International Journal for Pharmaceutical Research Scholars (IJPRS)
ISSN No: 2277-7873
RESEARCH ARTICLE **V-1, I-3, 2012**

Formulation and Evaluation of Aceclofenac Sustained Release Tablets Using Various Grades of HPMC Polymer

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Manuscript No: IJPRS/V1/I3/00139, Received On: 28/07/2012, Accepted On: 06/08/2012

ABSTRACT

The present work focuses on preparation of Aceclofenac sustained release tablets in order to reduce the dosing frequency, there by improve patient compliance and to produce uniform drug release for a prolonged period of time compared to the conventional Aceclofenac tablets. Six formulations were prepared by wet granulation method using HPMC K100M and HPMC K15M as release retardant polymers in the concentration of 5%, 6% and 7%. The prepared granules were evaluated for various pre-compression parameters like angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio. The FT-IR studies concluded that there was no drug-polymer interaction. The post compression parameters like appearance, thickness, hardness, weight variation, friability, drug content, *in-vitro* drug release and order of kinetics were studied. The drug release of best formulation F_6 was found to be 62.1±0.378 % at the end of 10 hours. The overall results revealed that as the concentration of polymer was increased, the drug release decreased. Plots of log cumulative Percentage drug remaining Vs Time were found to be linear with all the formulations indicating that the drug release from these formulations was according to the first order kinetics. Stability studies of Formulation F_6 revealed that the drug was stable even after stored at 25±2^{o}C/60±5%RH and 40±2^{o}C/75±5%RH for 45 days. From all the above observations, the formulation F_6 was found to be a better one which satisfied all the criteria for sustained release tablets.

KEYWORDS

Aceclofenac, Compressibility index, Hydroxypropyl methylcellulose, Kinetics, Stability, Sustained release.

INTRODUCTION

Aceclofenac is a new generation Non-Steroidal Anti-Inflammatory drug used in the symptomatic treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. The biological half life of aceclofenac is 3-4 hours and hence dosing frequency more than one per day is required to maintain its therapeutic effect throughout the day.

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Administration of conventional aceclofenac tablets 2-3 times a day will produce side effects such as nausea, vomiting, diarrhoea, dizziness, rash, gastric bleeding and gastric ulceration. As these conditions are chronic, sustained release tablets of aceclofenac is preferred over conventional dosage forms which reduces the frequency of dosing, side effects and improve the patient compliance. Hence aceclofenac is considered as an ideal candidate for formulation of sustained release [1]. In this study it was aimed to formulate sustained release tablets of Aceclofenac using various grades of

Hydroxypropyl methylcellulose such as HPMC K100M and HPMC K15M in three different drug polymer ratio by wet granulation method.

MATERIAL AND METHOD

MATERIALS

Aceclofenac, Hydroxypropyl methylcellulose K100M, Hydroxypropyl methylcellulose K15M were obtained from Sun Pharmaceuticals, Chennai, India. Microcrystalline Cellulose and Polyvinyl Pyrrolidone were obtained from Yarrow Chem Products, Mumbai, India. Talc and Magnesium stearate were procured from Loba Chemie Pvt. Ltd, Mumbai and Isopropyl alcohol was procured from S.D. Fine chem. Pvt. Ltd, Mumbai, India. All other reagents used were of analytical grade.

METHODS

FORMULATION OF ACECLOFENAC SR TABLETS

Aceclofenac SR tablets weighing 400 mg were prepared using HPMC K100M and HPMC K15M as release retardant polymers by wet granulation method. All the powders were passed through #60 mesh. Required quantity of drug, polymer and diluent were mixed thoroughly and a sufficient quantity of binding agent was added slowly. After enough cohesiveness was obtained, the mass was sieved through 16/22 mesh. The granules were dried at 50ºC for 2 hours and sized by passing through the sieve and mixed with fines (15%), lubricated with talc and magnesium stearate [2]. The tablets were compressed using Mini Press tablet compression machine (punch size 16/32 inch) to prepare tablets each weighing 400 mg. The composition of tablet formulations were presented in Table: 1.

DRUG- EXCIPIENT INTERACTION STUDIES [3]

To determine any interaction between drug and polymer, Fourier Transform Infra red (FT-IR) study was carried out. FT-IR analysis of pure drug, individual polymer and combination of drug and polymer in highest concentration were taken for the study. Samples were compressed with potassium chloride and transformed into disk. Disk was applied to the centre of the sample holding device and scanned between 4000-400 cm^{-1} in a SHIMADZU FT-IR (IR Affinity -1) spectrophotometer.

PRE-COMPRESSION PARAMETERS [4, 5, 6]

The prepared granules were evaluated for pre-compression parameters such as Angle of repose, Bulk density, Tapped density, Compressibility index and Hausner's ratio. The angle of repose was determined by fixed cone method. The bulk density and tapped density were determined by bulk density apparatus. The compressibility index was determined by Carr's compressibility index and the Hausner's ratio was calculated by using the formula:

Hausner's Ratio = Tapped density/ Bulk density

Carr's index (%) = [(TD-BD) / TD] ×100

TD = Tapped density, BD = bulk density

POST COMPRESSION PARAMETERS

The compressed tablets were evaluated for post compression parameters such as Appearance, Thickness, Hardness and Weight variation test. The tablets should be free from cracks, depressions, pinholes etc. The tablets were examined externally under a biconvex lens for surface cracks, depressions and pinholes. Thickness and diameter of tablets were determined using Vernier caliber. Hardness was measured using Monsanto tablet hardness tester[7]. The Tablets were subjected to weight variation test. Twenty tablets were selected at random and average weight was determined. The individual tablets were weighed and compared with average weight. Not more than two of the individual weights deviate from the average weight of tablets by more than 5% and none should deviate more than 2 times the percentage limit. The friability of tablets was determined using Roche Friabilator [8]. The drug content was estimated by measuring the absorbance of the 10µg/ml solution at 275 nm using UV visible double beam spectrophotometer [9].

Table 1: Formulation of Aceclofenac Sustained Release Tablets

INGREDIENTS	FORMULATION CODE					
	F_1 (mg)	F_2 (mg)	F_3 (mg)	F_4 (mg)	F_5 (mg)	F_6 (mg)
Aceclofenac	200	200	200	200	200	200
HPMC K100M	20	24	28	-	-	-
HPMC K15M	-	-	-	20	24	28
MCC	164	160	156	164	160	156
PVP	8	8	8	8	8	8
Isopropyl Alcohol	q.s	q.s	q.s	q.s	q.s	q.s
Talc	4	4	4	4	4	4
Mg. Stearate	4	4	4	4	4	4
Weight of each tablet is 400 mg						

IN VITRO DRUG RELEASE [10, 11]

The *in vitro* dissolution studies were carried out using USP Type-II dissolution test apparatus (paddle method). The dissolution test was carried out for a total period of 10 hours using phosphate buffer pH 6.8 (900 ml) as dissolution medium at a temperature of 37± 0.5ºC. One tablet was placed in each dissolution jar and the dissolution apparatus was operated at 50 RPM. At every 1 hour interval, 10 ml of samples were withdrawn and are replaced by same quantity of fresh dissolution medium. The samples were analysed after suitable dilution by UV Double beam spectrophotometer at 275 nm for concentration of drug in each sample.

DRUG RELEASE KINETICS

To determine the release kinetics, data obtained from *in vitro* drug release studies were tested with the following mathematical model such as Zero order equation, first order equation, Higuchi square root law and Korsmeyer- Peppas equation [12, 13].

STABILITY STUDIES

The best formulation was selected for the stability study and the formulation was divided into 2 sample sets and were stored at 25±2ºC/60±5% RH and 40±2ºC/75±5% RH for a period of 45 days [14, 15, 16]. The tablets were evaluated for appearance, hardness, drug content and *in vitro* drug release at every 15 days interval.

RESULTS AND DISCUSSION

When the characteristic peaks of aceclofenac were compared with the combination of aceclofenac and polymers, it was found that the peaks were also present in the drug-polymer combination with negligible differences. Thus FT-IR studies revealed that there was no shift in peaks of the combination containing aceclofenac, hydroxy propyl methyl cellulose when compared to pure aceclofenac, indicating that there was no interaction between aceclofenac and polymer used.

PRE-COMPRESSION PARAMETERS

The formulations were evaluated for pre-compression parameters and the values were found to be within the prescribed limits for all formulations. All the formulations showed good flowability as expressed in terms of pre-compression parameters. The results are presented in Table: 2.

POST COMPRESSION PARAMETERS

The results showed that all the tablets possessed uniform thickness and diameter.

Table 2: Pre-Compression Parameters

For m. Code	Bulk density (gm/ml)	Tapped density (gm/ml)	Angle of repose (θ) -	Carr 's Inde x (%)	Hausne r's ratio
F_1	0.3720±0.02	0.4160±0.04	28.50±2.3	11.05	1.12
F_2	0.3847±0.04	0.4272±0.08	27.89±1.8	8.89	1.09
F_3	0.3540±0.06	0.4061±0.01	26.42±2.1	11.57	1.13
F_4	0.3626±0.04	0.4128±0.02	23.42±1.9	12.13	1.13
F_5	0.3764±0.06	0.4324±0.04	22.64±2.3	8.60	1.14
F_6	0.3926±0.03	0.4308±0.01	28.32±1.6	8.83	1.09

*All the values are expressed as mean ± standard deviation; n= 3.

The hardness test revealed that the prepared tablets possessed good mechanical strength. All the tablets passed the weight variation test, as the percentage weight variation was within Pharmacopoeial limits of ±5% of the average weight.

The friability of the tablets was found in the range of 0.11 ± 0.01 to 0.18 ± 0.01 %. Hence all the tablets passed the friability test. The percentage drug content of all formulations was found to be in the range of 98.92 ± 0.02 to 99.52 ± 0.01 %. The percentage drug content results proved that the drug is uniformly distributed in all formulations. The results are presented in Table: 3.

IN VITRO DRUG RELEASE

The drug release of formulations F_1, F_2 and F_3 was found to be 90.0±0.528%, 84.6±0.288% and 63.0±0.574% respectively at the end of 10 hours. In the formulations F_1, F_2 and F_3, HPMC K100M was used as a polymer in the concentration of 5%, 6%, and 7% respectively. The drug release was rapid in formulation $F_1$and a slow drug release was observed in formulation F_3compared to formulations $F_1$and F_2.

The drug release of formulations F_4, F_5 and F_6 was found to be 83.7±0.487%, 80.1±0.367% and 62.1±0.378% respectively at the end of 10 hours. In the formulations F_4, F_5 and F_6, HPMC K15M was used as a polymer in the concentration of 5%, 6%, and 7% respectively. The drug release from the formulations were sustained in the following manner $F_4 > F_5 > F_6$. The overall results revealed that as the concentration of polymer was increased, the drug release was sustained. The results of *in vitro* release profiles are presented in Figure: 1.

Table: 3 - Evaluation of Aceclofenac SR Tablets

PARAMETERS	F_1	F_2	F_3	F_4	F_5	F_6
Thickness (mm)	2.58±0.02	2.62±0.04	2.53±0.01	2.54±0.09	2.57±0.06	2.52±0.06
Diameter (mm)	12.8±0.2	12.6±0.3	12.5±0.2	12.7±0.3	12.7±0.2	12.5±0.2
Hardness (kg/cm^2)	5.5±0.15	5.0±0.45	5.5±0.24	5.5±0.42	5.5±0.38	6.0±0.62
Weight Variation (mg)	396±0.98	402±1.50	400±0.90	401±1.15	400±0.96	402±0.20
Friability (%)	0.18 ±0.01	0.17±0.01	0.13±0.01	0.11±0.01	0.14±0.02	0.13±0.01
Drug Content (%)	98.92±0.02	99.12±0.02	99.20±0.01	98.98±0.01	99.42±0.01	99.52±0.01

*All the values are expressed as mean ± standard deviation; n=3.

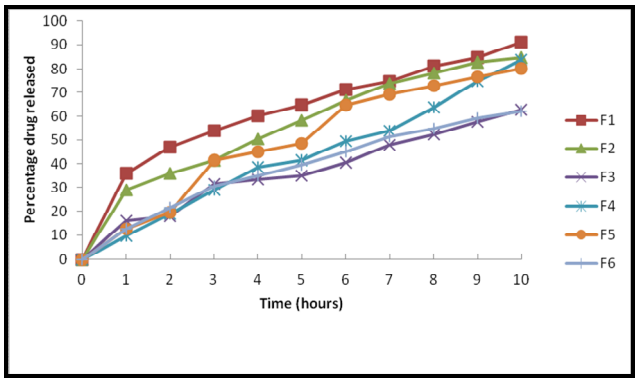

Figure 1: Dissolution Profiles of Aceclofenac SR Tablets

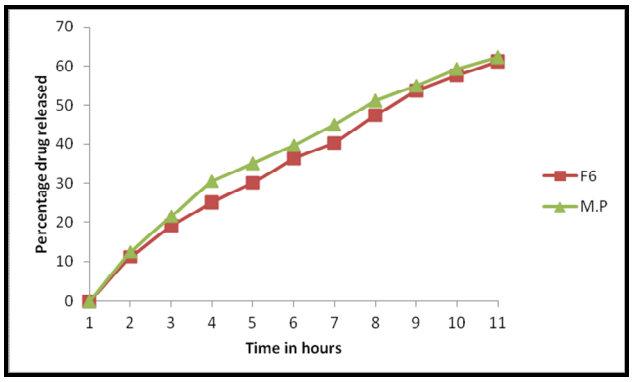

Figure 2: Comparative Dissolution Profiles of Aceclofenac SR Marketed Product and Formulation F_6

The drug release from the marketed Aceclofenac SR tablets was found to be 61.26±0.456% at the end of 10 hours. The release profiles of all the formulations were compared with the marketed Aceclofenac SR tablet. The formulation F_6 exhibited a similar release profile compared to the marketed Aceclofenac SR tablet. The percentage drug release was found to be increased by 1.38%, 3.36% and 1.02% at 1st hour, 5th hour and 10th hour respectively in formulation F_6 compared to the marketed product. The comparative dissolution profiles of aceclofenac SR marketed product and formulation F_6 were presented graphically in Figure: 2.

KINETIC ANALYSIS

The drug release data were subjected for mathematical treatment to check the release order kinetics. The kinetic data of dissolution studies of all formulations were presented in Table 4.

Plots of log cumulative percentage drug remaining Vs time were found to be linear with all the formulations indicating that the drug release from these formulations was according to the first order kinetics (Figure: 3 and 4).To confirm the drug release mechanism, the data was fitted into Korsmeyer-Peppas equation. All the formulations showed good linearity with slope (n) values ranging from 0.4353 to 0.8446. The formulation F1 showed behaviour of Fickian diffusion and remaining all formulations showed Non-Fickian diffusion. Non-Fickian refers to the combination of both erosion and diffusion controlled drug release.

Plots of log cumulative percentage drug remaining Vs time were found to be linear with all the formulations indicating that the drug release from these formulations was according to the first order kinetics (Figure: 3 and 4).

Table: 4 Kinetic Data of Release Profiles of Aceclofenac SR Tablets

Formulation code	Zero order	First order	Higuchi	Korsmeyer - Peppas	
	R	R	R	r	n
F_1	0.8373	0.8975	0.9973	0.9973	0.4353
F_2	0.9304	0.9805	0.9926	0.9906	0.5487
F_3	0.9963	0.9863	0.9756	0.9839	0.6317
F_4	0.9970	0.9970	0.9335	0.9975	0.8446
F_5	0.9658	0.9858	0.9739	0.9879	0.8003
F_6	0.9676	0.9977	0.9822	0.9981	0.7109

To confirm the drug release mechanism, the data was fitted into Korsmeyer-Peppas equation. All the formulations showed good linearity with slope (n) values ranging from 0.4353 to 0.8446. The formulation F_1 showed behaviour of Fickian diffusion and remaining all formulations showed Non-Fickian diffusion. Non-Fickian refers to the combination of both erosion and diffusion controlled drug release.

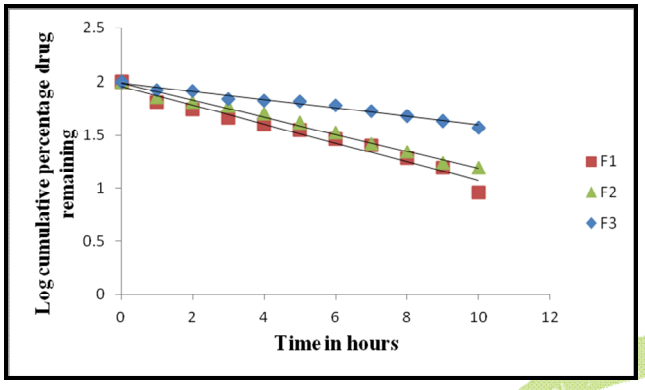

Figure 3: First Order Drug Release Plot of Formulations $F_1 – F_3$

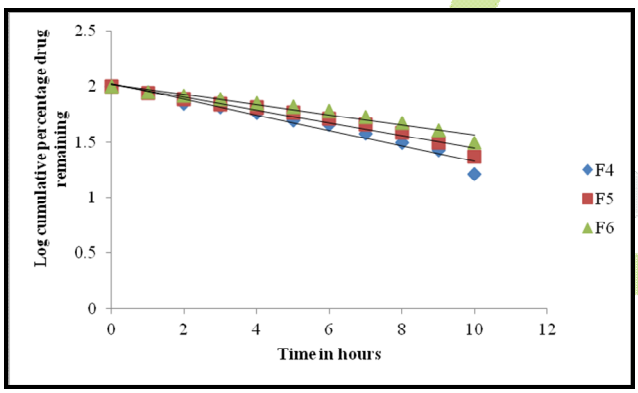

Figure: 4 First Order Drug Release Plot of Formulations F4 – F6

STABILITY STUDIES

Stability studies revealed that there was no significant change found in color, hardness, drug content and *in vitro* drug release of Aceclofenac SR tablets even after stored at25±2°C/60±5%RH and 40±2°C/75±5% RH for 45 days. The results proved that there was no significant effect of storage temperature on the drug release. The results of Aceclofenac SR tablets stored at 40±2°C/75±5% RH are given in Table 5.

Table 5: Stability Study Data of Formulation F_6 Stored at 40±2°c/75±5% RH

Parameters	Storage Condition: 40±2°C/75±5% RH			
	Initial period	After 15 Days	After 30 Days	After 45 Days
Color	White	White	White	White
Hardness (kg/cm²)	6.0±0.15	6.0±0.20	5.7±0.34	5.5±0.35
Drug content (%)	99.92±0.018	99.87±0.020	98.82±0.054	032
% drug release after 10 hours (%)	62.1±0.378	61.98±0.378	62.94±0.378	63.90±0.378

*All the values are expressed as mean ± standard deviation; n=3

CONCLUSION

In conclusion, from all the parameters studied, it can be revealed that formulation F_6 was found to be best regarding all the properties evaluated. The drug release was found to be 62.1±0.378% at the end of 10th hour. The formulation F_6 showed release profile close to that of marketed Aceclofenac SR tablet. The stability study indicated that the formulation F_6 was stable even after storing at 25±2°C/60±5%RH and 40±2°C/75±5% RH for 45 days. Hence it can be concluded that, preparation of aceclofenac sustained release tablets may be an effective strategy for the development of easy, reproducible and cost effective method to prove its potential for safe and effective sustained release for oral drug delivery therapy.

ACKNOWLEDGEMENT

The authors are thankful to Mr.S.Sriram Ashok B.E, Correspondent, Sankaralingam Bhuvaneswari College of Pharmacy, Anaikuttam, Sivakasi, for providing necessary facilities to carry out the work.

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