RESEARCH ARTICLE

FORMULATION AND EVALUATION OF ONCE DAILY SUSTAINED RELEASE MATRIX TABLET OF ACECLOFENAC USING NATURAL GUMS

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ABSTRACT

In present study, an attempt has been made to evaluate the effect of natural gums on the release profile of drug from matrix system for once daily sustained release tablets formulations. Aceclofenac NSAIDs was used as a model drug to evaluate it release characteristics from different matrices. Matrix tablets of Aceclofenac were prepared by direct compression process using natural gums (xanthan gum and karaya gum) in different ratios drug: gum ratios of FX, FK and FXK (FX and FK in 1:1 ratios). The tablets were evaluated for physical characteristic like hardness, weight variation, friability, swelling index and drug content, *in-vitro* release of drug was performed in Phosphate buffer pH 7.4 for 24 hours. All the physical characteristic of fabricated tablet was within acceptable limits. The release of Aceclofenac from a gelatinous swollen mass, which controls the diffusion of drug molecules through the polymeric materials in to aqueous medium. The FXK matrices show prices controlled release than FX and FK matrices because of burst effect and fast release in case of FX and FK matrices respectively and there was no chemical interaction between drug and polymers in FXK formulation as confirmed by FTIR studies.

The release mechanism was explained with zero order, first order, higuchi and korsmeyer equations via swelling and non fickian diffusion mechanism. The FXK matrices leads to more prices result than FX and FK alone by utilization of synergistic interaction between two biopolymers and uniformity in the hydration layer in dissolution media.

Key Words: Natural Gums, Sustained Release, Matrix Tablet, Aceclofenac

INTRODUCTION

Hydrophilic polymers are becoming very popular in formulating oral controlled-release tablets. As the dissolution medium or biological fluid penetrates the dosage form, the polymer material swells and drug molecules begin to move out of the system by diffusion at a determined rate by the nature and composition of the polymer as well as formulation type. [1, 2, 3, 5]

The use of naturally occurring hydrophilic biocompatible polymeric materials has been focused in recent research activity in the design of dosage form for oral controlled-release of drugs compare to synthetic polymers. The use of matrix devices to control the release of a variety of therapeutic agents has become very important in the development of controlled release dosage forms. The hydrophilic natural gums hydrate and swell on contact with water and these have been used for the preparation of single unit dosage forms. Also, the natural gums selected have an economic importance in being cheaper than many processed synthetic gums available. [2,7,8]

The use of hydrophilic polymers like xanthan gum (FX) and karaya gum (FK) alone and combination was used in this study for oral controlled release dosage forms. The Xanthan gum is water soluble, anionic-bacterial heteropolysaccharide,

while FK is a neutral plant galactomannan. Both materials have been extensively studied in a range of environment, with some sensitivity to pH and ionic strength demonstrated. The synergistic gelation of FX and FK has also been reported to decrease dramatically below pH 5, although it is independent of pH within the range of 5-10. Xanthan gum and FK are water soluble thickening agents, but when they are mixed, an original gelation occurs. The hydrophilic matrix system being investigated that two heteropolysaccharides are the principle of the formulation it utilizes the synergistic interaction of two biopolymers to control the drug release process. [3, 6]

Aceclofenac is a potent non-steroidal anti-inflammatory drug, which is commonly prescribed drug for the treatment of patients suffering with pain, rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. It is a weak acid (pKa =4.7) practically insoluble in water and acidic environment. The oral absorption is uniform, rapid and complete with a bioavailability of nearly 100% and an elimination half-life of 2-4 h. Aceclofenac is reported to have a short biological half-life (3.4 ± 0.7) requiring to be administered in 100 mg twice daily. Hence we have selected Aceclofenac for development of once daily sustained release matrix tablets. The pharmacokinetics and dosage schedule

supports once daily sustained release formulations for Aceclofenac for better control of pain, enhance clinical efficacy and patient compliance.[10]

The objective of present investigation is design and evaluates once daily sustained release tablets of Aceclofenac using natural gums (xanthan gum and karaya gum) as release retardant. Drug release from hydrophilic matrices is known to be a complex interaction between swelling, diffusion and erosion mechanisms. Previous work has demonstrated that naturally occurring FX has useful hydrogels for producing a constant *in-vitro* drug release. This work was an attempt to determine the relative contribution of the drug release mechanisms from Aceclofenac matrix tablets produced with xanthan (FX) and the highly hydrophilic karaya gum (FK). Different concentrations of gums, alone (FX or FK) and in physical mixture (FXK) of FX and FK in 1:1 ratio were tested to evaluate their performance as release-controlling agents. [5, 14]

MATERIALS AND METHODS

Materials:

Aceclofenac gift sample obtained from Pharma Synth Formulation Ltd 22/6B, Sidcul-IIE, xanthan gum (FX) was obtained from Maruti Pharmaceutical Ltd, india, karaya gum (FK) from Colorcon Asia Pvt., starch-1500 from Colorcon Asia Pvt. Limied. Talk and magnesium stearate were analitycal reagent grade and used without further putification.

Preparation of matrix tablets (Direct compression method)

Once daily sustained release matrix tablets of Aceclofenac with xanthan gum and karaya gum were prepared by using different drug: gum ratio viz. 1:0.500, 1:0.625, 1:0.750, prepared by direct compression technique and the formulations were name as FX1, FX2, FX3, FK1, FK2, FK3, FXK1, FXK2 and FXK3 respectively (table 1). All the powders were passed through mesh # 80. Talk and magnesium stearate were finally added as glidant and lubricants. The drug and powdered gum were compressed (10 mm diameter, biconvex punches) using a single punch tablet compression machine (Cadmach, Ahmedabad, india) prior to the compression, the powdered gum was evaluated for several tests. [4,5,8,9,10,11, 17]

Table 1: Composition of once daily matrix tablets (400 mg)

F. Code.	Drug	Xanthan	Karaya	Starch	Mg.	Total
	(mg)	gum(mg)	gum (mg)	1500	Stearate	(mg)
FX1	200	100	-	95	5	400
FX2	200	125	-	70	5	400
FX3	200	150	-	45	5	400
FK1	200	-	100	95	5	400
FK2	200	-	125	70	5	400
FK3	200	-	150	45	5	400
FXK1	200	50	50	95	5	400
FXK2	200	62.5	62.5	70	5	400
FXK3	200	75	75	45	5	400

EVALUATIONS

Evaluation of Powdered gum

Angle of Repose tablets (Fixed Funnel Method) [10 ,16,17]

The angle of repose of powdered gum was determined by the funnel method. The accurately weighed powders were taken in funnel. The height of funnel was adjusted in such a way that the tip of funnel just touched the apex of the heap of powder. The powder was allowed to flow through the funnel freely onto the surface. The diameter of powder cone was measured and angle of repose was calculated using the following equation

$$\theta = \tan^{-1} (h/r)$$

Here h and r are the height and radius of the pile respectively

Bulk Density tablets

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 2 g of powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 10 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 second intervals. The tapping was continued until no further change in volume was noted. LBD and TBD were calculated using the following formulas.

LBD = Weight of the Powder/Volume of the packing

TBD = Weight of the powder /Tapped volume of the packing. [10]

Compressibility Index tablets

The compressibility index of the gum powder was determined by Carr's compressibility index.

Carr's Index (%) = (TBD – LBD)/TBD X 100

Drug Content tablets

An accurately weighed amount of powdered matrix tablets (400 mg) was extracted with water and the solution was filtered through 0.45μ membrane (Nunc, New Delhi, India). The absorbance was measured at 274 nm after suitable dilution. . [9,10,14]

The above physical properties of formulated matrix tablets were shown in Table 2

Table 2: Micromeritic properties of matrix tablets

F. Code	Angle of repose (θ)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Hausner ratio (HR)	Carr's index
FX1	22.20±0.19	0.685±0.006	0.754±0.008	1.10±0.011	9.15±0.94
FX2	21.89±0.28	0.688±0.010	0.771±0.011	1.12±0.02	10.76±2.07
FX3	21.20±0.49	0.692±0.005	0.773±0.008	1.11±0.011	10.47±1.60
FK1	23.27±0.30	0.690±0.01	0.764±0.002	1.10±0.015	9.68±0.94
FK2	23.01±0.24	0.679±0.009	0.771±0.01	1.13±0.001	11.93±0.88
FK3	21.93±0.29	0.687±0.004	0.762±0.011	1.10±0.02	9.84±1.75
FXK1	21.78±0.60	0.682±0.004	0.758±0.01	1.11±0.02	10.02±1.65
FXK2	21.74±0.72	0.667±0.009	0.775±0.06	1.16±0.011	13.93±0.84
FXK3	22.05±1.00	0.678±0.005	0.774±0.05	1.14±0.02	12.40±1.71

Evaluation of Tablets

Thickness tablets

The thickness of the tablets was determined using a thickness screw gauge (Mitutoyo, New Delhi, India). Five tablets from each batch were used and average values were calculated. [10]

Uniformity of Weight tablets

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance (Denver APX-100, Arvada, Colorado) and the test was performed according to the official method. [3, 6, 7, 10]

Hardness and Friability tablets

For each formulation, the hardness and friability of tablets equivalent to 6.5g were determined using the Monsanto hardness tester (Cadmach, Ahmedabad, India) and theRoche friabilator (Campbell Electronics, Mumbai, India), respectively. [10]

Swelling behaviour of Sustained release matrix tablets tablets

The extent of swelling was measured in terms of % weight gain by the tablet. The swelling behavior of formulations FX1, FX2, FX3, FK1, FK2, FK3, FXK1, FXK2 and FXK3 were studied. One tablet from each formulation was kept in a Petri dish containing pH 7.4 phosphate buffers. At the end of 1 hour, the tablet was withdrawn, kept on tissue paper and weighed then. This procedure was repeated till 8 h. The % weight gain by the tablet was calculated by the following formula. [3,6,10]

$$S.I = \{(M_t - M_0) / M_0\} \times 100$$

Where, S.I = swelling index, M_t = weight of tablet at time 't' and

M_0 = weight of tablet at time t = 0. Swelling behavior of sustained release matrix tablets were represented in figure

***In-vitro* release studies tablets**

The in vitro dissolution studies were carried out using USP apparatus type II at 50 rpm. The dissolution medium consisted phosphate buffer pH 7.4 for 24 hours (900 ml), maintained at 37°C ± 0.5°C. The drug release at different time intervals was measured by UV-visible

spectrophotometer (UV spectrophotometer, Shimadzu 1700, Japan) at 274 nm. It was made clear that none of the ingredients used in the matrix formulations interfered with the assay. The release studies were conducted in triplicate (5 tablets in each set) and the mean values were plotted versus time with SDs of less than 3, indicating the reproducibility of the results. [3,9,10]

Table 3: show the Evaluation parameters of matrix tablets

F. Code	Thickness (mm)	% friability	% Drug content	% Weight variation	Hardness (Kg/cm^2)
FX1	6.00±0.00	0.69±0.04	92.85 ±2.40	2.23±1.4	4.23±0.15
FX2	6.00±0.00	0.52±0.04	94.91±2.21	0.93±0.87	4.46±0.15
FX3	6.00±0.00	0.54±0.07	99.63±1.71	1.64±1.63	4.60±0.20
FK1	6.00±0.00	0.39±0.09	93.18±1.12	1.86±1.65	4.40±0.26
FK2	6.00±0.00	0.48±0.10	95.45±1.35	1.91±1.44	4.53±0.22
FK3	6.00±0.00	0.51±0.12	98.36±2.45	1.37±0.92	4.90±0.71
FXK1	6.00±0.00	0.40±0.06	102.54±2.21	0.78±0.75	4.80±0.47
FXK2	6.00±0.00	0.42±0.07	103.16±2.07	1.10±0.76	5.00±0.42
FXK3	6.00±0.00	0.30±0.03	100.80±2.25	1.41±0.99	5.20±0.40

Kinetic analysis of release data of tablets

Drug release kinetics The Korsmeyer and Peppas equation was used to analyze the data obtained from the *in-vitro* release studies to evaluate the kinetic models and release mechanism of Aceclofenac from the matrices. The software PCP Disso V2.08 was used.

Korsmeyer and Peppas equation (Korsmeyer and Peppas, 1981) is:

$$Mt/ M\infty = kt^n$$

Where Mt/M∞ is the fraction of drug release at time t, k is a constant incorporating the properties of the macromolecular polymeric system and the drug. The n is an exponent used to characterize the transport mechanism. For example, n = 0.45 for Case I or Fickian diffusion, 0.45 < n < 0.89 for anomalous behaviour or non-Fickian transport, n = 0.89 for Case II transport, and n > 0.89 for Super Case II transport. Fickian diffusional release occurs by the usual molecular diffusion of the drug due to a chemical potential gradient. Case II relaxational release is the drug transport mechanism associated with stresses and state-transition in hydrophilic glassy polymers, which swell in water or biological fluids. Case II generally refers to erosion of polymeric chain and anomalous transport (non-fickian) refers to a combination of both diffusion and erosion controlled drug release.[1,3]

RESULT AND DISCUSSION

Analysis of Aceclofenac matrices the tablets with weight of 400 mg, a diameter of 9.0 mm and height of 6.0 mm were obtained and subjected to quality control tests such as hardness, friability and drug content (table 1). The contents of the formulations were found to be uniform, since the amount of the active ingredient in each of the 10 units tested was within the range of 92.85 ± 2.4 - 100.80 ± 2.25 %, indicating uniform mixing of gums, Starch-1500 and drug. The mean values for hardness were over 5.2 kg/cm^2 and all formulations exhibits friability less than 0.4% during the friability determination.

In-vitro drug release

The aqueous medium on contact with hydrophilic polymer matrix gradually begins to hydrate from the peripheral towards the centre, forming a gelatinous swollen mass, which controls the diffusion of drug molecules through the polymeric material into aqueous medium. The hydrated gel layer thickness determines the diffusional path length of drug.

The *in-vitro* drug release profiles of Aceclofenac from tablets containing FX, FK and FXK in different gum proportions are shown in Figure-1 respectively. After 2h, the initial pH 1.2 was changed to pH7.4 continue the dissolution up to 24 h. It was shown that as the amount of gum in the matrix increased, there would be a greater degree of gum hydration with simultaneous swelling. This resulted in corresponding lengthening of the drug diffusion pathway and drug release rate.

Drug release was generally linear for most of the formulations, especially FXK matrices. Such linear release was from hydrophilic matrices has been attributed to synchronization between swelling and erosion of the polymer in maintaining a constant gel layer. FK is a nonionic polysaccharide and their hydration process is independent of

pH. During the test, all the formulation swelled and the outer layer of most of tablets appeared to be hydrated after being
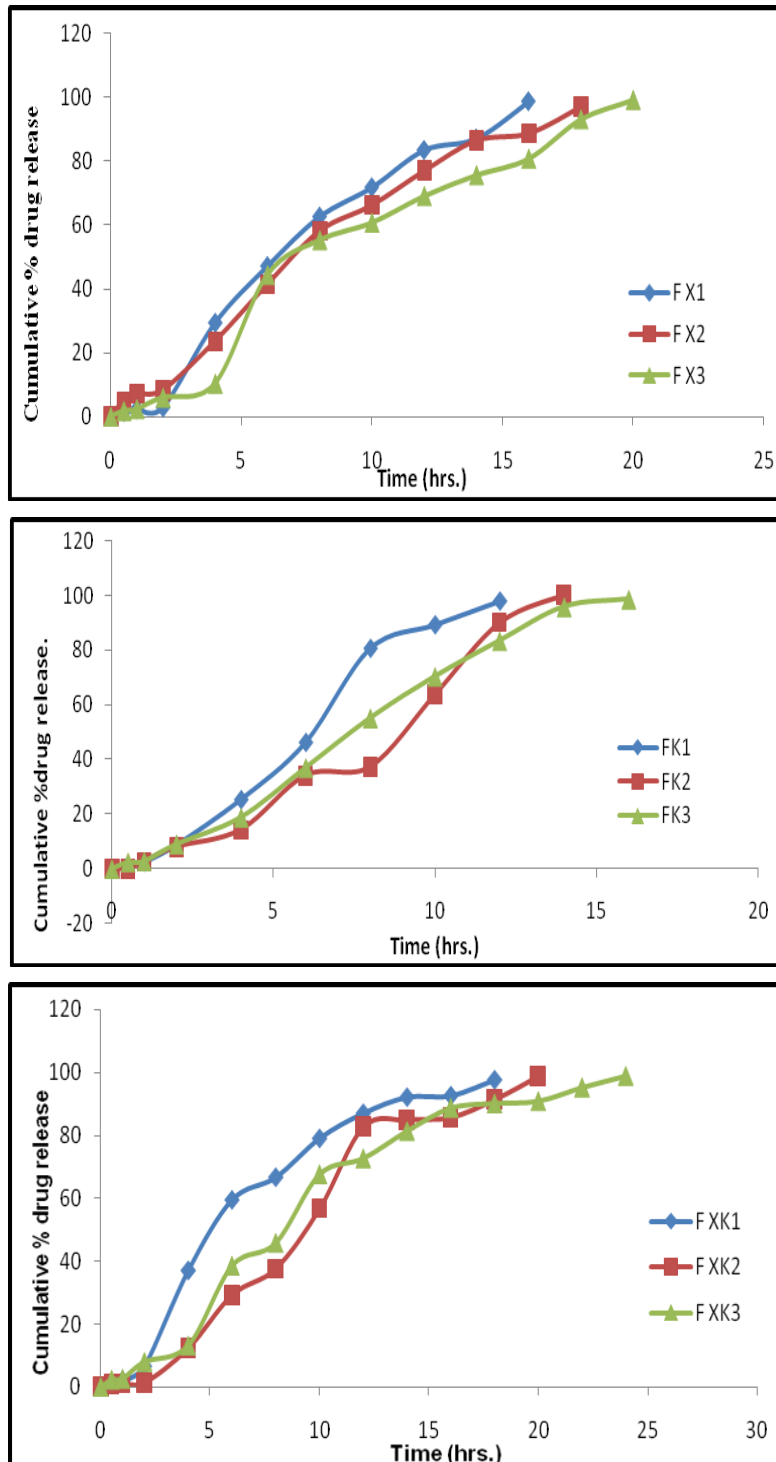
placed in dissolution medium.

Figure 1: In vitro release profile of Aceclofenac from tablets containing drug: gum, 1:0.500, 1:0.625 and 1:0.750 ratios of (FX) Xanthan gum (FK) Karaya gum and (FXK) Mixture of Xanthan and Karaya gum.

The profiles of the formulation of FX, FK, FXK, and the erosion and drug release at different drug: gum ratios of 1:0.500, 1:0.625 and 1:0.750 are shown in figure-1. In each case of FX there was an initial burst of xanthan gum erosion

from the matrices during the acidic pH thereafter, the erosion of xanthan gum slowed considerably. It follows, therefore, that the hydrated xanthan gum network maintains its tight integrity with drug release by erosion and dissolution of the

drug accounting for most of the weight loss during the remainder of the experimental period. Furthermore, there is a greater burst of xanthan gum erosion in the formulation containing the lower proportion of xanthan gum in 1:0.625 and 1:0.750 drugs: gum ratios. FK tablets formulations showed a higher tendency to loss of integrity than the FX and FXK. The swelling process of FK tablets was not uniform and the zones of high FK concentration appeared more swollen. In case of FK matrix a rapid erosion of the hydrated layer. This is because FK exhibit a less controlled release

effect but has a synergistic action along with the xanthan gum and shows precise controlled release effect.

In all the formulations, it has been observed that by increase the concentration of hydrophilic polymers in the formulations there by respectively retard the drug release form the matrices. In order to evaluate the role of FXK mixture, the drug release of Aceclofenac tablets with FX or FK alone, in same concentration of polysaccharide, was carried out and the results are shown in figure-1.
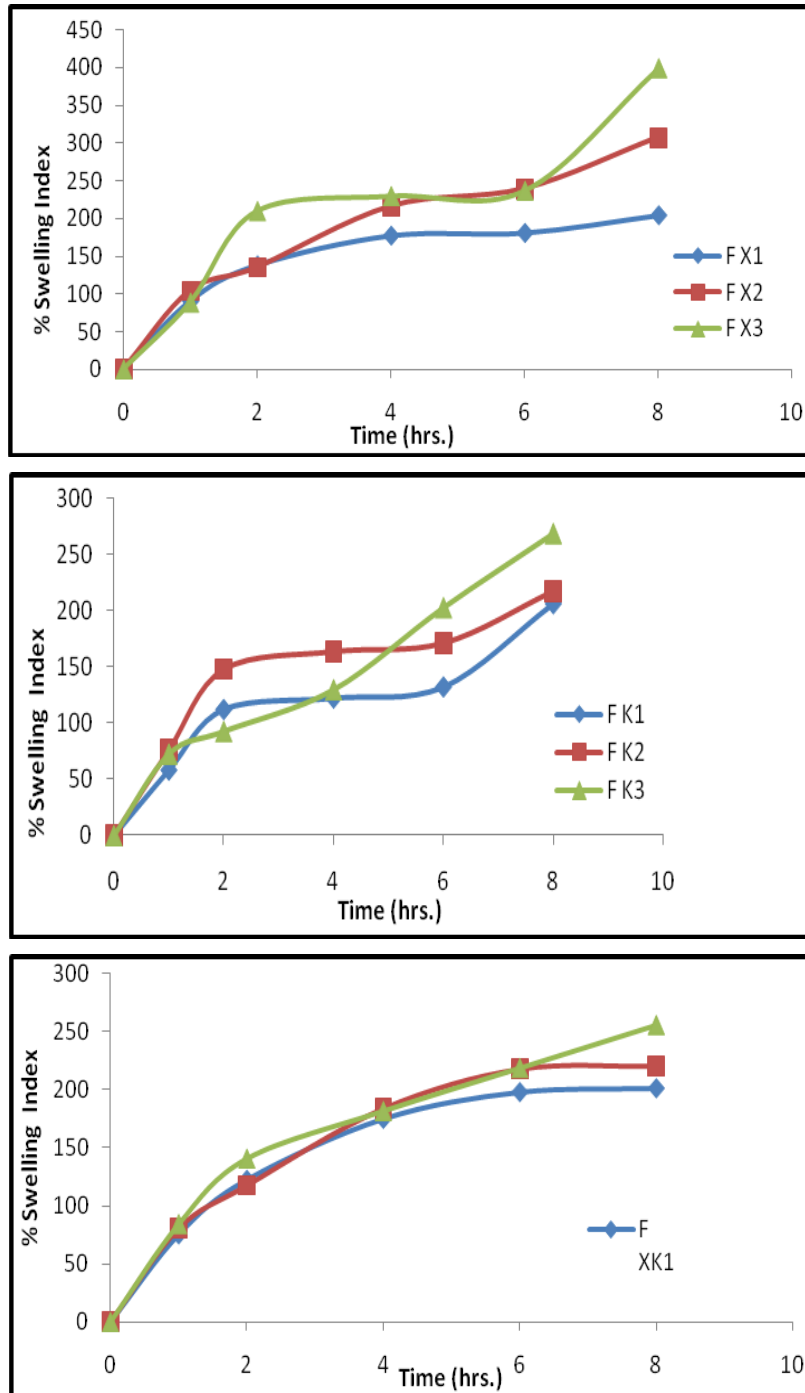

Figure 2: Swelling behaviour of FX, FK, And FXK in drug: gum ratio of 1:0.500, 1:0.625 and 1:0.750 at pH 7.4. Each point represents the mean value of five samples.

Table 4: Values of n (exponent for release kinetics)

Formulation	(drug: gum)	n values	r²	Transport Mechanism
FX1	(1:0.500)	1.179	0.926	Super case II
FX2	(1:0.625)	0.803	0.970	Anomalous
FX3	(1:0.750)	1.074	0.955	Super case II
FK1	(1:0.500)	1.297	0.989	Super case II
FK2	(1:0.625)	1.191	0.987	Super case II
FK3	(1:0.750)	0.776	0.991	Anomalous
FXK1	(1:0.500)	1.196	0.917	Super case II
FXK2	(1:0.625)	1.378	0.948	Super case II
FXK3	(1:0.750)	0.993	0.959	Super case II

r^2 determination coefficient.

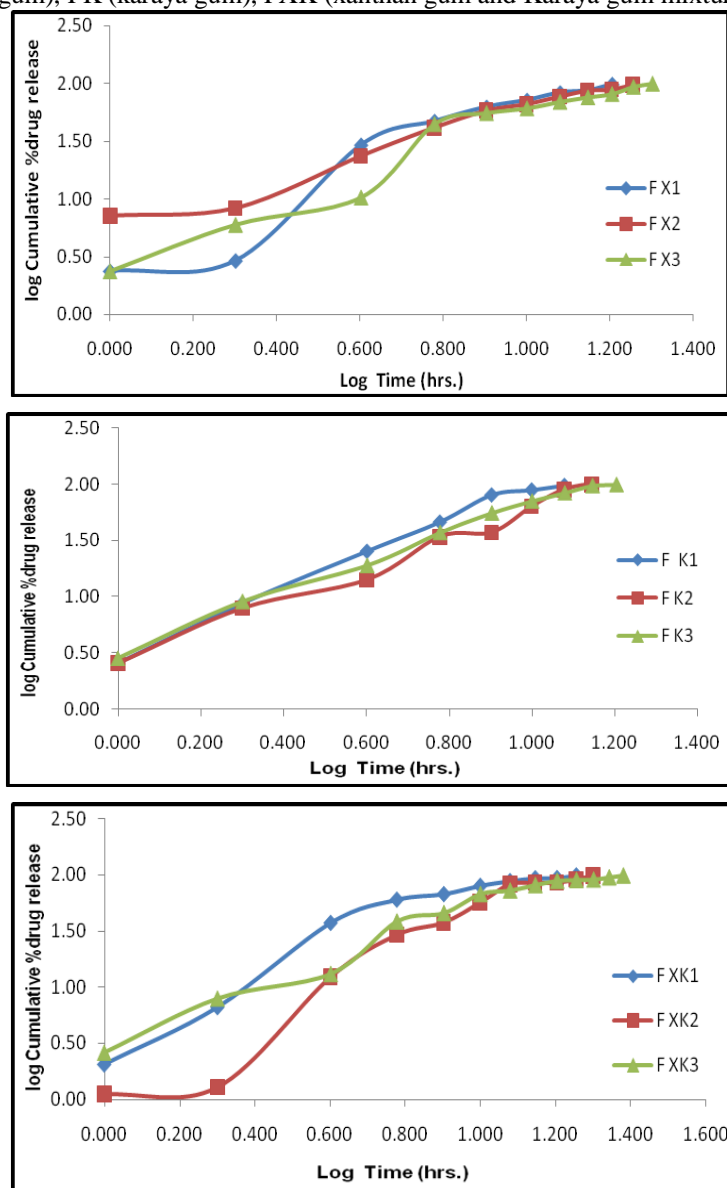FX (xanthan gum), FK (karaya gum), FXK (xanthan gum and Karaya gum mixture in 1:1 ratio).

Figure-3 Release kinetics of Aceclofenac formulation from (FX) Xanthan gum; (FK) karaya gum and (FXK) Mixture of Xanthan and karaya gum

The drug release was slower from the matrices with FXK compared to FX and FK matrices with the same total polymer concentration. The release of FX and FXK was similar but in case of FX the release of Aceclofenac at low concentration of xanthan gum a starting burst effect of release was seen in acidic pH. In case of FXK this type of burst effect was not seen in acidic pH. The FXK formulations exhibits good controlled release effect by the utilization of synergistic interaction between two biopolymers to produce a strong and elastic gel around the core of the matrices in the presence of a ternary component there by control the drug release form the matrices containing FXK formulation. Thereby FXK formulations show precise control release.

Swelling behaviour studies

The swelling behaviour studies were carried out with XLBG3 formulation of drug:gum ratio of 1:0.750, which resulted in the better dissolution profile. The results of swelling and erosion tests were shown in fig.2. The swelling behaviour indicates the rate at which this formulation absorbs water from dissolution media and swells. The change in weight is characteristic of water uptake and swelling, started from the beginning and continued until 8 h of experiment (figure-2)[3,10]

Determination of the release kinetics

To evaluate the drug release kinetics, formulations showing a significant slow release were chosen. In general, the mechanism of drug release from polymeric matrices can be described by the swelling phenomenon. The solvent molecules move inside the polymeric matrix like a "front" defined at an exact speed; simultaneously, the thickness of the area increased with time in the opposite direction. The mechanism of drug release can be described by a second phenomenon that involves the disentanglement and erosion of the polymer. The release process involves the penetration
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of water into dry matrix followed by hydration and swelling of the polymer, and diffusion of the drug dissolved in the matrix.

By using Korsmeyer and Peppas (Korsmeyer and Peppas, 1981) Equation, the n values were obtained between 0.77 and 1.378 (table 3) for all formulations. These values are characteristic of anomalous kinetics (non Fickian) and super case –II transport, suggesting that more than one mechanism may be involved in release kinetics. The release pattern of Aceclofenac from different formulation was obtained by plotting log M_t/M_∞ versus log time was shown in Figure-3. In case of FX and FXK of all formulations shows super case II transport kinetics.

For all the Aceclofenac matrix formulations, the contribution of polymer relaxation occurs throughout the entire dissolution time period. This was also apparent from the n values obtained (table 3), which approaches Anomalous and super case-II transport. In general, the relaxational contribution was higher for the formulations with higher n values. The FXK formulation showed the highest contribution of polymer relaxation, and swelling studies (figure-3). The formulations of FX and FK, showed the lowest n values, respectively then the FXK approaching less relaxational contribution. In the FXK3 formulation in the ratio of 1:0.750 reflects controlled delivery of Aceclofenac.

FTIR studies

The FTIR spectra of pure drug and formulation containing FXK are shown in figure-4. From the figure it is clear that the characteristic peaks at 3220(O-H stretching), 1717(C=O stretching), 1507(C-C stretching), 750(C-Cl stretching) cm^{-1} have been appeared in both the pure Aceclofenac drug and its formulation containing FXK matrices, without any change in their peak position, indicating no chemical interaction between and FXK as confirmed by the FTIR studies
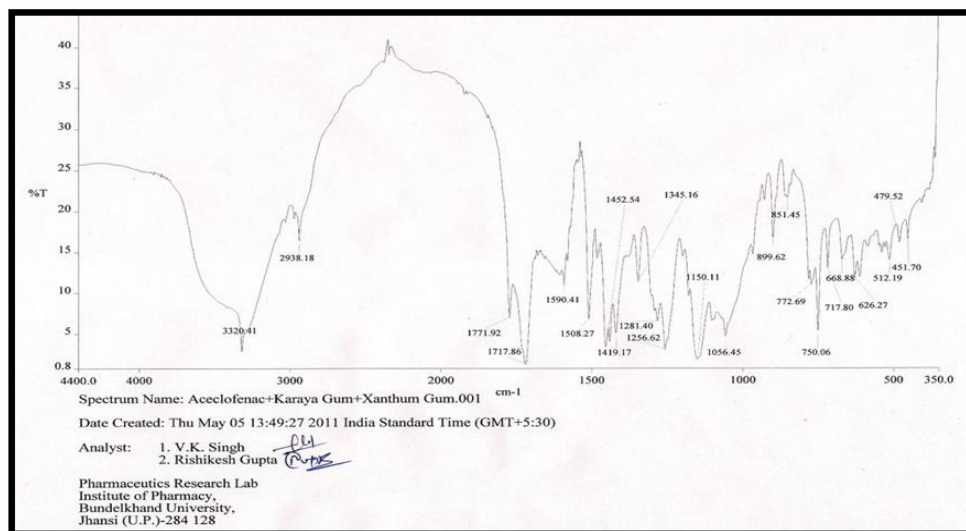

Figure 4: FITR Spectral obtained for pure drug and formulation containing FXK

CONCLUSION

The tablets with FXK resulted in more uniform controlled drug release matrices than FX and FK control the drug release process and the smallest average size of the particles. Xanthan gum matrices had marked sustained effect on the release of Aceclofenac than FK alone matrices. The FXK formulation was found to provide the required release rate, with zero-order release kinetics, it cost effective and more similar to reference standard. There was no chemical interaction between drug and polymer as been confirmed by FTIR studies. At the same total concentration, the FX matrices did not show controlled release but the FK has synergistic action with the xanthan shows precise controlled release effect. The predominant release mechanism varied with matrices composition and drug release was controlled by both diffusion and relaxation, with predominance of the latter mechanism mainly in FXK tablets.

ACKNOWLEDGEMENT

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