Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 3, Issue 4, 2011

Research Article

EFFECT OF TWO DIFFERENT DILUENTS ON RELEASE PROFILE OF ACECLOFENAC FROM SUSTAINED RELEASE MATRIX TABLETS USING GUM DAMAR AS RELEASE RETARDANT

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Received: 27 July 2011, Revised and Accepted: 25 Aug 2011

ABSTRACT

In the present work the effect of two different diluents namely dicalcium phosphate (DCP) and maize starch (MS) on the release of aceclofenac from sustained release matrix tablets has been studied. Gum damar (GD), a hydrophobic polymer with significant binding property was used as a release retarding agent. In the present study aceclofenac was used as a model drug for developing sustained release matrix tablets owing to its short biological half life (4 hours) and dosing frequency more than one tablet per day. Matrix tablet of aceclofenac using synthetically prepared hydrophilic polymers (e.g. HPMC) have been reported. However, low cost, ease of availability and non toxic property makes use of natural gums (e.g. gum damar), an alternative approach for development of sustained release matrix tablets. Compatibility between aceclofenac and GD was studied using FTIR. Sustained release matrix tablets of aceclofenac using GD as release retardant were prepared by wet granulation technique. Matrix tablets were prepared using different strengths of GD (10% - 30% w/w) with respect to total tablet weight and two different excipients DCP & MS as diluents. The tablet weight (400mg) and diameter (10mm) was kept constant. The physicochemical properties such as hardness, thickness, friability, uniformity of weight and the drug content of the formulated tablets were estimated The *in vitro* dissolution profile of the formulated tablets was compared with marketed sustained release aceclofenac tablets. The kinetics of release of aceclofenac from the matrix tablets were found to follow Hixon Crowell cube root law indicating a surface dependent release. The study revealed that GD as release retardant along with MS as diluent show results comparable to that of the marketed sustained release tablets of aceclofenac.

Keywords: Aceclofenac, Gum Damar, Sustained release, Matrix tablets.

INTRODUCTION

Aceclofenac, 2-[(2,6-dichlorophenyl)amino] phenylacetoxyacetic acid is a novel non steroidal anti-inflammatory drug used widely in the treatment of osteoarthritis, rheumatoid arthritis , ankylosing spondylitis and scapulohumeral periarthritis. Aceclofenac is especially well-tolerated among the non-steroidal anti-inflammatory drugs and has lower incidence of gastrointestinal adverse effects as compared to diclofenac[1,2]. The incidence of total and gastrointestinal adverse reactions is reported to be significantly lower with aceclofenac than with meloxicam or rofecoxib[3]. The usual dose of aceclofenac is 100 mg twice daily[4] . It is rapidly absorbed when taken orally but exhibits a short half life of 4 hours[5]. Short half life, dosing frequency more than one per day, fast onset of action and the therapeutic effectiveness of aceclofenac in management of various painful and inflammatory conditions, makes it an ideal candidate for sustained release formulation, resulting in more reproducible drug absorption and reducing risk of local irritations. Oral sustained release matrix tablets of aceclofenac prepared using a release retarding polymer is the simplest approach in designing a sustained release formulation of aceclofenac. A number of release retarding synthetic polymers such as hydroxyl propyl methyl cellulose of various grades[6-9], carbopol[10], polylactic-glycolic acid copolymers[11], combination of poly vinyl acetate and povidone[12], etc have been reported for formulation of sustained release matrix tablets of aceclofenac. Natural polymers in combination with synthetic polymers such as chitosan and hydroxypropyl methyl acetate phthalate[13], xanthan gum and ethyl cellulose[14], hydroxypropyl methyl cellulose, ethyl cellulose and guar gum[15] have also been reported. Synthetic polymers may be toxic, expensive, non eco-friendly, requiring longer time for synthesis as compared to natural polymers. Natural polymers have always attracted attention in the field of drug delivery because of their ready availability, low cost, eco friendliness, degradability and compatibility. Several plant based pharmaceutical excipients especially gums are being investigated for their usefulness as pharmaceutical excipients and can be modified to compete with the synthetic excipients available in the market[16]. In the present study an attempt has been made to formulate once a day sustained release (SR) matrix tablets of aceclofenac using a gum Damar (GD), a naturally occurring, low cost agent with significant binding characteristics[17]. GD is a whitish to yellowish natural gum of plant *Shorea Wisneri* (family Dipterocarpaceae). It contains about 40% alpha resin, 22% beta resin, 23% dammarol acid and 2.5% water. It is strongly hydrophobic in nature and possesses substantial binding property and compatibility with the physiologic environment[18]. The objective of the present study was to formulate and evaluate SR matrix tablets of aceclofenac using varying strengths of GD and to study the *in-vitro* release of aceclofenac from the sustained release matrix tablets prepared using two different diluents Viz: Dicalcium phosphate (DCP) and Maize starch (MS). The best formulation that would give an *in vitro* release comparable to that of a marketed SR tablet was determined.

MATERIALS AND METHODS

Aceclofenac was obtained as a gift sample from M/s Atra Pharmaceuticals, Mumbai and Gum damar was obtained from Rajesh Chemicals, Mumbai. All reagents used were of analytical grade. All other excipients were available from Research lab, Pune.

Preformulation studies

Solubility studies [6,19]

An excess quantity of aceclofenac was added to various solvents such as 10 ml of distilled water, 0.1 N HCl, 0.1 N HCl containing 1.5, 2.0, 2.5 % w/v sodium lauryl sulphate (SLS), phosphate buffer pH 6.8 , phosphate buffer pH 7.0 , phosphate buffer 7.4 and subjected to ultrasonication for 24 hours at room temperature. The solution was then filtered through whatmann filter and after making suitable dilutions the amount of drug dissolved in various solvents was analyzed spectrophotometrically using UV spectrophotometer (V-530, Jasco).

Drug- excipient compatibility study

Infrared spectra for aceclofenac, gum damar and the physical mixture of aceclofenac and gum damar was determined using Shimadzu FTIR 8300 spectrophotometer and the spectrum was recorded in the wavelength region of 4000 to 400 cm^{-1}. The procedure involved dispersing the sample in KBr and compressing into discs by applying a pressure of 5 tons for 5 minutes in a

hydraulic press. The pellet was placed in the light path and the spectrum was obtained

Construction of calibration curve for aceclofenac

Based on preformulation solubility studies, 0.1N HCL containing 2% SLS and phosphate buffer pH 7.0 were used for constructing the calibration curve for aceclofenac. The standard stock solution was diluted to obtain series of aceclofenac solutions in the concentration range 10-50 µg /ml. The absorbances of all the solutions were measured against respective blanks at 279 nm using UV spectrophotometer. A standard plot of absorbance Vs concentration of drug (µg/ml) was plotted in 0.1 N HCL containing 2.0 % SLS and pH 7.0 phosphate buffer respectively. This graph was used for estimation of drug content in the formulated SR tablets of aceclofenac and for *in vitro* drug release studies.

Formulation studies

Preparation of sustained release matrix tablets

Wet granulation technique was used for the preparation of matrix tablets of aceclofenac each weighing 400 mg and containing 200 mg of aceclofenac. The formulations are listed in table 1. Weighed amount of drug (aceclofenac), retarding agent (gum damar) and diluent were geometrically mixed by using stainless steel spatula. After mixing, a sufficient quantity of binder (isopropyl alcohol) was added to get uniform wet mass for granulation. The mass was sieved through sieve no. 16 and granules obtained were kept for drying in hot air oven at 40°C for 60 mins. After drying the dried granules were again passed through sieve no. 20 for uniform size. A sufficient quantity of lubricant (magnesium stearate & talc) was added prior to compression. Standard circular concave punches (10mm) were used for compression. Compression of tablets was carried out on multipunch tablet compression machine (Cadmach).

Table 1: Composition of aceclofenac sustained release matrix tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Aceclofenac	200	200	200	200	200	200
GumDamar (GD)	40 (10%)	80 (20%)	120 (30%)	40 (10%)	80 (20%)	120 (30%)
Dicalcium Phosphate (DCP)	150	110	70	-----	-----	-----
Maize Starch(MS)	----	-----	-----	150	110	70
Magnesium Stearate	8	8	8	8	8	8
Talc	2	2	2	2	2	2

Micromeritic properties

The dried granules of different formulations (F1-F6) were studied for various micromeritic properties such as bulk density, tap density angle of repose, carr's index and hausner's ratio Bulk density was determined using bulk density apparatus. The carr's index and hausner's ratio were calculated using the following formulae.

Carr's Index: (Tap density-Bulk density/Tap density) X 100.

Hausner's ratio: Tap density/Bulk density

The angle of repose of dried granules was determined by fixed funnel method using the formula: $\theta = \tan^{-1}$ (h/r) where h = height of the pile and r = radius of the pile.

Evaluation of aceclofenac tablets

Physicochemical characterization of tablets

The thickness and diameter of the tablets (n = 6) were determined using vernier callipers. The % friability of the tablets was determined using Roche Friabilator (n = 6). The hardness (n = 6) was determined by using digital hardness tester (Electro lab). The weight variation test (n=20) was carried out as per I.P 1996. The drug content was determined by crushing formulated tablets of aceclofenac in methanol. The solution was filtered through whatman and analyzed spectrophotometrically at 279 nm using pH 7.0 phosphate buffer for suitable dilutions.

***In vitro* dissolution studies**

The *in vitro* dissolution study was carried out using USP type 2 (paddle) dissolution apparatus (Model: Electrolab TDT – 06P). The study was carried out in 900 ml of 0.1 N HCL containing 2% SLS for the first two hours and in 900 ml of pH 7.0 phosphate buffer from 3 to 8 hours. The dissolution medium was kept in thermostatically controlled water bath, maintained at 37± 0.5°C. The paddle was lowered so that the lower end of the stirrer was 25 mm above from the base of the beaker. A pre-weighed tablet was then placed in each of the dissolution vessel and the paddle was rotated at 50 rpm. At different time intervals, 10 ml of the sample was withdrawn and analyzed spectrophotometrically at 279 nm for the drug release. At each time of withdrawal, 10 ml of fresh corresponding medium was replaced in the dissolution flask. The % cumulative amount of drug released from each formulation was calculated using the preconstructed calibration curves.

Drug release kinetics

The dissolution data obtained from the *in vitro* release study of the selected formulation was subjected to different kinetic models namely zero order (% cumulative release Vs time), first order (Log % cumulative released Vs time), Higuchi (% cumulative released Vs square root of time), Hixon Crowell (Cube root of % cumulative drug remaining Vs time) and Korsemeyer peppas equation (log Mt/M∞) Vs log t for studying the release profile.

RESULTS AND DISCUSSION

Solubility determination of aceclofenac

The solubility studies were carried out to determine the most suitable dissolution medium for *in vitro* drug release. The solubility of aceclofenac in water , 0.1 N HCL and pH 6.8 was found to be very low as shown in table 2. At pH 7.4 the solution was found to be cloudy. Aceclofenac showed best solubility in phosphate buffer (pH 7.0) while 2% SLS was found to be optimum for getting desired solubility in 0.1 N HCL.

Table 2: Solubility of aceclofenac in various solvent media

Solvent	Solubility (mg/ml)
Distilled water	0.082 ± 0.035
0.1 HCL	0.022 ±0.076
1.5% W/V SLS in 0.1 N HCL	0.421 ± 0.020
2.0% W/V SLS in 0.1 N HCL	0.486 ± 0.043
2.5% W/V SLS in 0.1 N HCL	0.479 ± 0.072
pH 6.8 phosphate buffer	6.230 ± 0.045
pH 7.0 phosphate buffer	9.231 ± 0.187
pH 7.4 phosphate buffer	Preparation was cloudy & showed precipitation

Drug excipient compatibility studies

The possibility of interaction between aceclofenac and gum damar was determined using FTIR spectrophotometer. The IR spectra of the aceclofenac (fig1), showed all principle peaks of the standard aceclofenac Viz. 3315.74cm^{-1} (-NH stretch), 2970.64cm^{-1} (-OH stretch), 1768.78, 1720.56 cm^{-1} (-C=O stretch) , 2935.76 (-CH

stretching superimposed on –OH stretching) and 669.5 cm^{-1} (-C - Cl stretch). FTIR spectra of GD is represented by fig.2. The fig.3 represents the I.R spectra of physical mixture of aceclofenac and GD. There is a reduction in peak intensity but no shifting of the band, indicating that there is no interaction between aceclofenac and gum damar.

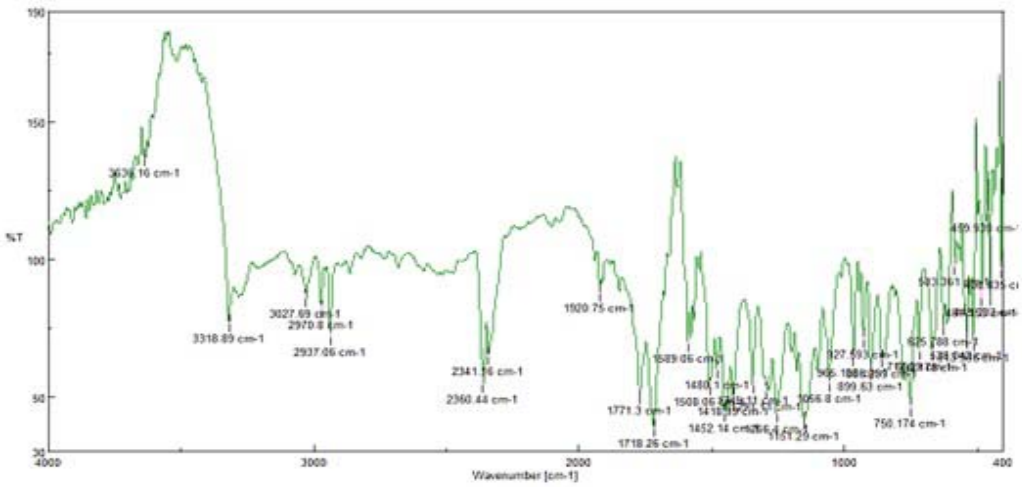


Fig 1: I.R spectra of aceclofenac

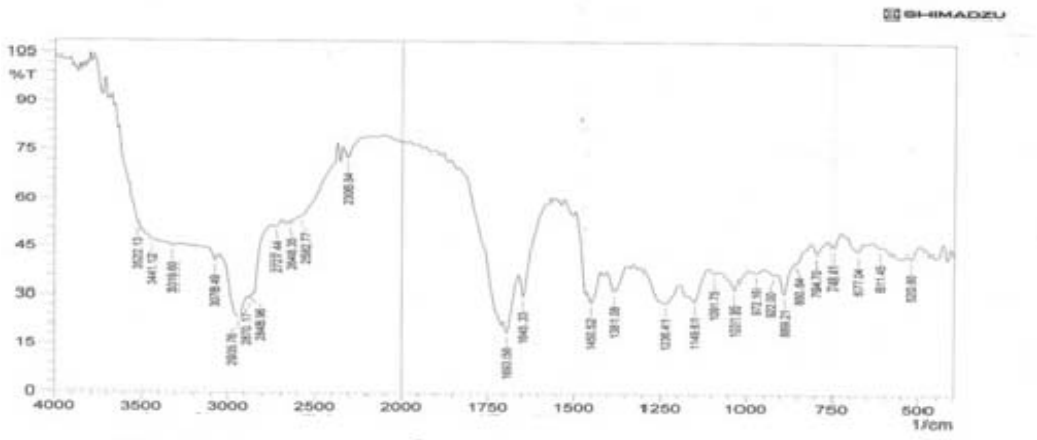


Fig. 2: I.R Spectra of Gum Damar

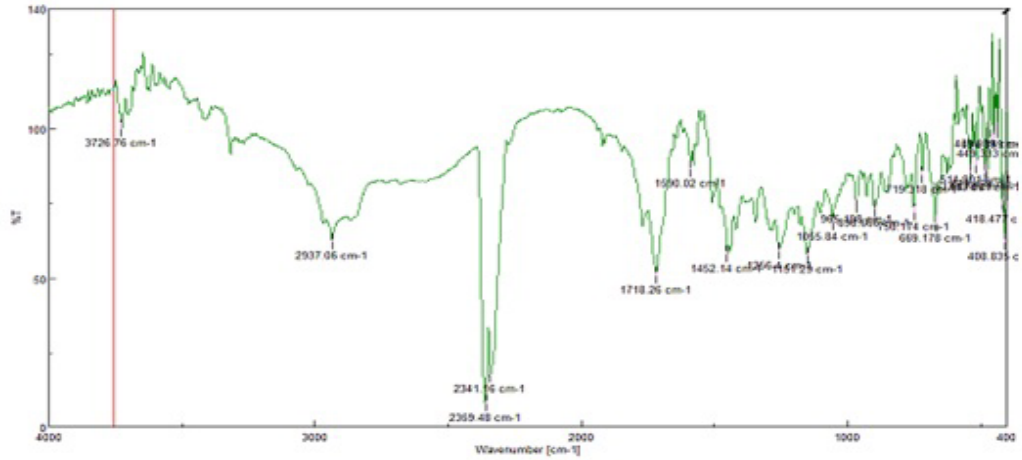


Fig. 3: I.R Spectra of physical mixture of aceclofenac and gum Damar

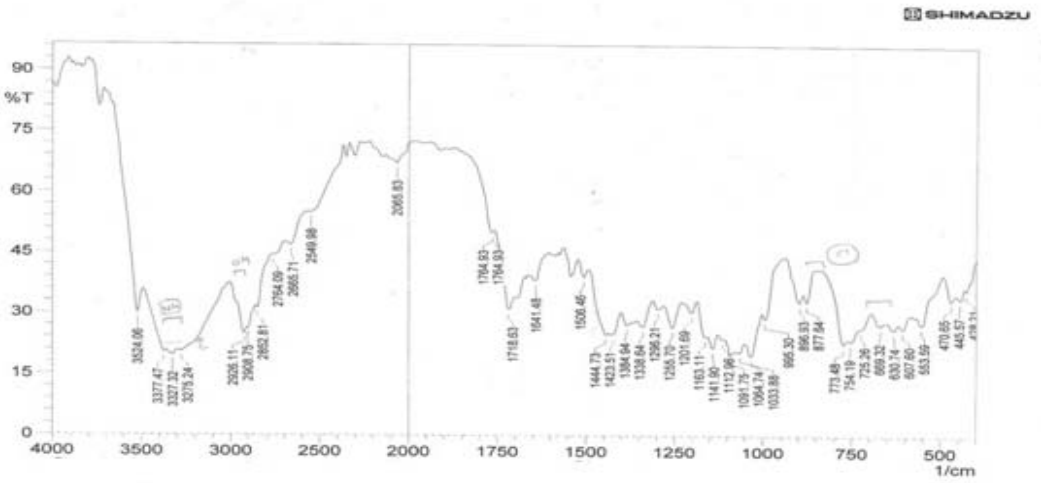


Fig. 4: I.R. Spectra of crushed tablet of aceclofenac (F1)

Micromeritic properties

The prepared granules of aceclofenac were studied for various micromeritic properties as shown in the table 3.

The micromeritic studies of dried granules showed that they exhibited good flow properties and a good compressibility index. All the formulations showed an uniformity in the drug content.

Table 3: Micromeritic properties of dried granules of aceclofenac

Properties	F1	F2	F3	F4	F5	F6
Fluff density (g/cc)	0.40	0.41	0.40	0.42	0.43	0.45
Tapped density (g/cc)	0.45	0.47	0.46	0.47	0.48	0.49
Angle of repose	29.26	28.26	27.12	28.21	27.89	27.35
Carr's index	7.0	13.0	13.0	11.0	10.0	8.0
Hausner's ratio	1.13	1.15	1.15	1.12	1.12	1.09
% Drug content	98.5 ±0.357	97.7 ±0.212	97.2 ±0.518	98.57±0.892	98.3 ±0.712	97.27±0.638

Table 4: Physicochemical Properties of aceclofenac tablets*

	Formulation					
Evaluation Parameters	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Thickness (mm)	6.10 ± 0.005	6.14 ±0.012	6.03 ±0.007	6.01±0.010	6.12 ±0.002	6.05 ±0.009
Diameter (mm)	10.02 ±.0.005	10.07±0.008	10.02±0.010	10.05+0.007	10.04 +0.004	10.05+0.013
Hardness(kg/cm^2)	5-7	5-7	5-7	5-7	5-7	5-7
Friability	0.77 +0.0057	0.44 +0.0085	0.50 +0.0091	0.60+0.0078	0.55+0.0032	0.50+0.0087
Weight (mg)	400 ±0.0577	401 +0.0576	403 +0.0577	401 +0.0575	402 +0.0576	400 +0.0577
% Drug Content(mg)	98.7 ±0.2645	97.2 +0.7377	96.3 +0.5887	99.3 +0.2081	97.5 +0.2529	98.8+0.4851

*All values other than hardness, weight (mg) are expressed as mean ± standard deviation (n = 6)

Physicochemical characteristics of aceclofenac tablets

The formulated tablets of aceclofenac were evaluated for various physical properties such as Thickness, diameter, % friability, hardness, weight variation and % drug content. The results obtained are reflected in table 4.

All the formulations showed an average thickness of around 6.10 mm, diameter 10.04 mm. Hardness in the range 5-7 kg/ cm^2. % friability for all the tablets was found to be less than 1%. The weight variation was also found to be within the prescribed limits as per I.P. (< 5%).The drug content was more than 97% w/w in all tablets and individual formulations showed an acceptable content uniformity.

***In vitro* drug release (Dissolution profile)**

The results of the *in vitro* drug release studies in 0.1 N HCl containing 2% SLS for first two hours and in pH 7.0 phosphate buffer from 3 to 8 hours are presented in figure 5. The aim was to determine the optimum concentration of gum damar necessary to formulate sustained release matrix tablets of aceclofenac. In all the formulations studied the release of aceclofenac from SR matrix tablets in the first 2 hours was < 10%. In pH 7.0 phosphate buffer the formulations F1, F2 and F3 containing 10%, 20% and 30% GD respectively and DCP as diluent showed less than 25% release of aceclofenac over a period of 8 hours. The reason for unusual slow release of aceclofenac from the SR tablets can be attributed to two reasons. One of the reasons is that the diluent used in all the three formulations (F1-F3) is DCP which is hydrophobic in nature. The second reason may be the probability of complex formation between GD and aceclofenac due to hydrogen bonding between –COOH group of GD and –OH & - C=O groups present in aceclofenac. This is evident from the I.R spectra of crushed tablet of F1 formulation (fig 4). The I.R spectrum resembles more to the spectrum of GD (fig 2) indicating that after granulation GD tightly binds to aceclofenac and hence its prominent peaks have been overshadowed by GD. Moreover the increase in the concentration of gum damar from 10% to 30% with DCP should have shown an increase in the retarded release of aceclofenac. However no significant difference in release retardation was observed. This may be attributed to the corresponding decrease in the concentration of DCP in the formulations. With the use of MS, a hydrophilic diluent, an improvement in the release profile was seen in the fig 5. All the formulations (F4, F5, and F6) prepared with

MS and containing 10%, 20% and 30% w/w of gum damar respectively showed an increase in the release after the first two hours and all the three formulations showed 60-80% release at the end of 8 hours. However the formulation F5 containing 20 %w/w of gum damar showed dissolution profile similar with the marketed formulation and hence was further studied for the kinetics of release. The *in vitro* release profile also suggests that GD, a natural release retardant can be used successfully for formulating SR matrix tablets. However a proper choice of diluents is necessary to get a desirable sustained release.

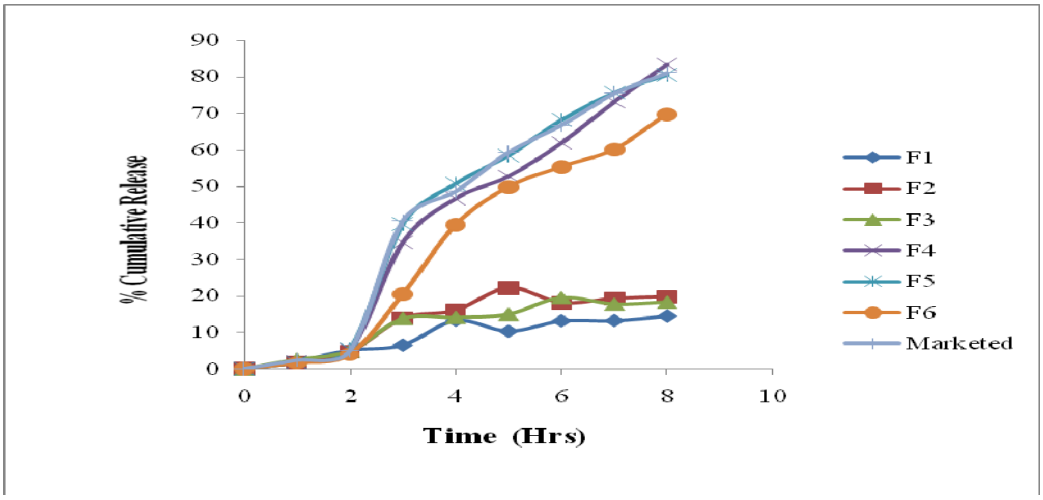


Fig. 5: Plot of % cumulative released Vs time for formulated aceclofenac tablets

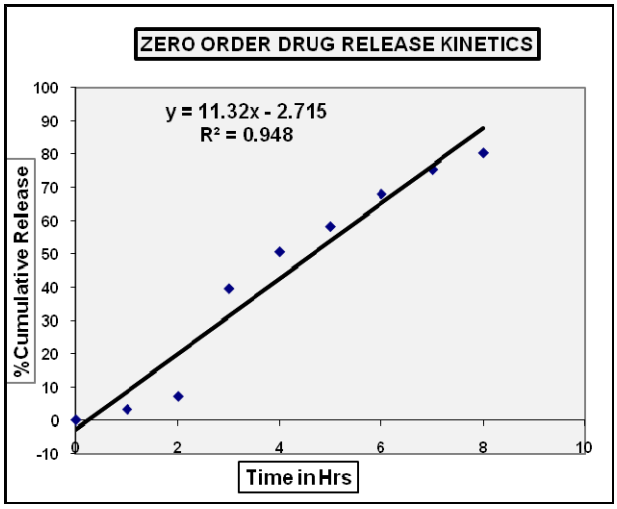
(F1: 10% G.D + DCP, F2: 20%G.D + DCP, F3: 30% G.D+DCP, F4: 10% G.D + MS, F5: 20%G.D + MS, F6: 30% G.D+MS) and marketed aceclofenac tablet.

Drug release kinetics

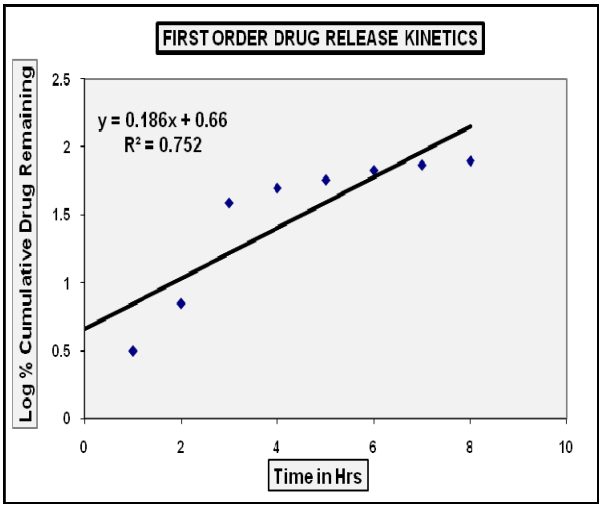
The dissolution data obtained for the *in vitro* release studies of F5 formulation was subjected to different kinetic models namely zero order (% cumulative release Vs time), first order (Log % cumulative released Vs time), Higuchi (% cumulative released Vs square root of time), Hixon Crowell (Cube root of % cumulative drug remaining Vs time) and Korsemeyer peppas equation (log Mt/M∞) Vs log t for studying the release profile. The respective plots are represented in fig 6. The correlation coefficients for formulation F5 based on different kinetic models are presented in table 5. The criterion for selecting the most appropriate model was chosen on the basis of goodness of fit test. The values of regression coefficient indicate that the release kinetics of aceclofenac from the sustained release matrix tablets follows Hixon crowell cube root law which indicates that the release is surface dependent. The value of n= 1.664 from korsemeyer peppas equation indicates that the release of the drug takes place by erosion of the polymer.

Table 5: Correlation coefficients based on different kinetic models

Kinetic Model	Correlation coefficient
Zero order	0.948
First order	0.752
Higuchi	0.796
Hixon Crowell	0.968
Korsemeyer Peppas	1.664



(a)



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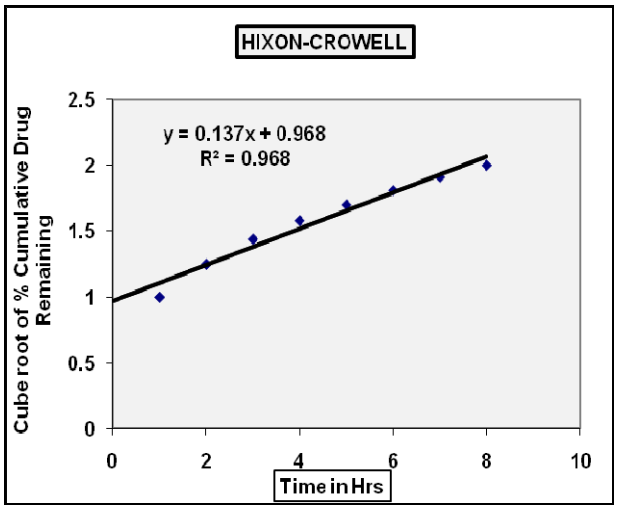

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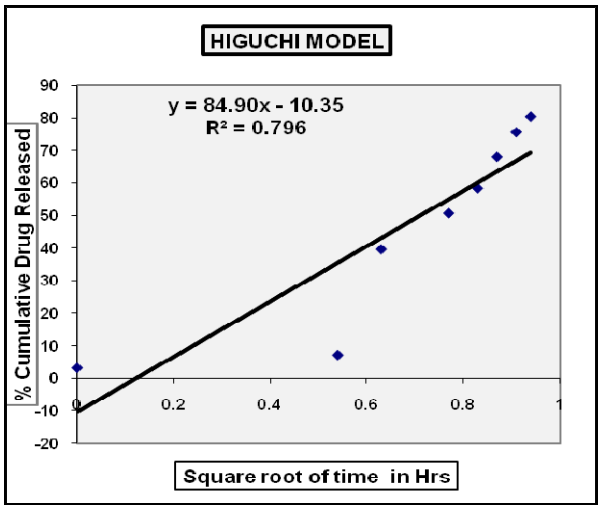

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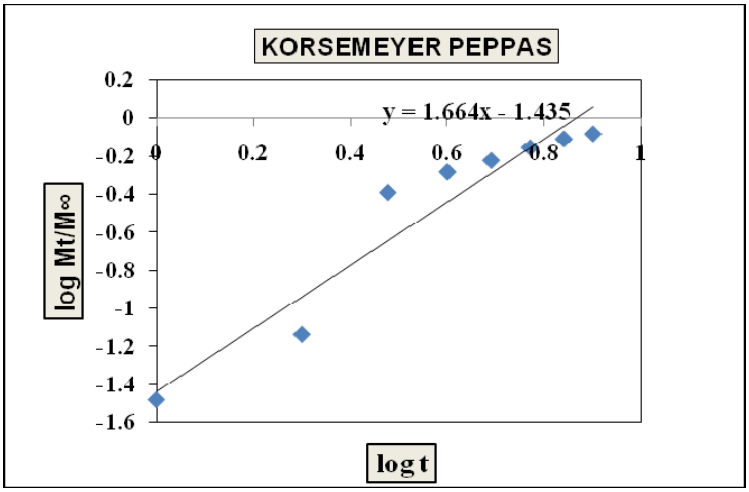

(e)

Fig. 6: Plots determining correlation coefficients based on different kinetic models for F5 sustained release matrix tablets of aceclofenac. (a: Zero order, b= first order, C=Hixon crowell, d =Higuchi, e = Korsemeyer peppas)

CONCLUSION

Studies indicate that SR matrix tablets of aceclofenac can be successfully prepared using gum damar as release retardant. Gum damar itself acts as good retardant however the choice of diluents showed a significant effect on the release of aceclofenac from sustained release matrix tablet. Use of hydrophobic diluent such as dicalcium phosphate showed a release of less than 25% in a time period of 8 hours whereas the release is extended to around 80% by using hydrophilic diluent such as maize starch. The release of aceclofenac from the selected formulation of sustained release matrix tablets was governed by Hixon Crowell's cube root law and was found to be comparable to marketed sustained release tablet of aceclofenac.

ACKNOWLEDGEMENT

The authors are thankful to M/s Atra Pharmaceuticals, Mumbai for providing gift sample of aceclofenac. The authors are also thankful to Dr. K. G. Bothara, Principal, Sinhgad Institute of Pharmacy for providing the necessary laboratory facilities and to Dr. C. R. Kokare, Professor of Pharmaceutics, Department of Pharmaceutics, Sinhgad Institute of Pharmacy for his support and guidance.

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