SUSTAINED RELEASE HYDROPHILIC MATRICES BASED ON XANTHAN GUM AND HYDROXYPROPYL METHYLCELLULOSE: DEVELOPMENT, OPTIMIZATION, IN VITRO AND IN VIVO EVALUATION

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ABSTRACT

Hydrophilic matrices of xanthan gum and hydroxypropyl methylcellulose were prepared by direct compression using diclofenac sodium as model drug. All formulations were subjected to physical tests, FTIR studies and dissolution studies at pH 1.2 and 6.8, to evaluate drug release kinetics. In vivo studies were carried out in rabbits using single latin cross over design and pharmacokinetic parameters were analyzed by using one way ANOVA and LSD. Physical parameters of all formulations were within limits with stability of drug during direct compression and absence of drug polymer interaction as evident by FTIR spectra. In vitro release studies showed that both polymers were able to retard the drug release but matrices containing XG showed initial greater burst release in acidic media (pH 1.2) which was absent in HPMC matrices due to delayed hydration and pH independent gelling mechanism in HPMC. XG matrices showed greater sustained release pattern in phosphate buffer solution (pH 6.8) over twenty-four hours of study due to formation of gel and viscous solution around matrices. All the formulation followed Higuchi kinetics and Korsmeyer-Peppas equation confirms the involvement of multiple drug release mechanisms release from hydrophilic matrices. Plasma drug concentration in rabbits after oral administration was used to calculate different pharmacokinetic parameters, which showed the inverse relationship of the AUC, AUMC and C_{max} of the drug with polymer concentrations. Statistical evaluation confirms the role of polymer concentration on delayed release. XG matrices demonstrated fewer time to reach T_{max}, higher C_{max} and $AUC_{0-\infty}$ values as compared to batches formulated with HPMC, owing to burst release of drug from XG matrices in acidic media. Both formulations showed poor IVIVC due to in vitro and in vivo difference of pH and ionic strength.

Keywords: Diclofenac sodium, Hydroxypropyl methylcellulose, Xanthan gum, Hydrophilic matrices, Gel

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INTRODUCTION

Drug is generally administered via oral route due to ease of administration, high patient compliance, least sterility constraints and flexibility in the design of dosage form. Hydrophilic polymers are widely used in the formulation of oral controlled release tablets. As the dissolution medium or biological fluid penetrates the dosage form, the polymeric material swells and drug molecules begin to move out by diffusion at a rate determined by formulation and formulation methodology [1].

Pharmaceutical scientists are trying to improve patient compliance and decrease the side effects, by better control of plasma drug levels and less frequent dosing. Several methods have been developed to date for modified drug release. The easiest way involves physical blending of drug with polymer matrix, followed by direct compression, compression molding, injection molding, extrusion, or solvent casting, which results in either monolithic or matrix device. There should be minimum number of excipients and processing steps in order to reduce variations, hence direct compression is the most suitable and easily up scalable technique. Directly compressed hydrophilic matrices are of high demand with both a scientific and economic appeal. As the cost of synthesizing and testing new polymers are high, a new focal point is to investigate the use of polymer blends to retard drug release [2]. In fact, hydrophilic matrix tablet is one of the least complicated approaches for developing modified release dosage form [3]. Sustained release dosage form can be formulated by incorporation of the drug into a matrix containing release retarding hydrophilic polymer [4].

Uses of Cellulose derivatives, especially hydroxylpropyl methylcellulose (HPMC) a synthetic polymer, was described in 1960s but it is fully characterized recently [1]. Hydroxypropyl methylcellulose (HPMC) is frequently used as basis for hydrophilic matrix tablet because it works as a pH independent gelling agent. Erosion and swelling occurs simultaneously and contributes to overall drug release.

Xanthan gum is a high molecular weight extracellular polysaccharide obtained from Xanthomonas campestris by fermentation process. Xanthan gum is known to tolerate high concentration of electrolyte in solution. The viscosity of the xanthan gum solution is nearly independent of pH and temperature. Xanthan gum is biodegradable and biocompatible and forms gel in water.

Thus, xanthan gum is used for fabrication of modified release dosage form. The overall compaction behavior of HPMC and xanthan gum is quiet similar. Xanthan gum is readily cheap and more readily flowable than HPMC.

Hydroxypropyl methylcellulose forms firm gel but do not hydrate quickly. On the other hand, xanthan gum hydrates very quickly. Xanthan gum cannot form a strong gel, causing erosion or dissolution of gel around the tablet, thereby requiring high concentration [3].

This gel forming properties of HPMC and XG can be used to develop sustained release dosage forms. Hydrophilic matrix system release drug sequentially by swelling to form gel, diffusion of drug molecules and finally surface erosion of matrix [5].

Diclofenac sodium (DS) is one of the most extensively used Non-steroidal anti-inflammatory drugs (NSAIDs) and approved for treatment of rheumatoid arthritis, osteoarthritis and soft tissue inflammation with dose of 75-150 mg/day [6]. DS is administered in two or three daily doses due to rapid clearance from body [7]. Properly designed sustained release formulation of DS can eradicate the problems associated with conventional formulation e.g. dosing frequency, patient compliance and plasma concentration fluctuations [8, 9].

This work sought to formulate sustained release matrices with varying proportions of polymers, using DS as model drug with least gastric effects and to investigate their physical properties, dissolution studies, drug release kinetics, drug polymer interaction, in vivo behavior and evaluation of in vitro in vivo correlation.

MATERIALS AND METHODS

1. Materials:

Diclofenac sodium was a kind gift from Wilson's Pharmaceuticals (Pvt) Ltd Pakistan. Hydroxypropyl methylcellulose (K 15 M) was purchased from Colorcon India. Xanthan gum was a kind gift from Hamaz Pharmaceuticals (Pvt) Ltd Pakistan. Microcrystalline cellulose (Avicel PH101), magnesium stearate from E. Merck, Potassium bromide (IR grade Fischer Scientific UK), hydrochloric acid (BDH), sodium hydroxide (BDH), potassium dihydrogen phosphate (Merck) and syringe filters (0.45µm) were used. All the chemicals used were of analytical grade.

2. Fabrication of hydrophilic matrix tablets by direct compression:

Hydrophilic matrices were prepared by slight modification of method used by Shah et al. [10].In all six formulations 25 mg of DS was employed in each tablet and formulations were prepared according to composition as shown in Table I. Drug, polymers and microcrystalline cellulose were employed in their specified ratios and mixed for 10 minutes in locally fabricated double cone blender. Then powder mixtures were passed through sieve no 20. The resulting powders were mixed with 1% w/w magnesium stearate for 5 minutes. The blend was then compressed by using triple punch tablet machine (Type: EK 0; ERWEKA, APPARATEBAU GmbH, Heusenstamm, Germany), using caplet shaped spherical punches.

Table I - Composition of the investigated hydrophilic matrix tablets

Formulation	Diclofenac sodium (mg)	HPMC (mg)	Xanthan Gum (mg)	Microcrystalline cellulose (mg)	Magnesium stearate (mg)
F1	25	15	-	59	1
F2	25	20	-	54	1
F3	25	25	-	49	1
F4	25	-	15	59	1
F5	25	-	20	54	1
F6	25	-	25	49	1

3. Physical evaluations of the tablets:

Tablets were evaluated for weight variation (n=20), thickness (n=10), hardness (n=10) and friability (n=10) [10].

4. Fourier transform infrared spectroscopy:

Drug polymer interaction was investigated by using Fourier transform infrared spectroscopy (FTIR) [Model: 8400 S; Shimadzu Scientific Instruments (SSI), Kyoto, Japan]. FTIR spectra of DS, XG, HPMC and the matrix tablets were obtained by triturating 2 mg of sample with 200 mg of IR grade KBr and then compressing the mixture at a suitable pressure to make the fine discs. The spectra were scanned over the wave number range from 4000 to 400 cm^{-1} [10].

5. In vitro dissolution studies:

In vitro dissolution studies of all the formulated tablets were done on USP apparatus II (Pharmatest type PT-DTT china). The dissolution was performed in 900 ml of dissolution media of 0.1N HCl of pH 1.2 for 2 hrs and thereafter in phosphate buffer of pH 6.8 for next 22 hrs with temperature maintained at 37 ± $1C^0$. The stirring speed was set at 100 rpm [11]. Five ml of dissolution medium was withdrawn at specified intervals and analyzed directly at 276nm using UV/Visible spectrophotometer (UV-Vis spectrophotometer IRMECO U2020). An equal volume of fresh dissolution medium, maintained at 37 ± $1C^0$, was added after withdrawing each sample to maintain the volume. The process was repeated in triplicate.

6. In-vitro assessment of dissolution data

In order to assess the mechanism and kinetics of drug release, in-vitro dissolution drug release data was analyzed by five different kinetics models [12].

Zero-order release equation describes systems where drug release is independent of its concentration [12].

$$Q_t = k_0\ t$$

First-order equation describes systems where drug release rate depends on its concentration [12].

$$\log Q_t = \log Q_0 - k_1\ t$$

Higuchi's model describes drug release from insoluble matrix by diffusion [12].

$$Q_t = k_H\ t^{1/2}$$

Hixson-Crowell equation [12].

$$Q_0^{1/3} - Q_t^{1/3} = k_{HC}\ t$$

Korsmeyer-Peppas equation [12].

$$\frac{M_t}{M_\infty} = k_{KP}\ t^n$$

Where Q_t is the amount of drug released at time t. Q_0 is the initial amount of the drug in the formulation, k_0, k_1, k_H, k_{HC}, k_{KP} is the release rate constant for zero-order, first order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas model respectively.

In Korsmeyer-Peppas equation M_t is the amount of drug released at time$t$, M_∞ is the amount of drug released at time ∞, n *is* the diffusional coefficient indicating release mechanism. When n approximates to 0.5 a Fickian/diffusion controlled release is implied, where 0.5<n<1.0 non Fickian and n is 1 for zero order (case II transport).When n value is greater than 1.0 it indicates super case II transport.

7. In vivo studies:

In vivo studies were performed in six healthy rabbits of either sex weighing 1.45 Kg using a single Latin square cross over design following standard protocols. All the rabbits were in good health. Tablets were given after overnight fast. Each formulation administration was separated by wash out period of one week.

7.1 Blood sampling

Blood samples (2ml) were collected from jugular vein before administration (pre-dose) and at 1.0, 2.0, 4.0, 6.0, 12 and 24 hrs post-dose. The blood samples were centrifuged at 4000 rpm for 15 minutes. The plasma was separated and kept frozen until analysis.

7.2 Plasma assay of diclofenac sodium

Plasma was analyzed by using HPLC (Perkin-Elmer) with Total Chrom software for data processing, consisting of pump Perkin-Elmer (Series 200), a column 5µm Hypersil ODS (C18) (250 mm x 4.6 mm I.D.), UV detector Perkin-Elmer (Series 200) and Interface (NC1900) Perkin-Elmer.

A standard curve was constructed to determine the plasma concentration from samples. Mobile phase consisting of acetonitrile and 0.01 M ammonium acetate buffer (40:60) adjusted to pH 3.4 with glacial acetic acid was prepared, filtered and degassed by sonication and was ran with a flow rate of 1.5 ml/min. Plasma samples (1mL) were treated with 2mL acetonitrile to precipitate the proteins, vortexed for 1 min, centrifuged for 5 min at 3500 rpm. Supernatant layers were transferred to the polypropylene tubes and evaporated to dryness under nitrogen flux using sample concentrator. The residues were reconstituted with 80 µl mobile phase and 20 µl of samples were injected and detected at λ_{max} of 276 nm (Perkin-Elmer series 200 UV).

7.3 Pharmacokinetic analysis

Maximum serum concentration (C_{max}) and maximum time to reach these concentrations (T_{max}) of diclofenac sodium were obtained from observed values of plasma concentration time profiles of each of six rabbits. Area under the plasma concentration time curves (AUC), area under the first moment curve (AUMC) were determined by kinetica 4.4(trial version) using linear trapezoidal rules. Mean residence time (MRT), elimination rate constant (K_e), volume of distribution (V_d), clearance ($C_{l)}$ and plasma half life ($t_{1/2}$) were calculated by non compartmental model, using kineta 4.4 (trial version) and MS excel windows professional XP.

7.4 Statistical analysis

The pharmacokinetic parameters were subjected to statistical analysis of one way ANOVA to observe the difference of release profile between different concentrations of hydrophilic polymers. Difference was considered to be statistically significant at $P<0.05$ and non significant at $P>0.05$.

Furthermore, when F-test in ANOVA signifies, then the pair wise comparison was made by LSD test to reveal any significant difference between the formulations.

RESULTS AND DISCUSSION

1. Physical evaluations of the tablets:

All the physical parameters of formulations are within the USP limits (Table II).

Table II - Physical characteristics of formulated hydrophilic matrix tablets

Formulation	Weight Variation (mg) (Mean±SD) n = 20	Thickness (mm) (Mean±SD) n = 20	Hardness (N) (Mean±SD) n = 20	Friability (%) n = 10
*F-1	99.73 ± 3.88	246.60 ± 8.30	65.70 ± 7.94	0.22
*F-2	100.04 ± 4.20	268.80 ± 9.13	68.30 ± 6.77	0.32
*F-3	100.14 ± 2.99	215.30 ± 7.13	68.78 ± 7.45	0.43
**F-4	100.07 ± 3.53	241.50 ± 6.69	70.30 ± 4.06	0.31
**F-5	99.60 ± 2.36	257.50 ± 9.20	69.10 ± 5.95	0.24
**F-6	99.84 ± 2.72	260.50 ± 10.39	69.70 ± 4.19	0.36

* Formulation with HPMC; ** Formulation with Xanthan Gum

2. Fourier transssform infrared spectroscopy:

FTIR spectroscopy of diclofenac sodium and diclofenac sodium loaded matrix tablets were conducted to study drug polymer interaction. All the FTIR spectrums are shown in Figure 1. FTIR of pure diclofenac sodium showed the principle peaks at 1280 and 1303 cm^{-1} which resulted from C-N stretching and the peak at 1501 and 1571 cm^{-1} resulted from C=C stretching and C=O stretching of carboxylate group, respectively.

There is no significant difference in characteristic peaks of pure drug and drug loaded matrix tablets suggesting the absence of drug polymer interactions and stability of drug during direct compression. Similar FTIR spectra for diclofenac sodium were revealed by Piyakulawat et al. who prepared chitosan/carrageenan beads for controlled release of diclofenac sodium [13].

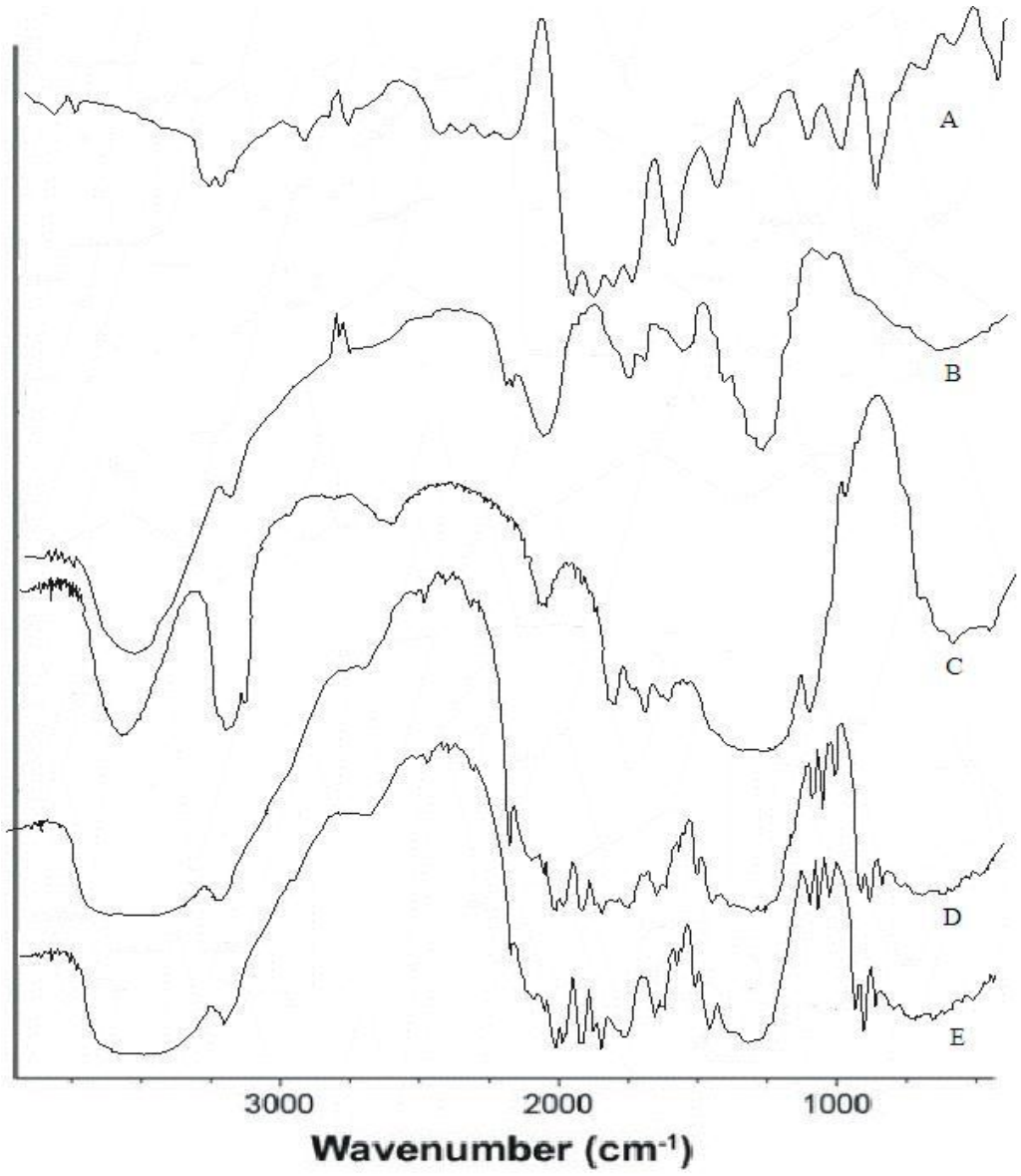

Figure 1 - FTIR spectra of (A) Diclofenac sodium (B) Xanthan gum (C) HPMC (D) Formulation F2 (E) Formulation F5

3. In vitro dissolution studies

Hydrophilic matrix tablets were formulated by using various proportions of HPMC and XG to manipulate the release of drug. Release profiles are shown in Figure 2. As the proportion of HPMC and XG increased, a corresponding decrease in the release rate of diclofenac sodium was observed. These observations are in harmony with reported studies [14, 4]. An initial burst release of drug was observed with XG matrices in acidic media, which was absent with HPMC matrices, it may be due to pH independent gelling and delayed

hydration properties of HPMC [3], but in phosphate buffer of pH 6.8, XG matrices showed greater sustained release pattern than HPMC matrices as previously studied [5, 15].

It is clear from Figure 2 that all the formulations showed almost negligible release at pH 1.2 in first 2 hours compared to considerable steady release pattern at pH 6.8. The negligible drug release in first 2 hours may be attributed to fact that diclofenac is a weak acidic drug (pKa 4.0) with partition coefficient of 13 in octanol/phosphate buffer (pH 7.4) and solubility of drug at acidic pH is less than 1 mg/L compared to 17.8 mg/L at neutral pH [16]. The low solubility of drug may hinder the penetrating dissolution media to leach the drug out from the tablet matrices. This effect was desired for the diclofenac matrices to avoid its gastric irritating effects that results from its contact with gastric mucosa in case of conventional oral drug delivery. Figure 2 clearly manifest that the drug release was significantly retarded when the concentration of HPMC was changed from 15% to 20% and 25% w/w, which is due to formation of polymeric gel and is more likely to be resistant to drug diffusion and erosion. Secondly in the presence of solvent mobility of polymeric chain changes from a glassy state to rubbery state. The gel structure formed around the tablets considerably retards the drug release since drug has to diffuse through this gel barrier into the bulk phase. The faster drug release in case of formulation containing low amount of HPMC may be due to less tortuous diffusion path. These results are in concurrence with previously described studies [3, 1].

Formulations formed with xanthan gum showed incomplete and slow drug release with increasing concentration of polymer which may be due to formation of a thick gel layer with increasing viscosity around the tablets by quick hydration of XG matrices. As a result, internal core might have remained dry due to poor penetration of dissolution media. Thus, drug release was considerably delayed due to thick gel formation and dry internal core.

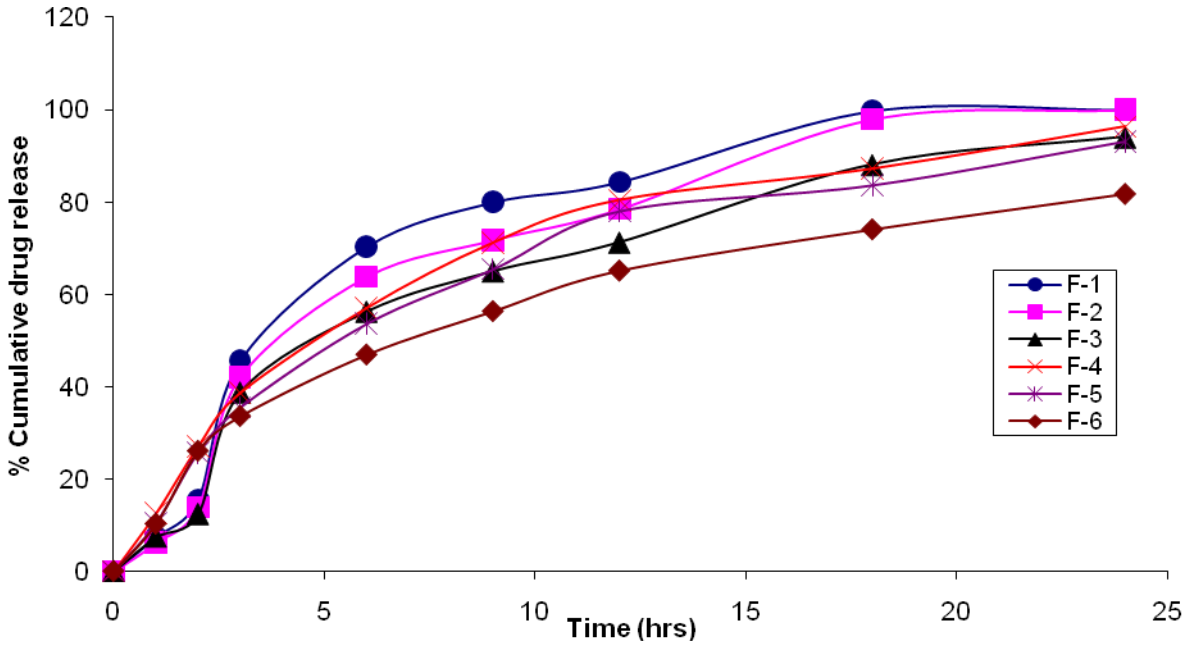

Figure 2- Drug release profiles of sustained release hydrophilic matrices of diclofenac sodium

4. In-vitro assessment of dissolution data:

Drug release mechanism and kinetics were determined by applying various kinetic equations to in-vitro dissolution data. Five different kinetics models were applied to analyze the in vitro data to find out the best fitting equation.

Drug release from all batches formed with HPMC showed Higuchi kinetics as plots showed highest linearity (Table III) and release mechanism was further confirmed by Peppas model where the value of "n" is greater than 1 showing super case II transport, indicating two or more mechanisms are involved, that is diffusion, erosin and chain relaxations. In case of formulation formed with xanthan gum all the formulation followed Higuchi model with super case II transport mechanism for F4 and F5, while F6 showed anamolous transport.

Diffusion mechanism prevailed as compared to the erosion mechanism which is due to the fact that hydrophilic polymers contributes to fickian diffusion but not due to the erosion mechanism as observed by increasing the concentration of polymers, release of drug was more inclined towards Higuchi profile. These findings were in line with previous findings [14, 4]. Sujja et al. [17] also concluded the same findings.

Table III- Release kinetics of hydrophilic matrix tablets

Formulation	Zero Order Kinetics	First Order Kinetics	Higuchi Kinetics	Hixson-Crowell Kinetics	Korsmeyer-Peppas Kinetics
	R^2	R^2	R^2	R^2	n
*F1	0.781	0.496	0.917	0.552	1.143
*F2	0.840	0.525	0.943	0.585	1.161
*F3	0.859	0.532	0.955	0.591	1.117
**F4	0.840	0.456	0.970	0.530	1.001
**F5	0.853	0.474	0.972	0.544	1.016
**F6	0.858	0.461	0.980	0.525	0.964

* Formulation with HPMC; ** Formulation with Xanthan Gum

5 In vivo studies:

5.1 Pharmacokinetic analysis

In vivo study was performed for all formulated batches of diclofenac sodium to correlate drug kinetics in living organisms. Six healthy rabbits were used. The mean plasma concentration of drug at different times for all formulations were determined (Figure 3) and then used to determine different pharmacokinetic parameters, as shown in Table IV. It was observed that all the formulated matrices gave more prolonged and constant plasma drug level profiles with increasing concentrations of polymers. Significant differences ($P<0.05$, at 95%) between the pharmacokinetic parameters of different formulations showed major impact of the polymer type and their corresponding concentrations on drug release (Table v). Batches with different proportions of xanthan gum showed less time to reach maximum plasma concentration (T_{max}), higher C_{max} and $AUC_{0-\infty}$ values as compared to batches formulated with hydroxypropyl methylcellulose (Figure 3) which may be due to quick hydration of XG and burst release of drug from XG matrices in acidic media. T_{max} was 6 and 4 hours for HPMC and XG matrices respectively. Increasing concentrations of matrix polymers caused the delayed drug release resulting in the greater MRT, Vd, and prolonged $t_{1/2}$ indicating sustained release of drug as evident from data in Table IV.

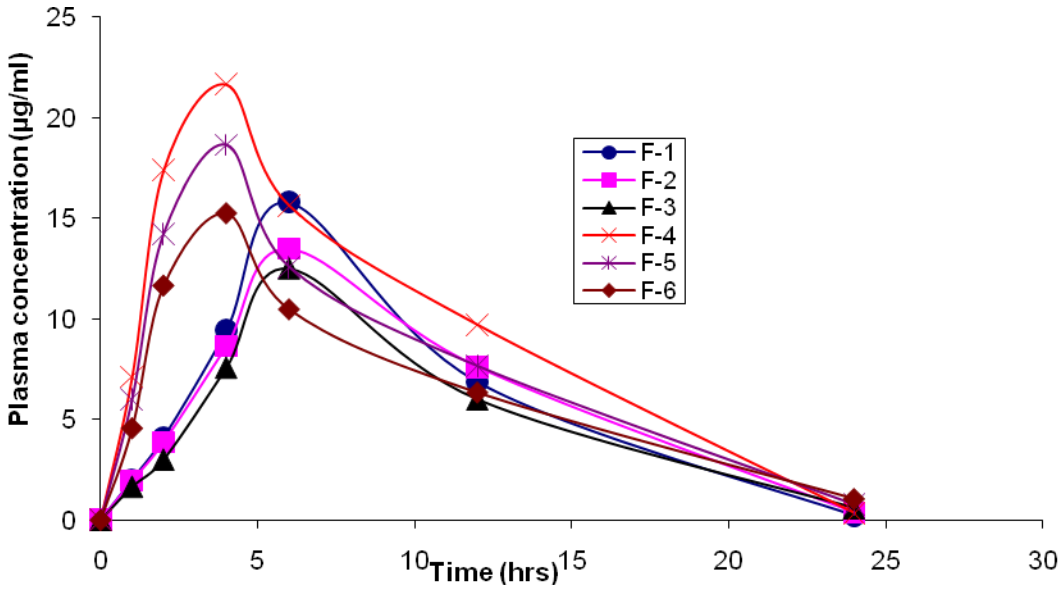

Figure 3- Plasma concentration vs. Time profiles of sustained release hydrophilic matrices of diclofenac sodium

Table IV- Pharmacokinetic parameters of hydrophilic matrix tablets

Formulation	**AUC** (µg.h/ml)	**AUMC**	**C_{max}** (µg/ml)	**K_e** (h^{-1})	**t_{max}** (h)	**MRT** (h)	**Vd** (l)	**$t_{1/2}$** (h)	**Cl** l/h
*F1	130.59	1099.60	15.80	0.239	6	8.42	3.062	2.77	0.765
*F2	130.35	1186.22	13.49	0.264	6	9.10	3.663	3.31	0.767
*F3	118.10	1147.60	12.49	0.267	6	9.72	4.888	4.00	0.847
**F4	201.57	1535.95	21.67	0.244	4	7.62	2.380	3.33	0.496
**F5	176.82	1507.56	18.66	0.254	4	8.53	3.550	4.39	0.565
**F6	155.21	1482.27	15.25	0.236	4	9.55	4.904	5.28	0.644

* Formulation with HPMC; ** Formulation with Xanthan Gum

5.2 Statistical evaluation:

The data was subjected to statistical analysis by using one-way ANOVA. P value for all the pharmacokinetic parameters were less than 0.05 indicating significant difference, which was further confirmed by LSD test (Table V).

IVIVC was found by subjecting invitro drug release to fraction of invivo drug absorbed. P values of all formulation were above 0.05 indicating results are not significant. A low correlation coefficient value (Table VI) suggests poor correlation between invitro and invivo data, which may be due to differences of ionic strength and pH in invitro and invivo conditions. Fukuda and colleagues [18], El-gazayerly [19] had concluded that gelation of polymers during dissolution is affected by ionic strength of media which ultimately effects drug release.

Table V- Pair wise comparison of Pharmacokinetic parameters of all formulations of diclofenac sodium by least significance difference test (LSD)

Pairwise LSD	**Pharmacokinetic Parameters**							
	AUC	**AUMC**	**C_{max}**	**Ke**	**Vd**	**MRT**	**$t_{1/2}$**	**Cl**
F1 F2	NS	NS	S	S	S	S	S	NS
F1 F3	S	S	S	S	S	S	S	S
F1 F4	S	S	S	S	S	S	S	S
F1 F5	S	S	S	S	S	S	S	S
F1 F6	S	S	S	S	S	S	S	S
F2 F3	S	S	S	S	S	S	S	S
F2 F4	S	S	S	NS	S	S	S	S
F2 F5	S	S	S	S	S	S	S	S
F2 F6	S	S	S	S	S	S	S	S
F3 F4	S	S	S	S	S	S	S	S
F3 F5	S	S	S	S	NS	S	S	S
F3 F5	S	S	S	S	S	S	S	S
F4 F5	S	S	S	S	S	S	S	S
F4 F6	S	S	S	S	S	S	S	S
F5 F6	S	NS	S	S	S	S	S	S

NS = Non significant S=Significant

Table VI- 'P' and 'r' values for point-to-point correlation between in-vitro and in-vivo data

Formulation	P	r
F1	0.504	0.344
F2	0.518	0.333
F3	0.555	0.306
F4	0.962	-0.025
F5	0.969	-0.020
F6	0.935	0.044

CONCLUSION

Hydrophilic matrices were successfully developed by direct compression using DS as model drug and optimum release was obtained by using varying proportion of polymers. All matrices show good physical parameters. FTIR spectra showed suitability of direct compression for hydrophilic matrices and absence of drug polymer interaction.

Both polymers have drug retarding abilities at pH 6.8 but in acidic media XG shows burst release, which is not suitable when we want to reduce gastric irritating effect of DS and decrease the dosing frequency. All formulation followed Higuchi kinetics and most of the formulations released the drug by multiple mechanisms. Both the formulations showed in vivo sustained release pattern but poor IVIVC.

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