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Comparative Bioavailability Assessment of Newly Developed Flurbiprofen Matrix Tablets and Froben SR® Tablets in Healthy Pakistani Volunteers

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Abstract

Background: Flurbiprofen is a non-selective cyclo-oxygenase inhibitor, member of series of alkanoic acid derivatives, has anti-inflammatory, analgesic activity. Also used to treat gout, osteoarthritis, rheumatoid arthritis and is effective in inhibiting surgically induced miosis in human eyes while cataract extraction. Oral sustained release formulation as a novel matrix system of flurbiprofen tablets were prepared using Carboxy methylcellulose as release retardant.

Objective: The aim of present study was comparative bioavailability assessment of newly developed flurbiprofen matrix tablets for sustained delivery, with commercially available Froben SR.

Methods: Randomized, open-label, 2-periods, cross-over study conducted on 24 male healthy volunteers in Pakistan. Small batch of flurbiprofen matrix tablets were manufactured and evaluated according to Pharmacopoeial specifications. Each volunteer received a 200-mg tablet of the test and reference formulations, separated by a 7-day washout period. Blood samples were obtained before dosing 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, and 24 hours after drug administration. Safety monitoring was performed which includes adverse events. Plasma concentrations of the 2 formulations were determined, and pharmacokinetic parameters were compared using noncompartmental analysis. In-vivo disposition kinetics was evaluated using single dose, cross over, complete two period of treatment design in twenty four healthy male human volunteers; the drug was assayed in plasma using HPLC-UV detection, and results were compared. Various pharmacokinetic parameters (C_{max}, T_{max}, area under the curve [AUC0-24], mean residence time) and relative bioavailability were compared.

Results: No significant differences were found for C_{max}, T_{max},AUC and other parameters. The rate and extent of drug release from matrix tablets was not significantly different from commercially available Froben SR tablets. An in vivo result indicates prolonged blood levels with delayed peak and comparable bioavailability.

Conclusions: The matrix tablets could also provide, sustained, gastrointestinal environmentalindependent release that may result in an improved therapeutic efficacy.

Keywords: Flurbiprofen matrix tablets; Bioavailability; Pharmacokinetics; Froben SR® tablets

Introduction

Flurbiprofen is a non-selective cyclo-oxygenase inhibitor and member of a series of alkanoic acid derivatives and has shown to have anti-inflammatory and analgesic activity [1, 2]. It is also used to treat gout, osteoarthritis, rheumatoid arthritis, and sunburn. Flurbiprofen is effective in inhibiting surgically induced miosis in human eyes while cataract extraction [3-7]. Flurbiprofen has also caused a dose dependent inhibition of collagen-induced platelet aggregation in-patients with platelet-rich plasma [8, 9]. The most frequently reported side effects of flurbiprofen are abdominal discomfort along with other gastrointestinal effects after oral administration [10]. The elimination half-life of flurbiprofen in humans was initially estimated to be between 3 and 4 hours, however, with the implementation of more sensitive assay methods, the half-life has been found to be approximately 7 to 8 hours [11]. It requires frequent dosing because of short elimination half-life and does not have any direct affect on cardiovascular and respiratory systems with other NSAIDs [12, 13].

The concomitant intake of food reduces the maximum attainable serum levels of flurbiprofen, but does not influence the total amount of drug that is absorbed. The peak levels are also prolonged, so that over the entire drug concentration absorbed was not significantly different when taken before or after food intake [14-16]. Flurbiprofen has analgesic and antipyretic actions. But because of its short biological half-life and hazards of adverse gastrointestinal (GI) reactions, the development of oral sustained release formulations of this drug is highly desirable, in order to achieve improved therapeutic efficacy and patient compliance. In the past few years the use of controlled-release technology for the pharmaceutical products formulations has become very important. So many efforts have been made toward achieving sustained release (SR) formulations of flurbiprofen [17, 18]. The aim of the present study was to compare the bioavailability and pharmacokinetics between newly developed sustained release flurbiprofen tablets by matrix method compounded for this study and commercially available Sustained release Froben SR ® in healthy male human volunteers.

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Subjects and Methods

Preparation of test drugs

The tablets were prepared by the wet granulation method. Ethanolic solutions of ethyl cellulose (EC), polyvinylpyrrolidone were used as granulating agents along with, sodium carboxymethylcellulose (CMC) which is a low cost soluble and polyanionic polysaccharide derivative of cellulose has been employed in medicine, as an emulsifying agent in Pharmaceuticals and cosmetics. The granules were evaluated for angle of repose, bulk density, compressibility index, total porosity and drug content. The tablets were subjected to thickness, diameter, weight variation test, drug content, hardness, friability, and in vitro release studies. The granules showed satisfactory flow properties, compressibility, and drug content. All the tablet formulations showed acceptable pharmacotechnical properties.

Study design

The study was an open label, randomized, single dose; two ways crossover with complete two periods of treatment dosing and conducted at Drugs Control and Traditional Medicines Division, National Institute of Health, Islamabad, Pakistan. Written informed consent was obtained from each subject before commencement of study. Twenty four healthy male human volunteers participated in the study. Each volunteer received single dose of Flurbiprofen 200 mg matrix tablets and Froben SR ® 200 mg tablets orally with a washout time of one week. The volunteers were instructed to fast over-night prior to treatment. The subjects were provided with standard breakfast and also provided lunch and evening tea with refreshment. The study was conducted in accordance with the principles of the Declaration of Helsinki and its amendments (WMA, Declaration of Helsinki (2000) and the Good Clinical Practice Guideline (EMA, ICH, Guideline for Good Clinical Practice, 2010)

Sample collection

A 20-gauge venous cannula was inserted into an antecubital for collection of blood samples for assessment of flurbiprofen concentration in the blood. A blood sample was collected before drug was given (zero time) and then at 0.25. 0.5, 0.75, 1, 1.5, 2, 3, 4.0, 5.0, 6.0, 12.0 and 24.0 hours after drug administration of Froben SR ® tablets and test drug. Three ml blood sample was collected each time. Blood Samples were centrifuged at 4000 rpm for 10 minutes and plasma was separated. The plasma samples were then frozen at -70°C in the freezer until assay. Stability of standards and plasma samples were evaluated at -700C for two months and at room temperature for 24 h. Under the above conditions, samples preserved their potency (>95%).

Preparation of the mobile phase

The mobile phase consisted of a mixture of acetonitrile (40:60, v/v) and dibasic potassium phosphate buffer 20 mM, pH of the buffer was adjusted to 3.0 with phosphoric acid. The mobile phase was filtered through a 0.45µm membrane filter before use. The mobile phase was completely degassed through sonicator for 0.5 hour. The flow rate was 1 ml/min at 40°C. The detection was performed at 274 nm [19, 20].

Methods for sample preparations

Preparation of stock solutions: Stock solution of Flurbiprofen was prepared fresh on daily basis by dissolving 25 mg drug in 25 ml of methanol to give a final concentration of 1 mg/ml (1000 µg/1000 µl).

Preparation of standard curve: Standard curve was constructed to encompass anticipated range of plasma Flurbiprofen concentration found in healthy volunteers. Standard curve was prepared by spiking different samples of 1ml plasma each with 20 µl of one of the above mentioned working solutions to produce the calibration curve points equivalent to 0.12, 0.25, 0.5, 1, 2, 4, 8, 16 and 32 µg/ml of Flurbiprofen. 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 flurbiprofen from the extraction procedure was calculated to 95% determined at different plasma concentrations (1000, 2000, 4000, 8000, and 32000 ng/ml). The intra-day (within-run) and inter-day (between-run) accuracy and precision of method were determined on three separate days.

Preparation of sample (Extraction): Extraction procedure was based on simple precipitation method. 0.5 ml of plasma was spiked with 0.5 ml of Methanol: 1% v/v phosphoric acid solution (80:20) in 2 ml centrifuge rube and mixed well, cooled in an ice bath. The mixture was stirred in vortex mixer for 1 minute and centrifuged at 3000 rpm for 5 minutes. Supernatant was mixed with 0.5 ml of acetonitrile and centrifuged for 10 minutes again. 0.5 ml of filtered supernatant was injected after filtration with syringe filter (0.45 u) before injection.

Bioanalytic methods

Analyses were performed by using sensitive and validated Shimadzu LC-9A HPLC with SPD-6 AV detector (Shimadzu) and C_{18} column (4.6x250 mm, 5um.). The flow rate was 1 ml/minute and 20 µl of each sample and standards were injected, with a run time of 8 minutes.

Safety analysis

Health assessment of volunteers which includes vital signs, physical examination and clinical laboratory testing was performed before and seven days after study. Subjects were interviewed at the beginning and end of each study period and were monitored throughout the confinement period to determine any adverse events potentially related to study.

Pharmacokinetic analysis

WinNonlin (Pharsight, USA) was used to calculate the pharmacokinetic parameters. Maximum concentration of Flurbiprofen in plasma (C_{max}), time to these peak plasma concentrations (T_{max}) and other bioparameters (AUC**0-,** AUMC**0-,** t1/2, Ke, MRT, Vd and Cl) were determined by using above software. SPSS 15 and MS-Excel softwares were employed using Paired t-test to calculate the difference whether significant or non-significant between the values of the bioparameters of the two different brands of Flurbiprofen i.e. Froben SR ® 200mg and Flurbiprofen (FN) 200mg sustained release matrix tablet. ANOVA for a crossover design was performed to evaluate the bioequivalence of the test and reference preparations. The two formulations were considered bioequivalent if the 90%CI for the ratios (test: reference) of log-transformed were between 0.80-1.25 (FDA, Guidance for Industry, 2010)

Results

The study was a randomized crossover in design and was a comparison of bioavailability of two products of Flurbiprofen i.e. Reference product Froben SR® and the test product Flurbiprofen (FN) sustained release matrix tablets. Standard solutions of Flurbiprofen in concentrations of 0.5, 1, 2, 4, 8, 16 and 32 µg/ml were prepared and analyzed. The concentration versus peak area was plotted The comparative dissolution profiles of the Froben SR and Test tablets are given in Figure 1-2 and Figure 3-4. The average mean age was 22.4 years (range, 19–26 years); weights, 65.2 kg (range, 62–71 kg) were

carefully selected and completed both study periods. All in vitro tests of weight variation, friability, hardness, disintegration, and dissolution of the Froben SR ® and sustained released matrix tablets (FN) complies with USP specifications. The reference product Froben SR® and test product (Flurbiprofen sustained release tablets) were administered to twenty four subjects in a single dose of 200 mg tablets with a gap of one week. The individual plasma concentrations of Flurbiprofen reference product and test product and their comparison are given in Table 1. The bioavailability and pharmacokinetic parameters of Froben SR ® and Flurbiprofen FN matrix tablets are given in Table 2 and Table 3. The comparison between various parameters of Froben SR ® and FN matrix tablets are given in Table 4. Froben SR® and Flurbiprofen FN sustained release matrix tablets were compared statistically by using paired t-test to observe the difference between plasma concentrations of two

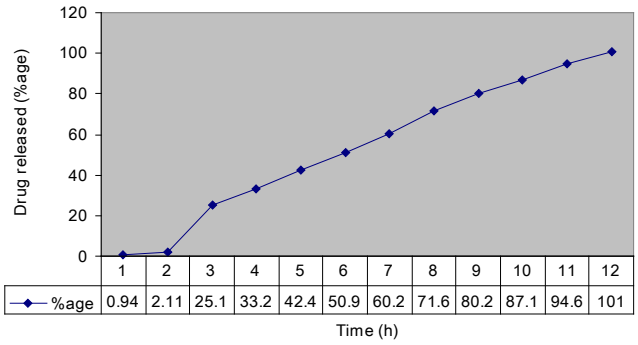

Figure 1: Cumulative dissolution profile of Froben SR Capsules.

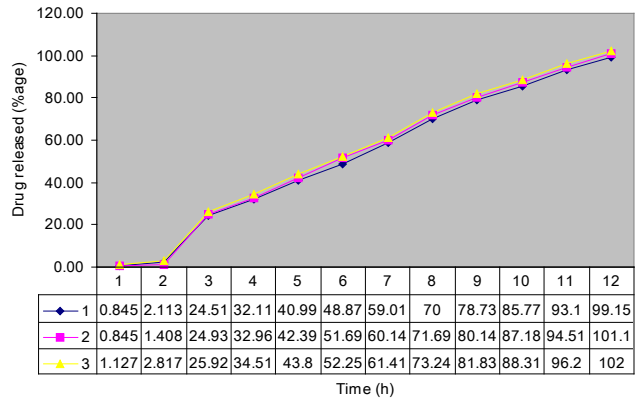

Figure 2: Cumulative dissolution profile of triplicate study of Froben SR Capsules.

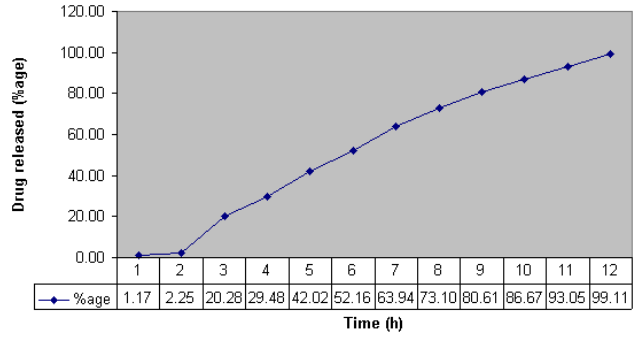

Figure 3: Cumulative dissolution profile of T-FN-15.

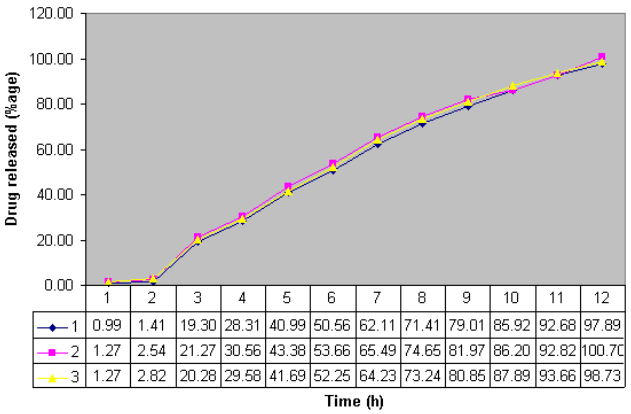

Figure 4: Cumulative dissolution profile of triplicate study of T-FN-15.

S. No.	Time (Hrs)	Concentration (µg/ml) (Mean ± SEM)	
		(Froben SR ® Knoll)	Flurbiprofen (FN) Sustained Release Matrix Tablets
1	0	0.000	0.000
2	0.25	3.653 ± 0.445	2.156 ± 0.643
3	0.50	7.281± 0.917	4.301 ± 0.503
4	0.75	10.728± 0.940	6.526 ± 0.721
5	1.0	13.651 ± 0.945	8.261± 0.909
6	1.5	13.842 ± 0.738	9.601 ± 0.533
7	2.0	14.005 ± 0.626	10.068 ± 0.788
8	3.0	13.440 ± 0.563	13.076 ± 0.828
9	4.0	12.271 ± 0.582	13.609b ± 0.285
10	6.0	10.889 ± 0.606	11.896 ± 0.249
11	8.0	9.595 ± 0.576	9.952 ± 0.389
12	12.0	7.406 ± 0.711	7.605 ± 0.473
13	18.00	4.176 ± 0.425	4.387 ± 0.373
14	24.00	1.920 ± 0.228	1.796 ± 0.226

Table 1: Mean Plasma (Mean ± SEM) concentration (g/ml) of (Froben SR ®and Flurbiprofen Sustained Release Tablets administered in an oral dose of 200 mg in twenty four subjects.

brands shown in Table as well. Plasma concentration vs. time profile of flurbiprofen test sample administered in oral dose of 200 mg tablets to twenty four healthy subjects are shown in Table 5 and Figure 5.

Discussion

In this study maximum plasma concentrations (C_{max}) for matrix tablets were found to be ranging from 13.06 ug/ml to 15.37ug/ml with mean 13.863 ± 0.238 ug/ml and for the

Froben SR maximum plasma concentrations (C_{max}) was ranged from 14.20ug/ml to 16.10 ug/ml with the mean value 15.o59 ± 0.247 ug/ml. In a previous study conducted on healthy young men maximum plasma concentration (C_{max}) was found to be 16.04 ± 3.69

u,g/ml [21]. The decrease in the C_{max} (11.36 ±0.88 ug/ml) of Flurbiprofen was also reported when taken with food (21). The value of C_{max} for the formulated drug (FN) in the present study was slightly lesser than Froben SR and the values, which have already been reported. The smaller value of C_{max} in the present study may be due to a change in the retardant material used in Froben SR and in the other drugs.

Subjects	AUMC (0-∞)	AUC (0-∞)	Cmax	Tmax	MRT	Ke (Hr-1)	$T_{1/2}$(el)	V_d	Vd L/Kg	CL(ml/h/kg)
MEAN	2570.233	285.406	15.059	1.983	8.760	0.114	6.122	6.342	0.077	0.595
S.D.	218.768	41.519	0.856	0.765	0.677	0.007	0.366	1.158	0.009	0.083
SEM	63.155	11.986	0.247	0.221	0.195	0.002	0.106	0.334	0.003	0.024
Sum	30842.800	3424.870	180.705	23.800	105.117	1.363	73.464	76.107	0.928	7.139

Table 2: Bioavailability and pharmacokinetic parameters of Froben SR in normal subjects administered in the oral dose of 200mg.

Subjects	AUMC (0-∞)	AUC (0-∞)	Cmax	Tmaxxx	MRT	Ke (Hr-1)	$T_{1/2}$(el)	$V_{d\ total}$	Vd L/Kg	CL(ml/h/kg)
MEAN	1992.317	184.029	13.863	3.833	10.062	0.097	7.172	11.336	0.172	0.922
S.D.	353.801	25.320	0.825	0.835	0.995	0.009	0.678	0.927	0.020	0.130
SEM	102.136	7.310	0.238	0.241	0.287	0.003	0.196	0.268	0.006	0.038
Sum	23907.8	2208.35	166.35	46	120.749	1.169	86.062	136.030	2.0622	11.0626

Table 3: Bioavailability and pharmacokinetic parameters of Flurbiprofen (FN) matrix tablets in normal subjects administered in the oral dose of 200mg.

Parameters	Flurbiprofen tablets (Mean ± SEM)	Froben SR (Mean ± SEM)
C_{max} (µg/ml)	13.863± 0.238	15.059± 0.247*
T_{max} (Hrs)	3.833± 0.241	1.983± 0.221*
AUC (µg h/ml)	184.029± 7.310	285.406± 11.986**
AUMC (µg h^2/ml)	1992.317± 102.136	2570.233± 63.155**
MRT (Hrs)	10.062± 0.287	8.760±0.195*
K_e (hr^{-1})	0.089± 0.003	0.114± 0.002*
$t_{1/2}$ (Hrs)	7.172± 0.196	6.122±0.102*
V_d (L/Kg)	11.336±0.268	11.336± 0.268 *
Cl (ml/h/Kg)	0.922± 0.038	0.595± 0.024*

**Highly significant difference at 99% Cl
* Significant différence at 95%

Table 4: Comparison of Bioavailability and pharmacokinetic parameters of Froben SR ® and Flurbiprofen sustained release Tablets administered in an oral dose of 200 mg in normal subjects.

The time to reach 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. In this study T_{max} for the Flurbiprofen microencapsulated tablets ranged from 3.0 to 6.0 hours with a mean value of 3.833 ± 0.241 hours and T_{max} of Froben SR ranged from 0.8 to 3.0 hours with mean a of 1.983 ± 0.221 hours. In a pervious study conducted on human volunteers, the Tmax of Flurbiprofen sustained release tablets had been reported as 3.85 ± 0.27 h [22]. The increased Tmax in the present study may be due to use of different polymer and their grades. The other factor may be a variation in the population in which the studies have been conducted. The AUC0. oo values of formulated drug (140.00 to 227.98 ug.h/ml) and Froben SR (241.36 to 366.48 ug.h/ml) show a highly significant difference (P<0.01)

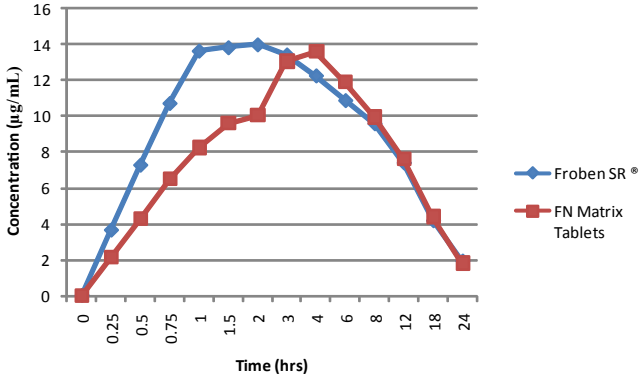

Figure 5: Plasma concentration vs. time profile of flurbiprofen test sample and Froben SR Tablets.

S. No	Time	Froben SR ®	FN Matrix Tablets
1	0	0.000	0.000
2	0.25	3.653	2.156
3	0.50	7.281	4.301
4	0.75	10.728	6.526
5	1.00	13.651	8.261
6	1.50	13.842	9.601
7	2.00	14.005	10.068
8	3.00	13.440	13.076
9	4.00	12.271	13.609
10	6.00	10.889	11.896
11	8.00	9.595	9.952
12	12.00	7.406	7.605
13	18.00	4.176	4.387
14	24.00	1.920	1.796

Table 5: Plasma concentration of Froben SR. vs. time profile of flurbiprofen Matrix new Tablet.

when compared statistically. In a previous study conducted on normal human volunteers for sustained release Flurbiprofen the value for AUCo-48 reported was 149.81 ± 12.24 ng. h/ml. [23]. This difference may be due to the measurement of AUC from 0 to 48 hours whereas in the present study it was from 0 to infinity. Another study concluded the value of AUC as 139 ± 39ug.h/ml. The AUMC is the area under the concentration time versus time curve. Area under the first moment curve (AUMC0-oo) in the current study of the formulated drug (FN) and Froben SR ranged from 1220.6 to 2824.6 ug.h2 /ml (mean 1992.317 ± 102.136ug-h2/mL) and 2095.6 to 2849.0 ug.h2/ml (mean 2570.24 ±

63.16 ug.h2./ ml), respectively. Mean residence time can be related to the average elimination rate constant as 1/MRT. The MRT is a function of the steady-state volume of distribution and time average clearance obtained from the dose and area under the curve (dose/AUC). The MRT is calculated by using the moment theory method (AUM/AUC). Mean Residence Time (MRT) of the FN tablets was found to be ranging from 8.718 to 12.39 hours (mean 10.062 hours) and MRT of Froben SR ranged from 7.774 to 9.61 hours (mean 8.760 hours). The MRT value of Froben SR was consistent with the already reported value of MRT i.e. 7.5 ± 1.6 [24]. The increased value of MRT of the formulated drug in this study could be due to release of the drug from the dosage form very slowly. In the present study, the half-life (t1/2) of the formulated drug (FN) ranged from 6.042 to 8.586 h (mean 7.172 ± 0.196 h) and for Froben SR the ti/2 was in the range of 5.387 to 6.66 h (mean 6.122 ± 0.102 h) which is comparable with a previous studies [25, 26] where the value of half-life has been reported as 6 hrs.

The elimination rate constant (Ke) in the present study was calculated to be in the range of 0.81 to 0.115 hr'1 (mean 0.089 ± 0.003 hr'1) and 0.107 to 0.129 hr 1 (mean 0.114± 0.002 hr"1) for the formulated drug (FN) and Froben SR, respectively. The formulated drug showed a statistically significant ($P<0.05$) lower value as compared with Froben SR, which shows that the elimination of the formulated drug was slower as compared with Froben SR, which is additionally evident from the higher value of half-life of the formulated drug. Total body clearance (Cl) is an important pharmacokinetic parameter that explains how rapidly drugs are eliminated, metabolized or distributed all over the body. It can be considered as the proportionality constant linking the rate of these processes and drug concentration. A clearance value for formulated drug (FN) was 0.877 to 1.429 ml/h/Kg (mean 0.922 ± 0.038 ml/h/Kg) and for Froben SR 0.546 to 0.829 ml/h/Kg (mean 0.595 ± 0.024 ml/h/Kg). Studies conducted previously (28, 29, 30) reported similar values of clearance i.e., 1.75 ± 0.34, 1.47 ± 0.50 and 0.65 ± 0.24 1/hr, respectively. Volume of distribution (Vd) for FN and Froben SR was in the range of 9.80 to 12.45 L/kg (mean 11.33 ± 0.268 L/kg) and 4.24 to 7.68 L/kg with mean (6.342 ±0.024L/kg), respectively [27]. In a previous study, reported the value of volume of distribution as 11.9 L/kg which is comparable with the present findings FN. The value for Froben SR was smaller than the present study. This may be due to the larger value of AUC. Pharmacokinetic parameter, volumes of distribution (Vd) is commonly calculated by two ways i.e, either by the steady-state method (Vdss) or the area method (Vd area). Vdss is considered as the most un-biased and most reliable indicator for determination of Vd. but Vdss has number of practical and theoretical limitations in comparison to Vd area. After administration of a drug in single doses or multiple devided doses, Vd area relates plasma drug concentration to the concentration in the body after distribution equilibrium is attained, at all times. The precise configuration of the initial distributional phase of the plasma concentration curve have greater impacts upon calculated values of Vdss, which may be difficult to delineate because of variance due to methodological errors or undetermined causes. Such variance can lead to large non-physiologic within- and between-individual variability in Vdss. Vd area, on the other hand, is relatively independent of changes in the initial profile of distribution. Finally, it is concluded from number of experimental observations that elimination of a drug depends physiologically on distribution of the drug keeping the changes constant in clearance. Whether the steady-state method or the area method is used to calculate Vd, there is a relation between distribution and elimination. Vd area is a more trustworthy and valid descriptor of the determination of extent of drug distribution than is Vdss [28]. The value of Vdss of the FN and Froben SR was ranging from 0.071 to 0.116 I/kg and 0.070 to 0.095 L/kg with a mean value of 1.111 ± 0.010 I/kg and 0.80 ± 0.003 I/kg, respectively, which are significantly ($P<0.05$) different when compared statistically. It has recently been reported that flurbiprofen-loaded solid dispersion at the weight ratio of flurbiprofen/Na-CMC/Tween 80 of 6/2.5/0.5 improved approximately 60-fold drug solubility. It gave higher AUC, $T(_{max})$, and $C(_{max})$ compared to commercial product [29].

Conclusion

Sustained Release Tablets containing non-steroidal anti-inflammatory drug Flurbiprofen were prepared by matrix method technique using carboxy methyl cellulose sodium (CMC sodium) as the retardant material. The In-vitro results of FN showed comparable results with Froben SR as well as the data available in the previous studies. Flurbiprofen FN and Froben SR were administered in the oral dose of 200 mg to the twenty four healthy human volunteers. Both the formulations showed good absorption but with slight differences. High performance liquid chromatograph was utilized for in-vivo comparison of FN and Froben SR in biosamples; method was simple, showed excellent limit of detection and quantification. Moreover the results were good in linearity and reproducibility. Peak plasma concentration for the FN matrix tablets was 13.863 ± 0.238 ug/ml and 15.059 ± 0.247 ug/ml for Froben SR. The Tmax for FN was 3.833 ± 0.241 hr and 1.983 ± 0.221 hr for Froben SR. Most of the pharmacokinetic and bioavailability parameters showed similarity with previous studies and Froben SR. These results showed that CMC sodium could be employed in formulating the sustained formulation of various drugs. The CMC sodium could also be used in different concentrations to have appropriate and beneficial effects of Flurbiprofen and other drugs. The other polymers could be tried for the improvement of bioavailability of the drug for longer duration of time.

Competing Interests

The author(s) declare that they have no competing interests.

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