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FORMULATION, EVALUATION AND OPTIMIZATION OF ACECLOFENAC SUSTAINED RELEASE MATRIX TABLETS

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ABSTRACT: The objective of the present study was to develop the oral sustained release matrix tablets of aceclofenac using hydrophilic and hydrophobic polymers. Aceclofenac is a non steroidal anti-inflammatory agent used in symptomatic treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis and its biological half life is 4 hrs. FTIR studies were carried to know the interaction between the drug and polymer. Controlled release formulations of aceclofenac (200 mg) were prepared by direct compression method. The tablets were subjected to physicochemical, in vitro drug release and stability studies.

Optimization of the formulation was done by studying effect of drug to polymer ratio on drug release. FTIR studies indicated absence of any interaction between aceclofenac and polymers. The physicochemical properties of tablets were found within the limits.

The drug release from optimized formulations F1, F4 and F7 was extended for a period of 12 hrs. The kinetic treatment to optimized formulations showed that the release of drug follows zero order model and Super Case II transport for F1 and F7 while the drug release of F4 was best explained by Higuchi's model and Super Case II transport. Release of the drug was retarded with increase in polymer concentrations. The optimized formulations were subjected to stability studies for three months at 45° temperature with RH 75±5%, and showed stability with respect to physicochemical parameters and release pattern. Results of the present study indicated the suitability of hydrophilic and hydrophobic polymers in the preparation of matrix based sustained release formulation of aceclofenac.

Keywords: Aceclofenac, Sustained release, Controlled release, Matrix tablets, Direct compression.

INTRODUCTION

A number of methods and techniques have been used in the manufacturing of oral extended-release dosage forms. Probably the simplest and least expensive way to control the release of an active agent is to disperse it in an inert polymeric matrix. In polymeric system, the active agent is physically blended with the polymer powder and then fused together by compression moulding, which is a common process in the pharmaceutical industry. These dosage forms are designed to deliver the drug at a controlled and predetermined rate, thus maintaining a therapeutically effective concentration of the drug in the systemic circulation for a long period of time and therefore reducing the frequency of dosing and improving patient compliance. Hydrophobic materials for an insoluble matrix carrier and water-soluble hydrophilic materials have been reported as the most commonly used matrix carriers[1].

Non-steroidal anti-inflammatory drugs (NSAIDs) are considered to be the first-line drugs in the symptomatic treatment of rheumatoid arthritis, osteoarthritis and

ankylosing spondylitis. Aceclofenac is one of the emerging NSAID molecules for arthritis treatment. It is a newer derivative of diclofenac and has less gastrointestinal complications. The successful treatment of arthritis depends on the maintenance of effective drug concentration level in the body for which a constant and uniform supply of drug is desired. Sustained release dosage forms deliver the drug at a slow release rate over an extended period of time and achieve this objective. The short biological half-life (about 4 h) and dosing frequency more than one per day make aceclofenac an ideal candidate for sustained release. To reduce the frequency of administration and to improve patient compliance, a once-daily sustained release formulation of aceclofenac is desirable[2-5]. For sustained release systems, the oral route of drug administration has, by far, received the most attention as it is natural, uncomplicated, convenient and safer route[6]. Matrix tablets composed of drug and release retarding material (e.g. polymer) offer the simplest approach in designing a sustained release system. Matrix tablets are prepared by either wet granulation or direct compression method. Currently available sustained matrix tablets are generally prepared by wet granulation method. The tablets prepared in the present study by direct compression method have advantages over the tablets prepared by wet granulation in time and energy consumption, thus making it possible to formulate tablets at a lower cost[7]. Because of their flexibility, hydrophilic polymer matrix systems are widely used in oral controlled drug delivery, but in the present study different combinations of hydrophilic and hydrophobic polymers have been used to get the optimum results.

The aim of the present work was to prepare sustained release matrix tablets of aceclofenac and to study the *in vitro* release characteristics and kinetics of the prepared formulations. The kinetics of the dissolution process were studied by the application of four kinetic equations to the dissolution data–namely, the zero-order, the first-order, the Highuchi-square root and Korsmeyer- Peppas equations.

EXPERIMENTAL

MATERIALS:

Aceclofenac, xanthan gum and microcrystalline cellulose (MCC; Avicel PH102) were obtained as gift samples from Lupin Research Park, Pune, India. Magnesium stearate and talc were purchased from S.D. Fine-Chem Limited, Mumbai, India. Ethyl cellulose was purchased from Sriram Chemicals Pvt. Ltd. Ghaziabad, India. All other chemicals used were of analytical grade.

METHOD:

Drug-excipient compatibility studies:

Infrared (IR) spectroscopy was conducted using a FT-IR 8201 PC Spectrophotometer (Shimadzu, Tokyo, Japan) and the spectrum was recorded in the wavelength region of 4000 to 400 cm^{-1}. The procedure consisted of dispersing a sample (drug alone or mixture of drug and excipients) in KBr and compressing into discs by applying a pressure of 5 tons for 5 min in a hydraulic press. The pellet was placed in the light path and the spectrum was obtained[2].

Preparation of tablets:

The compositions of the tablet formulations are given in Table 1. Weighed amounts of aceclofenac, xanthan gum, ethylcellulose and MCC were mixed using in a glass mortar using a pestle to get a uniform mixture. The mixture was then blended with magnesium stearate and talc (1% w/w each) as lubricant in a poly-bag and compressed into tablets employing direct compression method (Single station tablet compression machine, Cadmach, Ahmedabad, India) using 13 mm flat-faced punches.

Evaluation of physical properties of matrix tablets:

All prepared matrix tablets were evaluated for uniformity of weight and drug content, as per I.P. method[8]. Friability was determined using Roche friabilator. Hardness was measured by using Pfizer hardness tester. Diameter and thickness were measured by Vernier caliper.

Dissolution studies:

The in vitro dissolution study was carried out using USPType1 dissolution apparatus. The study was carried out in 900 ml of 0.1N HCl (pH 1.2) for first 2 hours and then 900 ml of phosphate buffer (pH 7.4) from 3 to 12 h. The dissolution medium was kept in thermostatically controlled water bath, maintained at 37±0.5°C. Basket rotation was adjusted to 100 rpm. At definite intervals, 5 ml sample was withdrawn and analyzed spectrophotometricaly at 276.5 nm for the drug release. At each time of withdrawal, 5 ml of fresh corresponding medium was replaced into the dissolution flask.

Kinetic treatment of dissolution data: [1, 9]

In order to describe the kinetics of the release process of drug in the different formulations, zero- order ($Q_t = Q_0 + K_0t$), first- order ($\ln Q_t = \ln Q_0 + K_1t$), Higuchi ($Q_t = K_Ht^{1/2}$) and Korsmeyer- Peppas ($Q_t/Q_\infty = Kt^n$) models were fitted to the dissolution data of optimized formulations F1, F4 and F7 using linear regression analysis. A value of n = 0.5 indicates case I (Fickian)

diffusion or square root of time kinetics, $0.5<n<1$ anomalous (non- Fickian) diffusion, n=1 Case –II transport and n>1 Super Case II transport.

Stability studies:

Accelerated stability study was carried out to observe the effect of temperature and relative humidity on optimized formulations (F1, F2 and F7), by keeping at 40°C, in airtight high density polyethylene bottles for three months, at RH 75±5%. Physical evaluation and *in vitro* drug release was carried out each month for three months.

RESULTS AND DISCUSSION

The possible interaction between the drug and the excipients was studied by IR spectroscopy. The IR spectra of pure aceclofenac and its physical mixtures revealed no considerable changes in the IR peaks of aceclofenac when mixed with excipients and it conformed absence of any chemical interactions between the drug and polymer (Fig.1-3).

The formulated matrix tablets met the pharmacopoeial requirement of uniformity of weight. All the tablets conformed to the requirement of assay, as per I.P. Hardness, % friability; diameter and thickness were well within acceptable limits (Table 2). Hardness within the range of 5.5 to 9.5 kg/cm^2. All formulations showed less than 1% (w/w) friability that indicates the ability of tablets to withstand shocks which may be encountered during transport. The manufactured tablets showed low weight variations and a high degree of drug content uniformity was found among different batches of the tablets, and drug content was more than 98%.

The release profile of aceclofenac from different batches of formulated matrix tablets is illustrated in figure 4. All the formulations showed very low drug release in 0.1N HCl (pH 1.2). This was due to the very low solubility of aceclofenac at pH 1.2. The in vitro release of drug shows the effect of polymer concentration on the drug release. As regards the effect of polymer concentration, decrease in drug release rate was observed when polymer content in the matrix was increased. This may be due to the reason that the polymer in higher concentrations in the tablets might have produced dense matrix around the drug particles, providing more barriers for them to escape and dissolve[10]. Xanthan gum based matrix tablets with Drug –Polymer ratio 1:0.5 (F1) showed 82.45% total drug release at the end of 12 h. However, tablets with greater Drug –Polymer ratio- viz., F2 and F3 were found effective in sustaining the drug release beyond 12 h. Hence formulation F1 is optimized formulation among xanthan gum based matrix tablets.

Tablets based on ethyl cellulose as release retarding material with Drug –Polymer ratio 1:0.5 (F4) showed 62.44% total drug release at the end of 12 h. Drug release decreased as the percent amount of ethyl cellulose in the tablet increased. It has been previously reported that high level of EC reduce drug release rate on account of formation of a strong matrix with reduced porosity. This increases diffusional path length leading to reduced water penetration through the micropores resulting in slower drug release. However on subsequent increase the amount of ethyl cellulose (F5 and F6), there was no appreciable decrease in the release rate and extension in duration of release. This indicated that a tight nonporous matrix had been formed in former case (F4) and addition of more polymer could not modify the matrix character any further[11]. Hence formulation F4 is optimized one in this case.

The formulations F7, F8, F9 are the combination of two polymers containing hydrophilic xanthan gum and hydrophobic EC. The formulation F7 showed 74.22% total drug release at the end of 12 h. Drug release decreased as the content of xanthan gum and ethyl cellulose in the tablet increased[12]. The formulations F7, F8 and F9 showed less release compared to the formulation F1, F2, and F3 this could be due to the presence of ethyl cellulose, which is hydrophobic in nature. Hence the formulation F7 was selected as optimized one in this case.

Table 3 shows data analysis of release profiles according to different kinetic models. The kinetic treatment reflected that release data of F1 showed r^2 value of 0.9758 which is close to 1, indicating that release of drug follows zero order kinetics. The in vitro drug release of F4 was best explained by Higuchi's equation, as the plots showed the highest linearity (r^2 = 0.9712). The drug release significantly follows a zero-order kinetic model for formulation F7 as the plot showed the highest linearity (r^2 = 0.9872). The 'n' values of all formulations (F1. F4 and F7) for Korsemeyer and Peppas diffusion model was >1and exhibited a Super Case II transport mechanism.

The results of stability studies of matrix tablets of aceclofenac (F1. F4 and F7) revealed that there was no significant change in hardness, friability, drug content, and dissolution profiles. Thus, formulation was stable at accelerated conditions of temperature and humidity.

Results of the present study demonstrated that both hydrophilic and hydrophobic polymers and their combination could be successfully employed for formulating sustained release matrix tablets of Aceclofenac. The sustained release tablets can be expected to reduce the frequency of administration and decrease the dose dependent side effects associated with repeated administration of conventional Aceclofenac.

Table 1: Composition of 200 Mg Aceclofenac Matrices

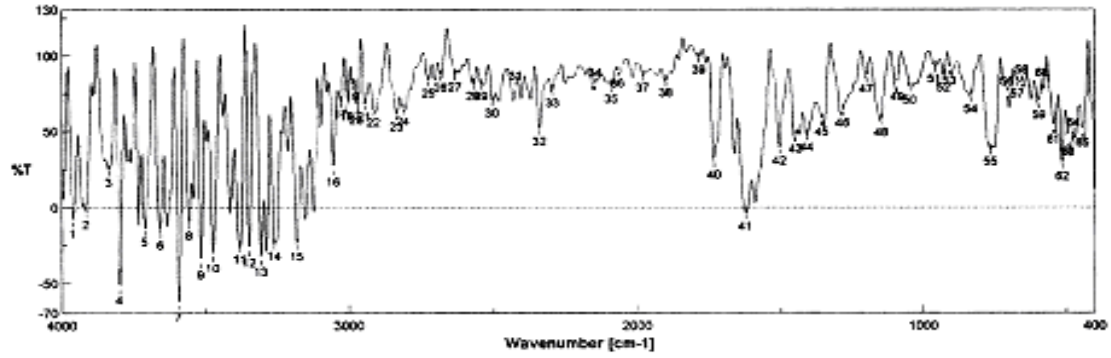
Ingredients (mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Aceclofenac	200	200	200	200	200	200	200	200	200
Xanthan gum	100	200	300	-	-	-	50	100	150
Ethyl cellulose	-	-	-	100	200	300	50	100	150
MCC	288	188	88	288	188	88	288	188	88
Magnesium stearate	6	6	6	6	6	6	6	6	6
Talc	6	6	6	6	6	6	6	6	6
Total weight	600	600	600	600	600	600	600	600	600

Table 2: Physical Properties of Acelofenac Matrix Tablets

Formulation Code	Drug Content (%)	Friability (%)	Hardness (kg/cm^2)	Diameter (mm) ±SD	Thickness (mm) ±SD
F1	99.65	0.59	8.6	11.2±0.2	4.2±0.5
F2	100.22	0.56	6.4	12.5±0.4	4.7±0.3
F3	99.56	0.82	8.2	11.6±0.2	4.7±0.5
F4	98.54	0.22	5.5	12.2±0.2	4.4±0.5
F5	99.25	0.55	6.8	11.8±0.3	4.5±0.3
F6	101.25	0.38	8.5	11.7±0.2	4.3±0.1
F7	100.56	0.47	7.5	11.4±0.5	4.5±0.4
F8	99.45	0.64	8.6	12.2±0.5	4.9±0.5
F9	101.45	0.44	9.5	11.6±0.2	4.3±0.1

Table 3: Kinetic Treatment of Dissolution Data of Optimized Formulations

Formulation	Zero- order (r^2)	First- order (r^2)	Higuchi (r^2)	Korsmeyer-Peppas (n)
F1	0.9758	0.7282	0.9651	1.8418
F4	0.9675	0.6820	0.9712	2.0529
F7	0.9872	0.7669	0.9570	1.9226



Accumulation	16
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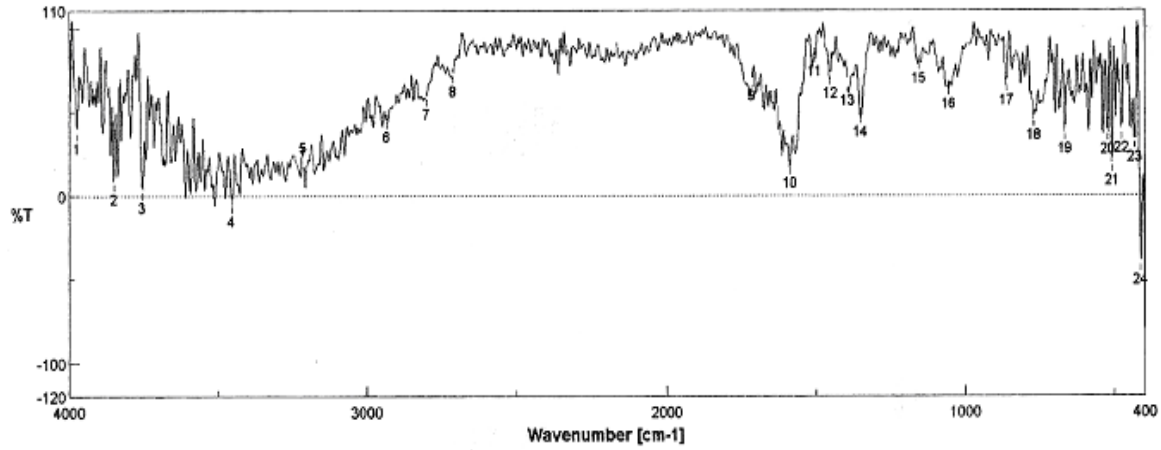
Gain	128
Date/Time	10/9/2006 3:41PM
Operator	
File Name	ACECLOFENAC
Sample Name	ACECLOFENAC
Comment	
Resolution	4 cm-1
Apodization	Cosine
Scanning Speed	2 mm/sec
Update	11/1/2006 3:57PM

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3958.14	-8.46708	2	3916.72	-3.417	3	3839.58	24.2075	4	3801.01	-53.5148	5	3712.3	-14.7336
6	3658.3	-17.319	7	3592.73	-64.4439	8	3556.09	-10.7303	9	3515.6	-36.7324	10	3475.1	-32.3082
11	3382.53	-28.519	12	3351.68	-28.4847	13	3311.18	-34.4502	14	3262.97	-24.3073	15	3183.9	-34.6085
16	3056.62	24.4548	17	3029.62	89.2153	18	3008.41	67.8104	19	2969.12	80.9031	20	2875.62	65.173
21	2948.7	67.6407	22	2915.84	83.725	23	2836.77	61.0338	24	2815.56	64.4655	25	2723	82.9098
26	2682.5	86.6882	27	2630.43	87.0476	28	2588.72	81.1216	29	2543.65	81.2069	30	2505.08	69.9499
31	2424.08	78.4957	32	2341.18	51.2215	33	2294.88	78.8604	34	2144.46	80.7932	35	2060.46	79.2928
36	2067.32	89.6581	37	1980.54	86.8542	38	1899.54	83.4732	39	1781.9	98.6011	40	1729.83	39.378
41	1621.84	-4.73565	42	1504.2	38.8375	43	1448.35	46.3678	44	1405.86	47.4213	45	1353.78	57.5778
46	1280.5	63.4416	47	1197.58	86.1382	48	1147.44	57.078	49	1089.58	80.717	50	1045.23	78.7574
51	956.52	82.6856	52	825.664	86.6548	53	804.451	91.1721	54	831.189	72.8533	55	765.931	37.8144
56	707.747	74.8184	57	673.035	82.5878	58	657.607	82.5871	59	595.896	68.757	60	586.254	80.5751

Fig. 1: IR Spectra of Pure drug (Aceclofenac)



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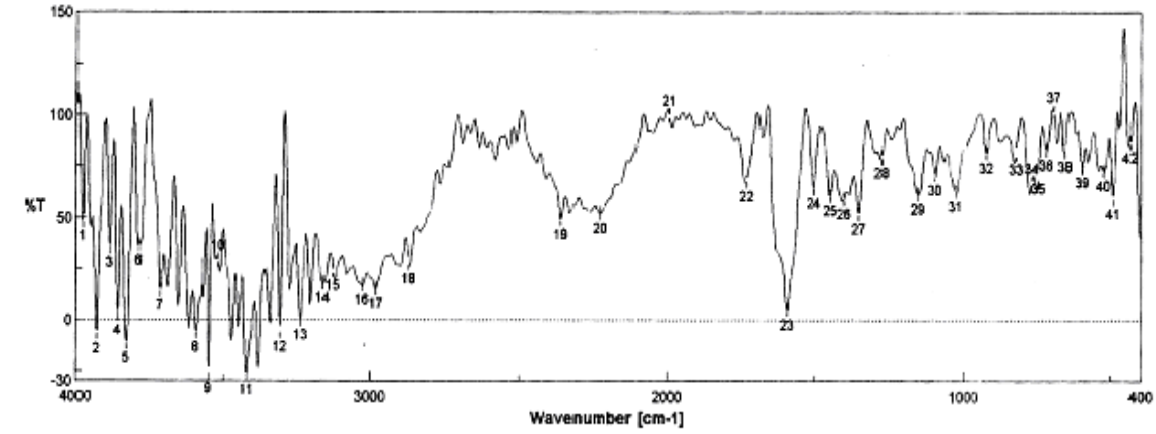
Gain	32
Date/Time	11/2/2006 11:45AM
Operator	govindarajan
File Name	xanthan
Sample Name	xanthan+Aceclofenac
Comment	
Resolution	4 cm-1
Apodization	Cosine
Scanning Speed	2 mm/sec
Update	11/2/2006 0:02PM

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3975.53	37.2019	2	3852.11	7.04475	3	3755.69	2.12567	4	3454.85	-6.25118	5	3212.83	19.325
6	2936.09	44.221	7	2801.1	57.7102	8	2712.39	71.1299	9	1714.41	68.7604	10	1590.99	16.3674
11	1504.2	83.2589	12	1451.17	70.1758	13	1392.35	65.6578	14	1349.93	46.9305	15	1159.97	78.7889
16	1057.76	63.6862	17	864.917	65.9208	18	775.244	45.0855	19	669.178	37.0817	20	521.65	36.3466
21	507.187	17.8348	22	475.367	37.2881	23	432.941	31.8449	24	414.82	-41.5539			

Fig. 2: IR Spectra of mixture of Xanthan gum and Aceclofenac



Accumulation	16	Resolution	4 cm-1
Zero Filling	OFF	Apodization	Cosine
Gain	64	Scanning Speed	2 mm/sec
Date/Time	10/9/2006 4:01 PM	Update	11/1/2006 4:03PM
Operator			
File Name	ETHYLCELLOSE		
Sample Name	ETHYL CELLOSE + ACECLOFENAC		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3978.43	48.3002	2	3832.14	-6.59455	3	3887.79	35.0834	4	3858.86	2.41165	5	3819.94	-11.2336
6	3787.51	36.2343	7	3716.16	14.5762	8	3590.81	-6.08889	9	3550.31	-25.9477	10	3519.45	29.2098
11	3419.17	-26.7309	12	3309.25	-5.63637	13	3237.9	0.0724892	14	3162.69	18.1499	15	3127.97	24.2996
16	3029.62	17.2134	17	2981.41	15.2242	18	2873.42	27.5545	19	2356.59	49.3056	20	2223.52	52.2878
21	1994.03	89.9452	22	1729.83	87.7083	23	1596.77	4.80928	24	1504.2	64.8401	25	1450.21	60.6875
26	1402	59.215	27	1349.93	51.8383	28	1276.65	78.0168	29	1157.08	61.5819	30	1097.3	70.8854
31	1027.87	62.9889	32	919.879	81.5745	33	823.455	80.8517	34	769.458	66.9847	35	746.317	71.508
36	721.247	82.6718	37	694.248	101.708	38	657.807	81.9847	39	599.753	74.3348	40	524.543	72.6704
41	489.831	59.3144	42	435.834	86.4228									

Fig. 3: IR Spectra of mixture of Ethyl Cellulose and Aceclofenac

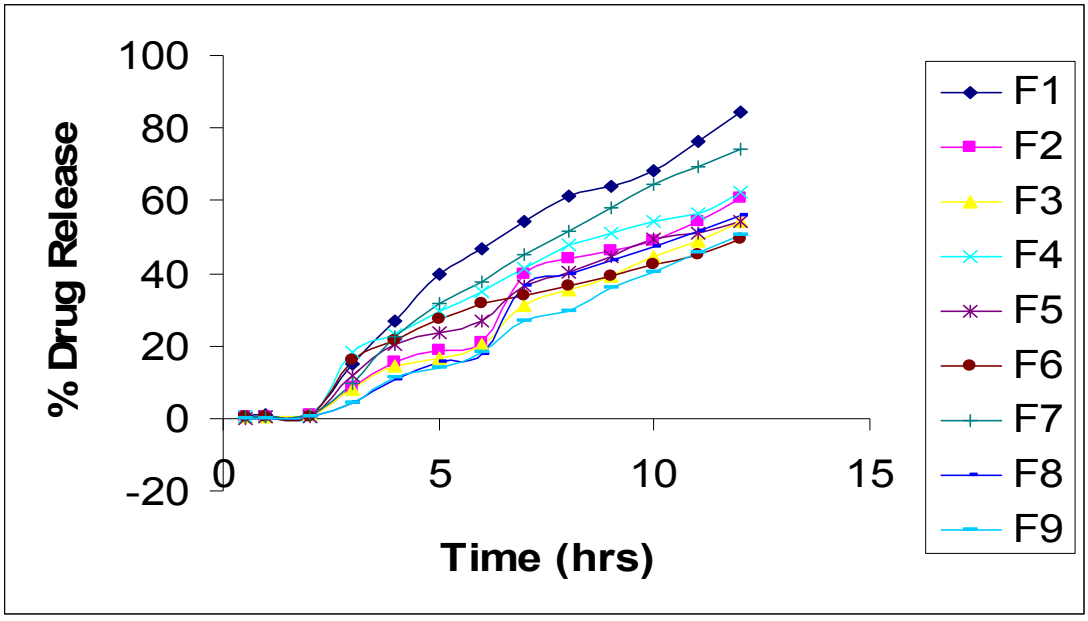


Fig. 4: release profile of aceclofenac matrix tablets of formulations ( ) F1,( ) F2,( ) F3, ( ) F4, ( )F5, ( )F6, ( )F7 ( )F8 and ( )F9

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