclofenac was carried out in goats so far.

Concentrations of diclofenac in urine were noted to be significantly higher from 0.042 to 4 h (except non-significantly higher concentration at 5 h) and significantly lower from 6 to 30 h when it was given with cefotaxime. However, no significant difference was noted from 36 to 48 h in both the groups. Peak concentration in urine was noted at 0.5 h in both the groups.

A and B = extrapolated zero time plasma drug concentration during distribution and elimination phase, respectively; C_p^o = theoretical zero time concentration; α and β = distribution and elimination rate constant, respectively; $t_{1/2}\alpha$ and $t_{1/2}\beta$ = distribution and elimination half life, respectively; AUC = area under plasma concentration time curve; AUMC = area under first moment of plasma concentration time curve; MRT = mean residential time; K_{12} and K_{21} = micro-rate constant of drug transfer from central to peripheral and peripheral to central compartment, respectively; Kel = rate constant drug elimination from central compartment; Fc = fraction of drug available for elimination from central compartment; T ≈ P = approximate tissue to plasma concentration ratio; Vd_C, Vd_B, Vd^{area}, and Vd_{ss} = volume of distribution from central compartment, elimination phase, AUC and steady state plasma level, respectively; Cl_B = total body clearance.

A significantly ($p< 0.01$) lower values for the A and C_p^o were obtained for diclofenac when it was administered in combination with cefotaxime as compared to its single administration by i.v. route.

Distribution rate constant (α) of 4.467 ± 0.827 h^{-1} and distribution half life ($t_{1/2}\alpha$) of 0.17 ± 0.02 h were calculated for diclofenac when given alone by i.v. route. The values did not differ significantly in goats when combined i.v. administration of diclofenac with cefotaxime was given, denoting similar rate of distribution of the drug occurred in goats between both the groups. Distribution half life ($t_{1/2}\alpha$) of 0.34 ± 0.08 h noted for diclofenac in buffalo calf [12] was found to be higher as compared to the $t_{1/2}\alpha$ value noted in the present study (0.17 ± 0.02) in goat which denotes faster distribution of diclofenac in goats as compared to buffalo calf.

The elimination rate constant (β) of 0.262 ± 0.04 h and elimination half life ($t_{1/2}$ β) of 2.97 ± 0.53 h were estimated after single i.v. administration of diclofenac. Significantly decreased β (0.119 ± 0.016 h-1) and significantly highly increased $t_{1/2}$ β (6.64 ± 1.50 h) were noted for diclofenac when it was given in combination with cefotaxime by i.v. route. The increased $t_{1/2}$ β observed after combined administration of diclofenac with cefotaxime indicates very slow removal of the drug from the body as compared to single administration of diclofenac. This is further supported by lower value of rate constant of drug elimination from central compartment (Kel) obtained in goats (0.755 ± 0.088 h^{-1}) after combined i.v. administration of diclofenac with cefotaxime. The $t_{1/2}$ β value of 1.1 h in man after i.v. administration of diclofenac [22] and 1.15 h in man after i.m. administration of diclofenac [23] were noted to be lower than the value obtained in goats in present study. The terminal half life ($t_{1/2}$ β) of diclofenac was similar in pig (2.4 h) and man (1.8 h) as observed [25, 22], respectively. Higher $t_{1/2}$ β of 4.06 ± 0.59 h was noted in buffalo calf [12].

The value of area under curve (AUC) was noted to be 19.40 ± 2.98 $mg.L^{-1}h$ when diclofenac (2 mg/kg) was given alone. This value did not differ significantly when diclofenac was given together with cefotaxime (50 mg/kg) after i.v. administration. The value of total area under first moment curve (AUMC) was noted to be 51.50 ± 17.56 $mg.L^{-1}h^2$ when diclofenac was given alone. This value noted to be significantly lower than those obtained when diclofenac was given together with cefotaxime (101.22 ± 40.50 $mg.L^{-1}h^2$). The value of mean residential time (MRT) was noted to be 2.62 ± 0.61h when diclofenac was given which was significantly lower ($p<0.001$) than those obtained when it was given together with cefotaxime (6.01 ± 1.00 h). On the same pattern, Kumar et al. [12] observed significantly higher ($p<0.01$) MRT value of 18.07 ± 9.12 h for diclofenac when it was given with enrofloxacin as compared to 4.72 ± 0.85 h when it was given alone in buffalo calf. Higher values of MRT in goats when diclofenac was given together with cefotaxime reflect that the drug remains in the body for comparatively longer duration in combination with cefotaxime.

The values of rate constant of drug transfer from central to peripheral compartment (K_{12}) and the rate constant for drug elimination from central compartment (Kel) were found to differ non-significantly between both the groups, while the value of rate constant of drug transfer from peripheral to central compartment (K_{21}) was found to be significantly lower for diclofenac when it was given together with cefotaxime.

Higher values of volume distribution (Vd_C, Vd_B, Vd_{area} and Vd_{SS}) were obtained when diclofenac was given along with cefotaxime as compared to its alone administration, though there was no significant difference in the data between both the groups. A non-significant high Vd_{area} (2.01 ± 0.97 $L.kg^{-1}$) of diclofenac was obtained when it was given in combination as compared to its alone administration (0.49 ± 0.11 $L.kg^{-1}$). A very low value of Vd_{area} (0.17 ± 0.11 $L.kg^{-1}$) in man was noted [22]. Kumar et al. [12] noted highly significantly ($p<0.01$) increase

in Vd_{area} (1.34 ± 0.04 $L.kg^{-1}$) when it was given in combination with enrofloxacin as compared to its alone (0.54 ± 0.10 $L.kg^{-1}$) administration in buffalo calf.

The total body clearance (Cl_B) was noted to differ non-significantly in case of combined administration with cefotaxime (4.10 ± 2.21 $ml.kg^{-1}.min^{-1}$) as compared to its single administration (1.91 ± 0.33 $ml.kg^{-1}.min^{-1}$). A high Cl_B value of 4.2 ± 0.9 $ml.kg^{-1}.min^{-1}$ in man [22] was observed. The value obtained [12] in buffalo calf (1.52 ± 0.07 $ml.kg^{-1}.min^{-1}$) is more or less similar to that of 1.91 ± 0.33 $ml.kg^{-1}.min^{-1}$.

CONCLUSION

In conclusion, the fact that general adverse reactions were not observed in any goats and favourable pharmacokinetic properties of diclofenac in combination with cefotaxime, such as long half-life and high mean residence time with wide penetration into different body fluids and tissues were observed as compared to diclofenac alone administration. Based on the present results, it can be concluded that diclofenac can be used safely and effectively along with cefotaxime to treat the drug sensitive microbial infections associated with fever, pain and other inflammatory conditions.

ACKNOWLEDGEMENT

Authors acknowledge to Dean, B.V.C, Patna and Vice-Chancellor, R.A.U., Pusa, India for providing necessary facilities and help for conducting this experiment.

REFERENCES

1. Brogden RN, Heel RC, Pakes GE, Speight TM, Avery GS. Diclofenac sodium: a review of its pharmacological properties and therapeutic use in rheumatic diseases and pain of various origins. Drugs 1980; 20(1): 24-48.
2. Neu HC. Antibacterial activity of desacetylcefotaxime alone and in combination with cefotaxime. Rev Infect Dis 1982a; 4: S374-S378.
3. Kalager T, Digranes A, Bakke K, Hellum KB, Bergan T, Solberg C. Cefotaxime in serious infections: A clinical and pharmacokinetic study. J Antimicro Chemother 1982; 9: 157-163.
4. Regamy C. Pharmacokinetic of ceftriaxone and its relation to concentration in extravascular compartments, comparison with cefotaxime. Chemotherapy 1985; 31: 85-94.
5. Hoffler P, Piper C. Pharmacotherapeutica 1981; 2: 637.
6. Neu HC. The in vitro activity, human pharmacology and clinical effectiveness of new beta-lactam antibiotics. Annual Rev Pharmacol Toxicol 1982b; 22: 599-642.
7. Kampmann J, Molhom HJ, Siersbock- Nielsen K, Laursen H. Effect of some drugs on penicillin half-life in blood. Clin Pharmocokinet 1972; 2: 252-68.
8. Carbon C, Contrepois A, Nivoche Y, Granjean M, Decourt S, Chou NP. Effect of phenylbutazone on extravascular diffusion protein binding and urinary excretion of cefazolin in rabbits. J Pharmacol Exp Therap 1981; 218: 537-543.
9. Carbon C, Dromer F, Brion N, Cremieux AC, Contrepois A. Renal disposition of ceftazidime illustrated by interference by probenicid, frusemide and indomethacin in rabbits. Antimicrob Agent Chemother 1984; 26: 373-377.

10. Kumari S. Pharmacokinetics of enrofloxacin and its interaction with paracetamol in goat. M.V.Sc. Thesis, Rajendra Agricultural University, Bihar, India, 1998.
11. Kumar N, Singh SD, Jayachandran C. Pharmacokinetics of enrofloxacin and its active metabolite ciprofloxacin and its interaction with diclofenac after intravenous administration in buffalo calves. The Vet J 2003a; 165: 302-306.
12. Kumar N, Singh SD, Jayachandran C. Pharmacokinetic study of diclofenac and its interaction with enrofloxacin in buffalo calves. *J Vet Sci* 2003b; 4(2): 155-159.
13. Rahal A, Kumar A, Ahmad AH, Malik JK. Pharmacokinetics of diclofenac and its interaction with enrofloxacin in sheep. Res Vet Sci 2008; 84(3):452-6.
14. Iqbal Z, Khan A, Naz A, Khan JA, Khan GS. Pharmacokinetic Interaction of Ciprofloxacin with Diclofenac: A Single-Dose, Two-Period Crossover Study in Healthy Adult Volunteers. Clinical Drug Investigation 2009; 29(4): 275-281.
15. Patel SD, Sadariya KA, Gothi AK, Patel UD, Gohil PA, Jain MR **et al.** Effect of Moxifloxacin administration on pharmacokinetics of tolfenamic acid in rats. Braz Arch Biol Technol 2011; 54(4) : 739-744.
16. El-Sayed YM, Abdel-Hameed ME, Suleiman MS, Najib NM. A rapid and sensitive high performance liquid chromatographic method for the determination of diclofenac sodium in serum and its use in pharmacokinetic studies. J Pharm Pharmacol 1988; 40: 727-729.
17. Gibaldi M, Perrier D. Pharmacokinetics. Marcel Dekkar, New York, 1975.
18. Baggot JD. Principles of drug distribution in domestic animals. The Basis of Veterinary Clinical Pharmacology, Edn 1, WB Saunders Company, Philadelphia, London, Toranto, 1977.
19. Notari RE. Biopharmaceutics and clinical pharmacokinetics. Edn 3, Marcel Dekker Inc, New York, 1988.
20. Gibaldi M, Weinstraub H. Some considerations as to determination and significance of biological half-life. J Pharm Sc 1982; 60: 624-26.
21. Snedecor GW, Cochran WG. Statistical methods. Edn 6, Oxford and IBH Publishing company, New Delhi, India, 1994.
22. Willis JV, Kendall MJ, Flinn RM, Thornbill DP, Welling PG. The pharmacokinetics of diclofenac sodium following i.v. administration. Eur J Clin Pharmacol 1979; 16: 405-410
23. Kurowski M. Pharmacokinetics and biological availability of diclofenac preparations following intramuscular injection of 75 mg and oral administration of 150 mg of active drug. Z Rheumatol 1988; 47: 37-42.
24. Peris-Ribera JE, Torres-Molina F, Garcia-Carbonell MC, Aristorena JC, Pla-Delfina JM. Pharmacokinetics and bioavailability of diclofenac in the rat. J Pharmacokinet Biopharm 1991; 19: 647-665.
25. Oberle RL, Das H, Wong SL, Chan KK, Sawchuk RJ. Pharmacokinetics and metabolism of diclofenac sodium in Yucatan miniature pigs. Pharm Res 1994; 11: 698-703.