

Research Article

Formulation and *in Vitro* Evaluation of Once Daily Sustained Release Formulation of Aceclofenac

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Abstract

Purpose: The objective of the study was to develop matrix tablets for oral controlled release of aceclofenac using ethyl cellulose, guar gum and various grades of cellulose polymers.

Methods: Possible drug-excipient interaction was evaluated by high performance liquid chromatography (HPLC) and Fourier infrared spectroscopy (FTIR). The tablets prepared were assessed for their physicochemical, *in vitro* drug release at pH 1.2, 4.5, 6.8 and 7.5 and stability characteristics. Comparison with a 'once daily' commercial aceclofenac product was made in the *in vitro* studies.

Results: There was no interaction between aceclofenac and the polymers used as excipients. Furthermore, the physicochemical properties of the tablets were satisfactory. The release profile of one of the formulated aceclofenac tablets (F7), which contained hydroxypropyl methyl cellulose (HPMC K4M), was statistically similar ($p < 0.05$) to that of the commercial aceclofenac brand in all the dissolution media. The formulated products were stable and showed no changes in physical appearance, drug content, or dissolution pattern after storage at 40 °C /75 %RH for 6 months.

Conclusion: The results indicate that it is feasible to achieve a stable 'once daily' sustained release aceclofenac tablet formulation by using HPMC K4M of 4000cps viscosity grade as matrix material.

Keywords: Aceclofenac, Sustained release, Matrix tablets, Cellulose polymers, Stability studies.

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INTRODUCTION

Aceclofenac is a newer derivative of the diclofenac group of non-steroidal anti-inflammatory drug (NSAID) that exhibits analgesic and anti-inflammatory activities. It directly blocks the prostaglandin synthesis and has less gastrointestinal complications [1-3]. It is a recommended first-line drug in the symptomatic treatment of rheumatoid arthritis, Osteoarthritis and ankylosing spondylitis. Aceclofenac, i.e., 2-[2-(2-(2,6-dichlorophenyl)amino)phenyl]acetyl]oxy]acetic acid, has a short biological half life of approx 4 h and a dosing frequency of 200 mg daily in two divided doses [4-6]. Consequently, the drug is a good candidate for sustained release formulation.

Several matrix based sustained release products of aceclofenac utilizing hydrophilic and hydrophobic polymers have been reported [7-13]. Polymer matrix systems have the advantages of prolonging drug release and reducing adverse effects in patients. An attempt has been made in the present study to achieve suitable aceclofenac therapeutic profile by formulating sustained release tablets using various viscosity grades of HPMC, guar gum and ethyl cellulose.

EXPERIMENTAL

Materials

Aceclofenac was a gift from Mepro Pharmaceuticals Pvt. Ltd. Surendranagar, India while Aroff SR tablets (Unichem Lab, Mumbai, India), used as a reference, were purchased from a local pharmacy. The excipients used in the production of the tablets were Methocel K4M, K15M and K100M Premium (Colorcon Asia Pvt Ltd, Singapore), which represent hydroxypropyl methylcellulose (HPMC) viscosity grades 4000, 15000 and 100000 cps, respectively; guar gum (Kachabo Gum, India); ethyl cellulose 20 cps (Feicheng Ruotai Fine Chemicals Co., Ltd, China); Methocel E 15 (Colorcon Asia Pvt. Ltd., Singapore), which

represents HPMC viscosity grade 15 cps and lactose (DMV International, USA). Others were polyvinyl pyrrolidone (PVP) K-30, (International Fine Chemicals Inc., Canada), sodium propyl paraben (Salicylates and Chem Pvt Ltd, India), fumaric acid, microcrystalline cellulose (MCC, Avicel PH102, FMC Biopolymers, U.S.A.), magnesium stearate (Nitika Chemicals, India), talc (Udaipur Mineral Development Syndicate Pvt Ltd, India), isopropyl alcohol (Ranbaxy Fine Chemicals, India), methylene chloride (Chemplast Sanmar Ltd, India) titanium dioxide (Dupont Company Pvt Ltd, Singapore), PEG-6000 (Manali Petro Chemicals, India), castor oil (Sundarballi Oil Mill, India) and Ponceau 4 R supra (Roha Dye Chem, India). All other chemicals used were of analytical grade.

Solubility studies on aceclofenac

Loose bulk density (LBD) and tapped bulk density (TBD) were determined with a density apparatus (Serwell, Bangalore, India) while Carr's index and the Hausner's ratio were calculated using Eqs 1 and 2.

$$\text{Carr's index (\%)} = \frac{\text{TBD} - \text{LBD}}{\text{TBD}} \times 100 \dots (1)$$

$$\text{Hausner's ratio} = \frac{\text{TBD}}{\text{LBD}} \dots (2)$$

Evaluation of drug-excipient compatibility

Different excipients were selected and mixed separately with aceclofenac in proportions generally used in tablet formulations. Sets (23 each) of mixture were prepared, and stored in a closed chamber for 2 weeks at 40°C/75% RH closed. The physicochemical compatibilities of the drug and the excipients were evaluated by high performance liquid chromatography (HPLC, Class VP series, Shimadzu Corporation, Kyoto, Japan).

Infrared (IR) spectroscopy was conducted using a Perkin Elmer FTIR Spectrum-100 spectrophotometer and the spectra were recorded in the wavelength region of 4000 to 450 cm⁻¹. The procedure consisted of

dispersing the sample (drug alone or mixture of drug and excipient) in KBr and then 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 obtained. The energy at which any peak in an absorption spectrum appears corresponds to the frequency of a vibration of a part of a sample molecule [14].

Assay of aceclofenac

Quantitative determination of aceclofenac was performed by HPLC. A gradient HPLC (Shimadzu Corporation, Kyoto, Japan) with 2LC -10AT VP pumps, a variable wavelength programmable UV/VIS Detector SPD-10A VP, aCTO-10AS VP column oven and Inertsil ODS, C18, 250 x 4.6 mm, 5 μ column was used. The HPLC system was equipped with the software Class -VP series version 5.03. The mobile phase used was a mixture of buffer and acetonitrile in a ratio of 3:2 (The buffer was prepared by mixing 1.2 ml of glacial acetate with water and making it up to 1000 ml with more water while adjusting the pH to 5.2 with triethyl amine). The filtered mobile phase was pumped at a flow rate of 1.5 ml/min and the column temperature was maintained at 30 °C. The eluent was detected by a UV detector at 281 nm.

Preparation of matrix tablets

The tablets were prepared by a wet granulation technique. The composition of the tablet formulations are given in Table 1. Aceclofenac, HPMC, guar gum, ethyl cellulose, lactose/maize starch, sodium propyl parabenzoate and fumaric acid were screened through a 425 μ m sieve and mixed manually in a bowl for 5 min. The blend was granulated with the aid of PVP K-30 and water. The mass was sieved through a 500 μ m sieve and then dried in a hot air oven at 50 °C. Magnesium stearate, talc and colloidal silicon dioxide were then added to the dried granules, mixed for about 5 min in a polythene bag and compressed into tablets using a 12- station tablet compression

machine (CIP Machineries, Ahmadabad, India) equipped with a 11mm biconcave-faced punches. To mask the bitterness of the aceclofenac API, a selected batch (F7) was coated in a laboratory coater (Model GAC-250, Gansons Ltd, Mumbai, India) with HPMC 5 cps as coating polymer dissolved in isopropyl alcohol and methylene chloride; titanium dioxide and ponceau 4 R supra as colouring agents, PEG-6000 (polyethylene glycol-6000) and castor oil were used as plasticizers.

Physicochemical characterization of the tablets

Tablet weight variation was evaluated using 10 tablets with an electronic balance (Mettler Toledo, Mettler, Griefensee, Switzerland) while tablet hardness and friability were determined for 10 tablets using a Monsanto (standard type) tablet hardness tester and a Campbell electronic friabilator for 4 min at 25 rpm, respectively.

Evaluation of *in-vitro* release

In vitro dissolution test was carried out using USP Type 2 dissolution apparatus in 900 ml of simulated pH1.2 for the first 2 h and then in phosphate buffer (pH 7.5) from 3 to 12 h. The dissolution medium was kept in thermostatically controlled water bath, maintained at 37 \pm 0.5°C. The pre-weighed tablet was then introduced into the dissolution jar and the paddle was rotated at 100 rpm. At different time intervals, a 5ml sample was withdrawn and analyzed spectrophotometrically at 275 nm for the drug release. At each time of withdrawal, 5 ml of the fresh corresponding medium was added to the dissolution flask. The studies were also carried out were also repeated but substituting acetate buffer (pH 4.5) or phosphate buffer (pH 6.8) for phosphate buffer (pH 6.8). The dissolution data obtained were fitted to zero order, first order, Higuchi, Hixson-Crowell and Korsmeyer- Peppas models to determine the rate and mechanism

Table 1: Composition of sustained release tablet formulations

Ingredient	F1	F2	F3	F4	F5 (mg/tablet)	F6	F7	F8	F9	F10
Methocel K4M	20	--	---	---	---	--	37.5	---	---	---
Methocel K15M	---	20	---	---	---	---	---	15	---	---
Methocel K100M	---	---	15	---	---	---	---	---	10	---
Guar gum	---	---	---	15	---	---	---	---	---	---
Ethyl cellulose (20cps)	----	---	---	---	20	---	---	---	---	40
Methocel E15	----	---	---	---	---	50	---	---	----	--
Avicel PH102	9.5	9.5	9.5	9.5	9.5	--	--	---	---	--
Colloidal silicon dioxide (Aerosil)	4	4	4	4	4	4	4	4	4	-----
Maize starch	33	33	38	38	33	12.5	33	47.5	52.5	28
Lactose	30	30	30	30	30	30	30	30	30	28.5
Purified water	Q.S	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.

Each formulation also contains 200mg aceclofenac; 7.5 mg PVP K-30; 2 mg sodium propyl paraben; 10 mg fumaric acid; 4mg magnesium stearate; and 5 mg talc. Compressing weight of each formulation was 325 mg.

of aceclofenac release using eqs. 5,6,7,8 and 9, respectively.

$$Q = k_0t \dots\dots\dots (3)$$

where Q is the amount of drug release at time t and k₀ is the zero order release constant and t is time

$$\ln (100 - Q) = \ln Q_0 - k \dots\dots\dots (4)$$

where Q is the amount of drug release at time t and K₁ first order release constant

$$Q = k_{ht}^{1/2} \dots\dots\dots (5)$$

where Q is the amount of drug release at time t and k_h is the Higuchi square root of time release constant.

$$W_0^{1/3} - W^{1/3} = K^{1/D} \dots\dots\dots (6)$$

where W₀ is the initial weight ,W is the weight remaining and K^{1/D} is the cube root dissolution expression.

$$Q_t/Q = kt^n \dots\dots\dots (7)$$

where Q_t/Q is the fraction of drug released at time t, k is a constant comprising the structural and geometric characteristics of the tablet and n is the release exponent.

Difference factor (f1) and similarity factor (f2) were also calculated using Eqs 8 and 9 to compare dissolution profiles [15].

$$f1 = \{(\sum_{i=1}^n |R_t - T_t|) / (\sum_{i=1}^n R_t)\} \cdot 100 \dots\dots\dots (8)$$

$$f2 = 50 \cdot \log \{ (1 + (1/n) \sum_{i=1}^n (R_t - T_t)^2)^{0.5} \cdot 100 \} \dots\dots (9)$$

where n = no. of full points, R_t = the reference profile at the time point, t, and T_t = the test profile at the same point.

Stability studies

Stability studies were conducted on a strip pack of one of the aceclofenac test formulation (F7) in order to assess its stability after storage at 40 °C/75 %RH for 6 months. Samples were withdrawn at 1, 3 and 6 months and evaluated for appearance, friability, hardness, drug content and *in vitro* drug release.

Data analysis

Student's t-test was employed to analyze the results using Graph Pad InStat Software, version 1.13. Differences below the probability level of 0.05 were considered statistically significant.

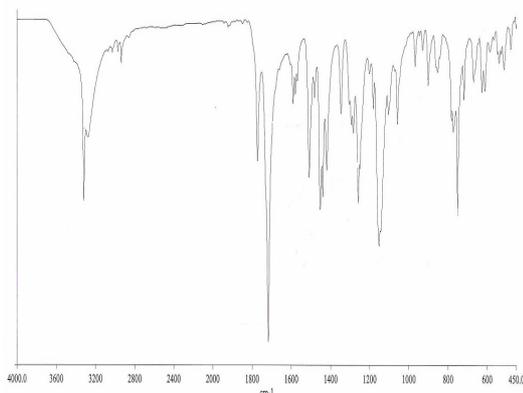


Figure 1: FTIR spectrum of pure aceclofenac

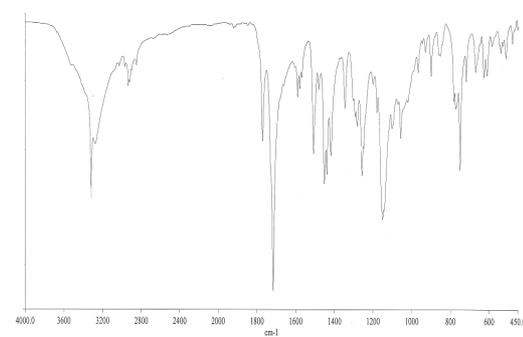


Figure 2: FTIR spectrum of aceclofenac tablets (F7)

RESULTS

Solubility of aceclofenac

The solubility of aceclofenac (mg/ml) was as follows: water, 0.077 ± 0.010 ; 0.1M HCl (pH1.2), 0.012 ± 0.010 ; pH 4.5 acetate buffer, 0.184 ± 0.010 ; pH 6.8 phosphate buffer, 0.784 ± 0.010 and pH 7.5 phosphate buffer, 0.796 ± 0.010 .

Micromeritic properties

Aceclofenac powder exhibited an angle of repose of $52.03 \pm 0.034^\circ$, Carr's index of 22.91 and Hausner's ratio of 1.297.

Drug-excipient compatibility

The pure aceclofenac powder, when kept for 2 weeks at 60°C in a well-closed container, turned lumpy and off-white from the initial white crystalline powder. On the other hand, no change in appearance and level of impurity (determined by HPLC) was noticed when it was stored at $40^\circ\text{C}/75\%\text{RH}$ for 2 weeks.

Figs 1 and 2 show the spectra of the pure drug and tablet formulation (F7), respectively. The spectrum for pure aceclofenac showed major peaks at the following wave numbers: 3319.39, 1771.71, 1717.12, 1589.69, 1508.14, 1452.50, 1418.56, 1344.80, 1256.64, 1150.53, 1056.35, 899.33, 749.96, 668.15 and 625.98 cm^{-1} . Formulation F7 spectrum also showed similar peaks at the above wave numbers.

The difference factor (f_1) and similarity factor (f_2), when the drug release data for F7 and the reference product were compared in various dissolution media were as follows: pH1.2, $f_1 = 4.04$, $f_2 = 99.29$; pH 4.5, $f_1 = 3.04$, $f_2 = 94.94$; pH 6.8, $f_1 = 3.68$, $f_2 = 82.06$; and pH 7.5, $f_1 = 2.44$, $f_2 = 82.89$. Drug release from F7 in the various pH media was similar to that of the reference tablet thus indicating that both formulations behaved in a similar manner in all the tested dissolution media. For the test product to be identical with reference product for drug release pattern, low f_1 values (usually < 15) and high f_2 values (> 50) are desirable.

Physicochemical properties of the formulated tablets

Tablet thickness was in the range 3.6 -3.9 mm; diameter, 11.0mm; and hardness, 5.0 - 8.0 kg/cm^2 . Tablet friability and coefficient of

Table 2 *In vitro* release profile of the prepared aceclofenac sustained release tablets in pH 1.2 and pH7.5 media

Formulation	Drug release (%)				
	2 h	4 h	6 h	8 h	12 h
F1	2.0±0.2 ns	49±0.20 s	70±0.12 s	88±0.12 s	96±0.15 ns
F2	1.8±0.3 ns	27±0.17 s	30±0.17 s	42±0.11 s	52±0.09 s
F3	0.7±0.2 s	18±0.15 s	26±0.21 s	38±0.13 s	42±0.04 s
F4	1.5±0.3 ns	22±0.12 s	32±0.22 s	47±0.12 s	58±0.06 s
F5	2.2±0.1 ns	42±0.11 s	72±0.14 s	86±0.11 s	97±0.01 ns
F6	2.8±0.2ns	76±0.17s	88±0.11s	99±0.13s	103±0.01s
F7	2.4±0.2ns	40±0.09s	59±0.12ns	70±0.12s	92±0.06s
F8	2.0±0.2ns	34±0.11s	50±0.12s	60±0.15s	66±0.04s
F9	2.5±0.3ns	26±0.12s	32±0.13s	46±0.14s	59±0.08s
F10	2.1±0.2ns	32±0.15s	69±0.12s	89±0.15s	95±0.09ns
Reference	2.2±0.3	39±0.11	59±0.11s	68±0.14	96±0.14

*All values are expressed as mean ± SD (n=20); s = significantly different; and ns = not significantly different, when compared to reference product (p > 0.05)

Table 3: Comparative *in vitro* release profile of a test aceclofenac sustained release formulation (F7) and reference product at pH1.2, 4.5 and 6.8

Product	Dissolution medium	Drug release (%)				
		2 h	4 h	6 h	8 h	12 h
F7	pH 4.5	9.0 ns	11.5 ns	22.2 ns	25.0 s	39.2 ns
Reference	pH 4.5	9.2	11.7	23.1	26.2	38.4
F7	pH6.8	20.0 ns	37.0 s	55.0 s	65.0 s	85.0 s
Reference	pH6.8	19.7	35.0	52.0	63.0	83.0

Note: Results are mean ± S.E.M. (n = 3); s = significantly different; ns = not -significantly different (p > 0.05), compared to the reference product.

weight variation of all the tablet batches were in the ranges 0.5 to 0.8 % and 1.4 to 3.5 %, respectively. Drug content was satisfactory and uniform (> 99 %) for all the batches of tablet formulations.

***In vitro* drug release**

The results of the *in vitro* drug release studies in simulated gastric and intestinal fluids are presented in Table 2. It is evident that, after 2 h in pH1.2 and from 3 to 12 h in pH 7.5 buffer, formulations F1, F5 and F6 followed Hixson-Crowell cube root release pattern, while formulations F2, F3, F4, F8 and F9 followed Korsmeyer-Peppas release pattern; formulation F7, Higuchi release pattern; and formulation F10, first order release pattern.

As shown in Table 3, drug release data for the reference tablets and test formulation F7 in different pH media were similar, indicating both exhibited similar characteristics.

Accelerated stability studies

The results obtained from accelerated stability studies indicate that F7 tablets (which were packed in aluminium strips) did not show any physical changes (appearance, friability and hardness) after 6 months. Drug content (mean ± SD, n=3) was 100.4 ± 0.22 % at 0 month; 100 ± 0.44 % at month 1 ; 99.8 ± 0.51 % at month 3; and 98.6 ± 0.20 % at month 6 . These data were not significantly different (p < 0.05). Furthermore, there was also no significant change (p > 0.05) in the

drug release profile of the formulation over

the period of the accelerated study.

DISCUSSION

Solubility study

The available literature on the solubility profile of aceclofenac indicates that the drug is freely soluble in acetone and practically insoluble in water [3]. In the present study, aceclofenac showed pH-dependent solubility; as pH was raised from 1.2 to 7.5, solubility improved considerably.

Micromeritic properties

Aceclofenac powder has very poor flow properties as shown by high values of Carr's index and Hausner's ratio. However, aceclofenac granules exhibited considerably better flow properties with angle of repose, Carr's index and Hausner's ratio of 30^o, 18.5 % and 1.22, respectively.

Compatibility and tablet properties

There was no interaction between aceclofenac and the excipients used, thus indicating that the choice of excipients for the matrix tablets was suitable. Furthermore, all the formulations showed satisfactory hardness, friability and drug content.

In vitro drug release

All the matrix formulations, except F6, did not disintegrate within the 2-hour dissolution test period in pH 1.2 buffer. The disintegration of F6 tablets is probably due to the fact its matrix consisted of low – viscosity HPMC which is more soluble than the higher viscosity grades of the polymer. F1, F7 and the reference tablets, though swollen, retained their shape throughout the 12-hour dissolution test period. However, all the formulations, including the reference, showed biphasic release profile with slow drug release from 0 to 2 h followed by faster but controlled release from the 2nd to 12th hour. Such biphasic release pattern may be

beneficial in providing therapeutically effective extended plasma concentration. The drug present on the surface of the matrix tablet did not produce a 'burst' release due probably to the low solubility of the drug at pH 1.2.

Over the dissolution period of 12 h, release rate decreased as the concentration of HPMC increased. HPMC matrix generates an additional osmotic gradient, thereby resulting in a faster rate of polymer swelling and a large increase in gel thickness. At higher polymer loading, the viscosity of the gel matrix increases which resulted in a decrease in the effective diffusion coefficient of the drug [16]. Wan et al have also reported that other factors that may contribute to differences in drug dissolution profile as a function of changes in total polymer concentration include differences in water penetration rate, water absorption capacity and polymer swelling [17]. Incorporation of either ethyl cellulose (F4 and F10) or guar gum (F4) also resulted in controlled drug release. This may be attributed to decreased penetration of the dissolution fluid in the presence of the hydrophobic polymers, leading to reduced diffusion of the drug from the matrix.

In order to more closely compare the release properties of formulation F7 and the reference product, further dissolution studies were carried out at pH 1.2 for 2 h and then sequentially in acetate buffer (pH 4.5) and phosphate buffer (pH 6.8) from 3 to 12h. The results indicated close similarity between the two products based on the low *f1* (< 15) and high *f2* values (> 50). Thus it can be said that the F7 tablets (containing 18.75 %w/w HPMC K4M) was similar to the commercial brand of aceclofenac (reference) with regard to drug release.

On subjecting the release data to Hixson-Crowell cube root models, F1, F5 and F6 showed linearity with regression coefficients

of between 0.9711 and 0.9915. The model characterizes drug release from a matrix tablet containing hydrophilic polymers and generally involves factors of diffusion. Drug release from swollen matrices is dependent on the diffusion and relaxation behavior of the dosage form. Diffusional release occurs by molecular diffusion and relaxation behavior of the dosage form. Diffusional release occurs by molecular movement down a chemical potential gradient while relaxational release is by a drug transport mechanism that is associated with stresses and state transitions involved in the swelling of the hydrophilic polymer. Thus, the swelling of the polymer would be expected to alter drug concentration gradient in the gel layer and hence diffusion path length and drug release [18]. This explains why a drug diffuses at a comparatively slower rate as the diffusion path length increases; this is governed by the square – root or Higuchi model. F7 showed high linearity ($r^2 = 0.9948$) and thus fitted well to the Higuchi model. Further elucidation of the release mechanisms involved indicate that F2, F3, F4, F8 and F9 fitted into the Korsmeyer-Peppas model, with r^2 values of 0.9718 to 0.9918. This indicates a coupling of diffusion and erosion mechanisms - the so-called anomalous diffusion. On the other hand, F10 fitted best to first order release kinetics with r^2 values of 0.9651.

CONCLUSION

We found that the incorporation of HPMC K4M (4000 cps) in matrix tablets of aceclofenac not only aided initial retardation in drug release but also enhanced the attainment of controlled drug release after a suitable lag time. The formulation method employed is simple and should be adaptable for commercial scale up.

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