International Scholars Journals

International Journal of Urology and Nephrology ISSN 2091-1254 Vol. 6 (3), pp. 001-008, March, 2018. Available online at www.internationalscholarsjournals.org © International Scholars Journals

Full Length Research paper

Preparation and evaluation of aceclofenac sustained release formulation and comparison of formulated and marketed product

Santanu Ghosh* and B. B. Barik

Utkal University, Department of Pharmaceutical Sciences, Bhubaneswar, Orissa.-751004, India.

Accepted 12 October, 2017

The objective of the study was to develop matrix tablets for oral controlled release of aceclofenac. Matrix tablets of aceclofenac, using various viscosity of hydrophilic polymer HPMC in two different proportions, hydrophobic polymer ethyl cellulose and Guar gum were prepared by wet granulation method and subjected to *in vitro* drug release studies. The drug release from all HPMC matrix tablets followed various release kinetics, formulation no -F7 followed higuchi kinetics. Furthermore, the results of the *in vitro* studies in pH 7.5 phosphate buffer medium showed that F7 tablets provided controlled release comparable with market sustained release formulation (Aeroff-SR tablets). F7 tablets showed no change in physical appearance, drug content, or in dissolution pattern after storage at 40°C with 75% RH for 6 months. Based on the results of the *in vitro* studies, it was concluded that the HPMC matrix tablets provided oral controlled release of aceclofenac.

Key words: Aceclofenac, sustained release, matrix tablets, hydroxypropyl methylcellulose.

INTRODUCTION

Aceclofenac is a newer derivative of the diclofenac group of non-steroidal anti inflammatory drug (NSAID) that exhi-bits analgesic and anti-inflammatory activities. It directly blocks the prostaglandin synthesis. It has less gastro-intestinal complications (Parfitt et al., 1999; British Phar-macopoeia, 2005). It is considered to be the first-line drug in the symptomatic treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. The aim of this work was to prepare and evaluate the aceclofenac once daily sustained release tablets and to compare them with marketed products. Wet granulation method was adopted for the preparation of tablets using different retardant polymer excipients namely; hydroxypropyl methyl cellulose K4M/K15M/K100M and 15CPS, Guar gum, ethyl cellulose, directly compressible microcrystalline cellulose (pH 102), colloidal silicon dioxide, lactose, fumaric acid, povidone (PVPK- 30), sodium propyl paraben, mag-nesium stearate and talcum. Film coating of batch no F7 was done by using different excipients namely hydroxypropyl methylcellulose 6cps, titanium dioxide, polyethylene glycol 6000, castor oil and ponceau 4R supra. Methylene chloride and isopropyl alcohol were used as non aqueous solvents. The effect of excipients on the drug release from prepared tablets was also studied. All the tablet quality control tests were studied. All formulations showed good mechanical properties and complied with the USP 32 pharmacopeia's standard requirements for uniformity of dosage units and friability. Formula No.7 containing HPMC K4M (18.75% drugs) exhibited almost similar drug release profile in pH 7.5 phosphate buffer medium as that of marketed tablet.

Non steroidal anti-inflammatory drugs (NSAIDs) are highly effective in the treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. But their long term use has led to gastrointestinal (GI) complications like ulceration, perforation and obstruction (Dhikav et al., 2003; Lain, 2003; Burke et al., 2005). Aceclofenac is a 2-[2-[2-[2,6-dichlorophenyl) amino]phenyl] acetyl]oxy] -acetic acid a highly potent member of a new class of compounds of non steroidal anti-inflammatory drug (NSAID) available in oral formulations for the management of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. Aceclofenac directly blocks PGE2 secretion at the site of inflammation by inhibiting IL-Beta and TNF in the inflammatory cells. Due to its short biological half

*Corresponding author. E-mail: santanu97@rediffmail.com Tel: 09282118780.

Table 1. Composition of sustained release tablet formulation.

Ingredients (mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Aceclofenac	200	200	200	200	200	200	200	200	200	200
Methocel K4M	20	--	---	---	---	---	37.5	---	---	---
Methocel K15M	---	20	---	---	---	---	---	15	---	---
Methocel K100M	---	---	15	---	---	---	---	---	10	---
Guar gum	---	---	---	15	---	---	---	---	---	---
Ethyl cellulose20cps	----	---	---	---	20	---	---	---	---	40
HPMC15cps	----	---	---	---	---	50	---	---	----	--
M.C.C.P 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
Povidone (PVPK-30)	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Sodium propyl Paraben	2	2	2	2	2	2	2	2	2	2
Purified Water	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
Fumaric Acid	10	10	10	10	10	10	10	10	10	10
Magnesium stearate	4	4	4	4	4	4	4	4	4	4
Talcum	5	5	5	5	5	5	5	5	5	5
Total	325	325	325	325	325	325	325	325	325	325

life (about 4 h) and dosing frequency (200 mg daily in 2 divided doses) of more than one per day, aceclofenac is an ideal candidate for sustained release formulation (Mutalik and Hiremath, 2000; Reddy et al., 2003; Kuksal et al., 2006)

Several matrixes based sustained release products of aceclofenac have been reported based on their use as either a hydrophilic or hydrophobic polymers (Khan and Zhu, 2001; Vueba et al., 2005; Rekhi and Jambekhar, 1995; Vueba et al., 2006; Sajeev and Saha, 2001; De Brabander et al., 2003; Lopes et al., 2006). The reported sustained release formulations of aceclofenac did not involve any attempt to prevent drug release in the upper GI tract. The matrix system of a polymer intended with drugs provides long duration of treatment and reduced adverse effects in patients. An attempt has been made here to achieve a better therapeutic profile through tablets with various viscosity of HPMC, Guar gum and ethyl cellulose. The *in vitro* release of the experimental formulation, which showed a release profile similar to that of the innovator's product, was compared with that of a commercially sustained release formulation. Furthermore, the purpose of the study was also to establish an *in vitro* release rate profile for various prepared aceclofenac matrix sustained release tablet and a commercial formulation.

MATERIALS AND METHODS

Materials

Aceclofenac was a kind gift from Mepro Pharmaceuticals Pvt. Ltd. Surendranagar, Gujarat and Aroff SR tablet (marketed product) was purchased from a local market in India. Each tablet was labeled to contain 200 mg of Aceclofenac BP. Table 1 lists the formulations evaluated for this study. The excipients were present in the tablets: hydroxypropyl methylcellulose-K4M (HPMC; Methocel K4M Premium, Colorcon Asia Pvt. Ltd., Singapore), hydroxypropyl methylcellulose-K15M (HPMC; Methocel K4M Premium, Colorcon Asia Pvt. Ltd., Singapore), hydroxypropyl methylcellulose- K100M (HPMC; Methocel K100M Premium, Colorcon Asia Pvt. Ltd., Singapore) Guar gum, ethyl cellulose 20cps, hydroxypropyl methylcellulose 15cps (Colorcon Asia Pvt. Ltd., Singapore), lactose (DMV International, U.S.A.), PVPK-30 sodium propyl paraben, fumaric acid microcrystalline cellulose (MCC; Avicel pH102, FMC biopolymer, U.S.A.), magnesium Stearate , talc, Isopropyl alcohol, methylene chloride, titanium dioxide,PEG-6000, castor oil and Ponceau 4 R supra. All other chemicals used were of analytical grade.

Assay method

The quantitative determination of aceclofenac was performed by HPLC. A gradient HPLC (Shimadzu HPLC Class VP series, 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 × 4.6 mm, 5µ column. The HPLC system was equipped with the software Class –VP series version 5.03(Shimadzu) . The mobile phase used was a mixture of buffer and acetonitrile in the ratio of 600: 400 (buffer was prepared by 1.2 ml of glacial acetate in 1000 ml of water and pH was adjusted to 5.2 with triethylamine). The filtered mobile phase components were pumped from the respective reservoirs at a flow rate of 1.5 ml/min. The column temperature was maintained at 30°C.The eluent was detected by UV detector at 281 nm and the data were acquired, stored and analyzed. A standard curve was constructed for aceclofenac in the range of 25 to 75 ppm. A good linear relationship was observed between the concentration of aceclofenac (r^2 = 1.00). The method was found to be precise and accurate. The standard curve, constructed as described, was used for estimating aceclofenac in HPMC K4M matrix tablets.

Table 2. Composition of sustained release tablet formulations.

Ingredients	Quantity/Tablet (mg)
H.P.M.C (6CPS)	7.5
Isopropyl Alcohol	0.13
Methylene Chloride	0.32
Titanium dioxide	1.65
PEG 6000	0.85
Castor Oil	2.50
Ponceau 4 R supra colour	0.9

Table 3. Physical properties of the prepared aceclofenac sustained release tablets.

Trial	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm2)	Friability (%)
F1	325 ± 2%	3.9 ± 0.2	5-6	0.24
F2	327 ± 2%	3.8 ± 0.2	5-7	0.26
F3	329 ± 2%	3.6 ± 0.2	4-7	0.12
F4	324 ± 2%	3.6 ± 0.2	5-8	0.12
F5	327 ± 2%	3.7 ± 0.2	3-5	0.43
F6	325 ± 2%	3.7 ± 0.2	5-8	0.19
F7	325 ± 2%	3.6 ± 0.2	5-7	0.18
F8	326 ± 2%	3.7 ± 0.2	5-8	0.35
F9	325 ± 2%	3.7 ± 0.2	4-8	0.16
F10	327 ± 2%	3.8 ± 0.2	4-7	0.23

Preparation of Matrix tablets

The tablets were prepared by wet granulation technique. The compositions of the tablet formulations are given in Table 1. Weighed amounts of aceclofenac, retardant (HPMC, Guar gum, ethylcellulose and diluents (lactose/maize starch), Preservative (sodium propyl paraben) and stabilizer (fumaric acid) were taken into a bowl by passing through a 40 mesh screen and mixed manually for 5 min. Then the blend was granulated with PVPK-30 using water as the granulating agent. The mass was dried in a hot air oven at 50°C and sieved through a 30 mesh screen. Magnesium stearate, talc and colloidal silicon dioxide were then added to the dried, sieved granules and mixed for about 5 min in a poly-bag. The produced mixture was compressed into tablets using a 12 station tablet compression machine, (CIP Machineries, Ahmadabad, India) equipped with an 11 mm biconcave-faced punches. The selected batch (F7) was coated using the coating formula as given in Table 2 and using a laboratory coater under controlled condition. The efficiency of mixing was verified by the determination of drug content.

Coating

F7 batch was coated using a laboratory coater (Model GAC-250, Gansons ltd, Mumbai, India) under controlled condition.

Physiochemical characterization of tablets

The weight variation was evaluated on 10 tablets using an electronic balance (Mettler Toledo, Mettler, Griefensee, Switzerland). Tablet hardness was determined for 10 tablets using a Monsanto (Standard type) tablet hardness tester in a Campbell Electronic Friabilator for 4 min at 25 rpm. The physicochemical properties of of designed tablets are shown in Table 3.

***In-vitro* release rate studies**

The *in vitro* dissolution study was carried out using USP Type 2 dissolution apparatus. The study was carried out in 900 ml of phosphate buffer pH 7.5 from 2 to 12 h. The dissolution medium was kept in a 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 the base of the beaker. The pre-weighed tablet was then introduced into the dissolution jar and the paddle was rotated at 100 rpm. At different time intervals, 5 ml sample was withdrawn and analyzed spectrophotometrically at 275 nm for drug release. At each time of withdrawal, 5 ml of fresh corresponding medium was replaced into the dissolution flask.

Determination of release kinetics

The dissolution data obtained was fitted to Zero order, first order, Higuchi, Hixson Crowell and Korsmeyer Peppas equations to understand the rate and mechanism of aceclofenac release from the prepared formulations and commercial product. The release kinetics parameters for formulations studied in a pH 7.5 phosphate buffer are listed in Table 6. The correlation coefficients were calculated and used to find the fitness of the data.

Stability studies

Stability studies were conducted on aceclofenac matrix tablet

Table 4. Assay and *in vitro* release profile of the prepared aceclofenac sustained release tablets

Trial	Assay (%)	% of Drug released (After 2 h)	% of Drug Released (After 4 h)	%of Drug released (After 6 h)	% of Drug released (After 8 h)	% of Drug released (After 12 h)
F1	104.5 ± 0.35	32	49	70	88	96
F2	99.08 ± 0.39	16	27	30	42	52
F3	99.75 ± 0.42	8	18	26	38	42
F4	99.33 ± 0.50	12	22	32	47	58
F5	99.46 ± 0.49	22	42	72	86	97
F6	100.05 ± 0.34	52	76	88	99	103
F7	100.75 ± 0.28	22	40	59	70	92
F8	99.89 ± 0.44	20	34	50	60	66
F9	101.11 ± 0.25	12	26	32	46	59
F10	102.33 ± 0.35	20	32	69	89	95

Results are the mean ± S.E.M. of three independent experiments

containing 11.4% of HPMCK4M (F7) to assess their stability with respect to their physical appearance, drug content and drug release characteristics after storing them at 40° C/ 75% RH for 6 months. Samples were withdrawn at 0, 90 and 180 days for evaluation of appearance, drug content and in vitro drug release.

Data analysis

The differences in release data for the different formulations were compared using Microsoft Office 2007, Excel package.

RESULTS AND DISCUSSION

The physical properties of the finished good are shown in Table 3. The following parameters; weight uniformity, drug content, thickness, hardness and friability were calculated. Tablets prepared by wet granulation were uniform in weight and thickness and complied with the USP 32 requirements. From the obtained data in Table 4, the percentage of drug contents in prepared tablets was found to be within the range of 99.08 to 104.5%. The values of the disintegration time of the prepared tablets were within the allowable range of the USP 32 for uncoated tablets. The friability of the tablets was higher than marketed products. Generally, the values for friability ranged from 0.12 to 0.43%, which was an acceptable value according to the USP 32 requirements. The prepared tablets showed hardness levels in the range of 3.0 to 8.0 kg/sq.cm.

Aceclofenac is highly soluble (199mg/ 250 ml) in an alkaline medium (pH 6.5–7.5) and is reported. Therefore, dissolution studies were carried out in a phosphate buffer pH (7.5) for 0 -12 h. This medium was considered as most suitable as the drug was freely soluble at this pH and it also mimics the alkaline environment of the small intestine. The selection of wet granulation technique for matrix tablet preparation was based on a previously reported study which suggested wet granulation in time and energy consumption when compared to direct compression. In our study, the use of water as a granulating vehicle was based on the partial solubility of PVPK-30 in this granulating vehicle which resulted in providing the necessary adhesion between the various matrix components and precluded the use of a separate binder.

The drug release profile from the developed formulations manufactured in this study as compared to the marketed product is shown in Figure 2. It was found that the *in vitro* dissolution profile of aceclofenac from tablets containing HPMC K4M (18.75%) formula no. F7 is almost similar with that of marketed product (Aroff SR) . This is further confirmed by the values of the Higuchi release rate constants (k) given in Tables 7 and 8, as there is no marked difference between these values. The results of the study indicated that the release of aceclofenac from the marketed as well as F7 followed Higuchi's order of release kinetics via anomalous (non-Fickian) diffusion. The *in vitro* drug release studies of these tablets showed that the cumulative drug release was in the following order F6>F5>F1>F10>F7>F8>- F9>F4>F2>F3.This might be due to the nature, viscosity and concentration of the various polymers used, that is different viscosity containing HPMC, Guar gum and ethyl cellulose and has a powerful retardant property resulting in matrix formation which is required for sustained release formulation.

The similarity in the release profiles of marketed tablet and formulation F7 was compared by making use of the "Model independent approach". A simple model independent approach uses a difference factor (*f1*) and a similarity factor (*f2*) to compare dissolution profiles (www.fda- .gov./cder/guidance). For F7 formulation, when compared with marketed tablet, *f1* and *f2* values were found to be 2.44 and 82.89 respectively, indicating a good equivalence between these two formulations (Table 5 and Figure 2)

The release profiles of the matrix tablets of aceclofenac containing varying proportions of HPMC K4M (10 and 18.75% w/w of drug) that is, F1 and F7 respectively are shown in Figure 1. The $t_{50\%}$ values varied between 4.01 to 5.10 h for these formulations indicating that the initial

Table 5. Similarity (f_2) and dissimilarity (f_1) for comparative dissolution study in pH 7.5 phosphate buffer (AROFF SR 200MG sustained release tablet and batch no. F7 formulation).

Time point (h)	Rt-Tt	$(Rt-Tt)^2$	|Rt-Tt|
0.00	0.00	0.00	0.00
2	-1.00	1.00	1.00
4	1.00	1.00	1.00
6	0.00	0.00	0.00
8	2.00	4.00	2.00
10	1.00	1.00	1.00
12	-4.00	16.00	4.00
SUM		23.00	9.00
Number of Time points or intervals [Excluding zero]			6
Difference Factor – f_1 [Acceptance Criteria: 0 - 50]			2.44
Similarity Factor - f_2 [Acceptance Criteria: 50 - 100]			82.89

Rt = Average percentage of drug release of reference sample at particular time point. Tt = Average percentage of drug release of test sample at particular time point.

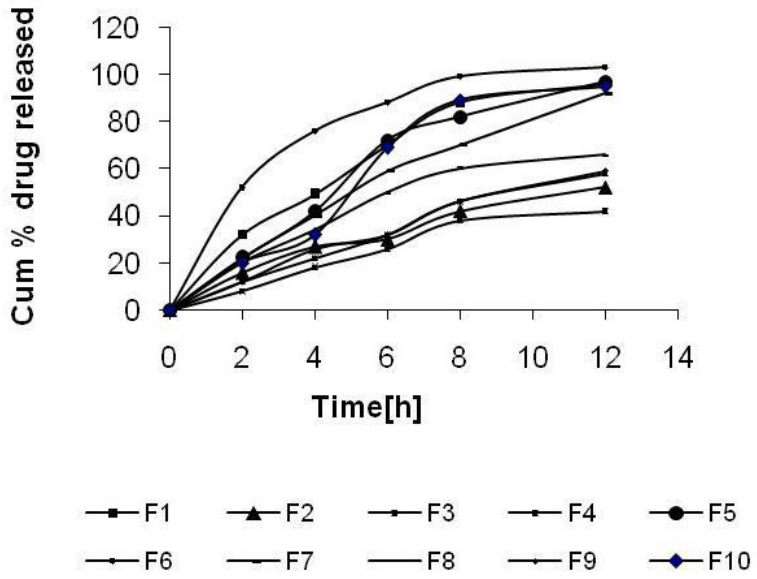

Figure 1. Release profile of aceclofenac from the various formulations.

plays an important role for drug release rate of drugs from the matrix formulation and most probably this is due to reduced water penetration through capillary. The same result has been seen in matrix formulation F3 and F9 containing HPMCK100M.

Higher concentration with low viscosity HPMC 15cps containing formulation F6 does not sustain the release rate of aceclofenac tablet. That indicated that HPMC6cps has no longer sustaining the tablet due to its low viscosity.

The release pattern of aceclofenac from the matrices made with 7.5% w/w of hydrophobic polymer Guar gum as shown in Figure 1 indicates that the hard matrix had been formed and decreased the release rate.

However, on subsequent increase from 7.5 to 20% w/w of drug, there was no appreciable decrease in the release rate and extension in duration of release. This indicated that a tight non-porous matrix had been formed in the former case and addition of more polymer could not modify the matrix character any further.

The drug release from F1, F5 and F6 formulation followed Hixson –Crowell's cube root model; F2, F3, F4, F8 and F9 formulation, followed Korsmeyer-Peppas model, F7 formulation followed Higuchi model and F10 formulation followed first order release kinetics which is indicated by the correlation coefficients (r^2) value.

Table 6. *In vitro* profile of aceclofenac various trial formulations based on t_{50} and t_{90}.

Formulation code	t_{50}^{a}	t_{90}^{b}
F1	4.01 hrs	11.25 hrs
F2	11.54 hrs	----
F3	14.29 hrs	----
F4	9.62 hrs	----
F5	4.76 hrs	9.78 hrs
F6	1.925 hrs	6.14 hrs
F7	5.10 hrs	11.74 hrs
F8	6.00 hrs	----
F9	9.10 hrs	----
F10	4.35 hrs	9.78 hrs

t_{50}^{a} = time for 50% drug release (in h); t_{90}^{b}= time for 90% drug release (in h)

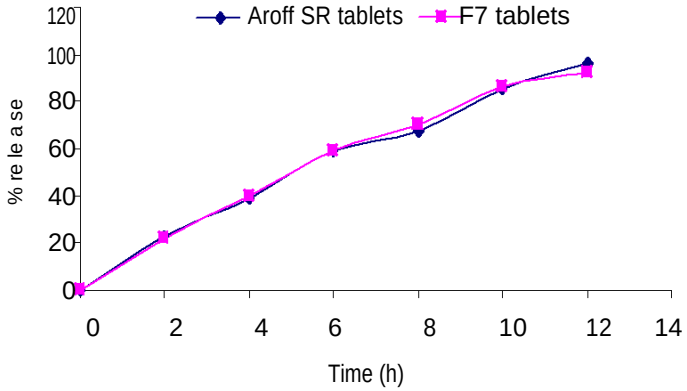

Figure 2. Dissolution comparison graph between AROFF SR tablet and Batch No. F7.

Table 7. Release kinetic parameters with correlation coefficient for designed formulations.

Kinetic model	F1	F2	F3	F4	F5
First order release	0.9603	0.9829	0.9466	0.9863	0.9832
Zero order release	0.9342	0.9588	0.9570	0.9841	0.9403
Higuchi	0.9850	0.9798	0.9684	0.9838	0.9602
Hixson- Crowell cube root	0.9915	0.9795	0.9655	0.9908	0.9901
Korsmeyer-Peppas	0.9867	0.9832	0.9735	0.9919	0.9645
Highest correlation or best fit	Hixson-Crowell cube root	Korsmeyer-Peppas model	Korsmeyer-Peppas model	Korsmeyer-Peppas model	Hixson-Crowell cube root

Film coating was applied over the tablet to mask the bitter taste of aceclofenac. No significant difference was observed in the release profile of coated and uncoated tablets at pH 7.5 phosphate buffer medium. Also, since 90% drug release was attained in about 11-12 h, it can be expected that drug release would be com-plete within the residence time of the dosage form in the GI tract. The reason was attributed to the preferential solubility of the drug above pH 6.0 and HPMC 6cps is likely to be soluble from pH 1.2 to 6.8. This is due to the formation of a

Table 8. Release kinetic parameters with correlation coefficient for designed formulations.

Kinetic Model	F6	F7	F8	F9	F10
First order release model	0.7522	0.9660	0.9541	0.9860	0.9651
Zero order release model	0.7904	0.9787	0.9234	0.9833	0.9291
Higuchi model	0.9301	0.9948	0.9637	0.9860	0.9269
Hixson-Crowell cube root	0.9711	0.9903	0.9562	0.9865	0.9581
Korsmeyer-Peppas model	0.9533	0.9941	0.9718	0.9870	0.9423
Highest correlation or best fit	Hixson-Crowell cube root	Higuchi model	Korsmeyer-Peppas model	Korsmeyer-Peppas model	First order release model

Table 9. Stability studies on formulated F7 formulation

Parameter	Initial tablets	Strip pack at 400C with 75% RH	
		90days	180days
Drug content (%)	99.55 ± 0.96	98.90 ± 0.97	98.5 ± 0.99
t^{50} (h)	5.10 h	5.12 h	5.10 h
t^{90} (h)	11.74 h	11.80 h	11.78 h

Results are the mean ± S.E.M. of three independent experiments. Other values represent an average of two experiments.

porous and eroded matrix upon dissolution of HPMC 6cps at a higher pH.

No significant difference was observed in the release profile of different batches of each matrix formulation, indicating that the manufacturing process employed was reliable and reproducible. Also, the release kinetics remained unaltered for up to one year of storage and there were no changes in the tablet's characteristics, suggesting that aceclofenac was stable in HPMC K4M matrices. The data for stability studies carried out for F7 formulation at 40°C with 75% RH for 180d revealed no considerable differences in drug content and dissolution rate (Table 9).

In conclusion, matrix embedding technique using HPMCK4M as the retardant has successfully extended the release of aceclofenac from its tablet formulations. In the present case, we found that the incorporation of HPMC K4M in the matrix not only helped to provide good initial retardation in the release but also helps to enhance the overall release rate of the drug after a suitable lag time. The manufacturing method employed is simple and easily adaptable in the conventional tablet.

Conclusions

In the present study, the formulation and production technology of aceclofenac 200 mg hydrophilic matrix tablets have been developed, which produced SR formulation with good physical characteristics, predictable and reproducible drug release profiles similar to the marketed reference product. This study demonstrated that Methocel K4 MCR provides a reliable sustained release matrix formulation recommendations for high dose and BCS II class drugs such as aceclofenac.

ACKNOWLEDGEMENTS

The authors are thankful to Mepro Pharmaceuticals and Medo Pharm Pvt. Ltd., for providing a reference standard and the raw materials of aceclofenac.

REFERENCES

British Pharmacopoeia (2005). The Stationary office, MHRA, British Pharmacopoeial Commission office, London, p. 1.

Burke A, Smyth EM, FitzGerald GA (2005). Analgesics-Antipyretics and Antiinflammatory agents: Pharmacotherapy of Gout. In: Brunton LL, Lazo KS, Parker KL, editors. The Pharmacological Basis of Therapeutics, 11th ed. New York: McGraw-Hill Professional. p. 671.

De Brabander C, Vervaet C, Remon JP (2003). Development and evaluation of sustained release mini-matrices prepared via hot melt extrusion. J. Control Release 89: 235-247.

Dhikav V,SindhuS, Anand KS (2003). Newernon-steroidal anti-inflammatory drugs; A review of their therapeutic potential and adverse drug reactions. J. Indian Acad. Clin. Med. 3: 332-338

Khan GM, Meidan VK (2001). Drug release kinetics from tablet matrices based upon ethyl cellulose ether-derivatives: A comparison between different formulations. Drug Dev. Ind. Pharm. 1: 355-360.

Khan GM, Zhu JB (2007). Controlled release coprecipitates of Ibuprofen and Carbopol 934- Preparation, characterization and *In vitro* release. Sciences 33: 627-639.

Kuksal A, Tiwary AK, Jain NK, Jain S (2006). Formulation and *In Vitro*, *In Vivo* Evaluation of Extended release Matrix Tablet of Zidovudine: Influence of Combination of Hydrophilic and Hydrophobic Matrix Formers. AAPS. Pharm. Sci. Technol. 1: 1-9.

Lain L (2003). Serious lower gastrointestinal clinical events with non-

selective NSAIDs and COXIB use. Gastroenterol. 124: 288-292.
Lopes C, Manuel S, Lobo J, Costa P, Pinto J (2006). Directly compressed mini matrix tablets containing ibuprofen- preparation and evaluation of sustained release. Drug Dev. Ind. Pharm. 32: 95-106.
Mutalik S, Hiremath D (2000). Formulation and evaluation of chitosan matrix tablets of Nifedipine. The Eastern. Pharm. 10: 109-111.
Parfitt K (1999). Analgesics Anti-inflammatory and antipyretics, In Reynolds, JEF (ed.) Martindale. p. 56
Reddy R, Mutalik S, Reddy MS (2003).Once daily sustained release matrix tablets of nicorandil: Formulation and *in vitro* evaluation. AAPS. Pharm. Sci. Technol61 (Supp4): 1-9.
Rekhi GS, Jambekhar SS (1995). Ethylcellulose: A polymer review. Drug Dev. Ind. Pharm. 21: 61-77.
Sajeev C, Saha RN (2001). Formulation and comparative evaluation of controlled release diclofenac tablets prepared by matrix- embedding technique, membrane barrier technique and combination of the two. Drug Dev. Res. 53: 1-8.
Vueba ML, Batista de Carvalho LA, Veiga F, Sousa JJ (2006). Pina ME Influence of cellulose ether mixtures on ibuprofen release: MC25, HPC and HPMC K100M. Pharm. Dev. Technol. 11: 213-228.
Vueba ML, Batista de Carvalho LA, Veiga F, Sousa JJ, Pina ME (2005). Role of cellulose etherpolymers on ibuprofen release from matrix tablets. Drug Dev. Ind. Pharm. 31: 65365.