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Preparation and Evaluation of Sustained Release Matrix Tablets of Acelofenac and Comparision of Formulated and Marketed Product

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Abstract

The aim of performing this study is to develop matrix tablet to improve the dissolution rate of aceclofenac and release the drug in a controlled manner over a period of 24 hours. 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. Tablets were evaluated for in vitro drug release profile in phosphate buffer with pH 7.5. The thickness and hardness of prepared tablets were 3.8 ± 0.2 to 3.9 ±0.2 mm and 4 ± 3 to 5 ± 3 kg/cm2, respectively. The friability was within the acceptable limits of pharmacopeial specifications (0.31 to 0.71%), which indicates the good mechanical strength of the tablets. The in vitro drug release from the proposed system was best explained by Higuchi's model, indicating that drug release from tablets displayed a diffusion-controlled mechanism. Based on the study results, formulation F7 was selected as the best formulation.

Keywords: Aceclofenac, Matrix tablets, Sustained release, Wet granulation method, hydroxypropyl methylcellulose.

INTRODUCTION

Aceclofenac is one of the emerging newer derivatives of the diclofenac group of non-steroidal anti-inflammatory drug (NSAID) that exhi bits analgesic and anti-inflammatory activities, which directly blocks the prostaglandin synthesis, and has less gastro- intestinal complications [1]. Non-steroidal anti-inflammatory drug (NSAID) 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. But their long-term use has led to gastrointestinal (GI) complications like ulceration, perforation and obstruction [2, 3]. Matrix systems are widely used for sustained release. It is the release system that prolongs and controls the release of the dissolved or dispersed drugs [4]. A matrix is a well- mixed mixture of one or more drugs and a gelling agent, such as hydrophilic polymers. The sustained release approach allows for therapeutically efficient accumulation in the systemic circulation over a more extended period, resulting in improved patient compliance [4]. Matrix tablets are considered to be the commercially feasible sustained action dosage forms that involve the least processing variables, utilize the conventional facilities and accommodate large doses of drug. There remains an interest in developing novel formulations that allow for sustained the drug release using readily available, inexpensive excipient by matrix-based formulation. During the last two decades there has been remarkable increase in interest in sustained release drug delivery system. This has been due to various factors like the prohibitive cost of developing new drug entities, expiration of existing international patients, discovery of new polymeric materials suitable for prolonging the drug release, and the improvement in therapeutic efficiency and safety achieved by these delivery systems. Now a days the technology of sustained release is also being applied to veterinary products also [5]. Aceclofenac is a perfect applicant for a sustained release tablet. It reduces the frequency of drug administration and improves bioavailability, and increases patient compliance6. Aceclofenac has a short biological half-life of 2-4 hours;

thus, it does not show the pharmacological effect for a long time [7]. 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-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 [8].

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

Sustained-release tablets have the properties to release slowly, and they maintain the bioavailability of drugs for a long time. Therefore, in this study, we made a sustained release tablet of aceclofenac and determined all *in vitro* parameters of sustained-release tablets [9].

MATERIALS AND METHODS

Materials

The material used were aceclofenac was a kind gift from Akums Pvt. Ltd. Haidwar, (U.K), HPMC K15M, Guar gum, lactose, polyvinylpyrrolidone (PVP) K-30, isopropyl alcohol (IPA), talc, magnesium stearate, phosphate buffer pH 6.8, HCl, distilled water, and KBr. The instruments used include melting point apparatus, water bath shaker, UV spectrophotometer (Labindia), Fourier Transform Infrared (FTIR) Spectroscopy (Shimadzu), sieve #10, #18, #40, digital analytical balance, micromeritics instrument, micrometer (Mitutoyo), Monsanto tablet hardness tester, Roche friabilator, and dissolution apparatus type 1 basket.

Methods

Preparation of Matrix Tablets

The tablets were prepared by wet granulation technique. The com- positions of the tablet formulations are given in Table 1. Weighed amounts of aceclofenac, retardant (HPMC, Guar gum, ethylcellu- lose 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, equip- ped 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 [10].

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

Physiochemical Characterization of Tablets

Examination of Tablet Appearance

Twenty tablets of each formulation were randomly taken and examined to check any physical or surface roughness in the tablets.

Determination of Tablet Thickness

Tablet thickness was an essential parameter in reproducing appearance and also in counting by suing filling equipment. Many tablet filling/packaging equipment utilizes the uniform thickness of the tablets as

a counting mechanism [11]. In the present study, 10 tablets were randomly selected, and their thickness was recorded using a micrometer.

Determination of Uniformity of Weight

The weight variation test would be a satisfactory method of determining the drug content uniformity. USP procedure for uniformity of weight was followed. The allowed weight variation limits were 10%, 7.5%, and 5% for tablets having weight 130 mg or less, 130-324 mg, and>324 mg, respectively [12]. Briefly, 20 tablets were taken and weighed individually and collectively using a digital analytical balance. The average weight of one tablet was determined from the collective weight.

Determination of Tablet Hardness

The hardness of the tablet was defined as the force applied across the diameter of the tablet to break it. The resistance of a tablet to chipping, abrasion, or breakage under the condition of storage, transportation, and handling before use depends on its hardness or strength [13]. For the determination of tablet hardness, 10 tablets from each batch were randomly selected, and hardness was determined using Monsanto tablet hardness tester.

Determination of Tablet Friability

The friability of the prepared tablets was determined using Roche friabilator. This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at the height of 6 inches in each revolution. Previously weighed, 20 tablets were placed in the friabilator and subjected to 100 revolutions. Tablets were de-dusted using a soft muslin cloth and re-weighed. The percentage friability was determined using the equation as reported by Ahmed *et al*., [14].

Determination of in Vitro Dissolution Profile

The *in vitro* dissolution studies were carried out in the USP tablet dissolution test apparatus, type 1 (basket). As much as 900 mL of phosphate buffer pH 7.5 fro 2 to 12 hr. was used as a dissolution medium. Dissolution studies were carried out for 24 hours. The temperature of the dissolution medium was maintained at 37±0.5°C. The paddle was rotated at 75 rpm. Sample (5 mL) was withdrawn data predetermined interval for 24 hours. Complete sink condition was maintained by replacing the same volume of fresh dissolution medium after each sampling. The samples were diluted to a suitable volume with phosphate buffer, and the absorbance was recorded at 273.5 nm using a UV spectrophotometer [15].

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

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 4. The correlation coefficients were calculated and used to find the fitness of the data [16].

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. 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.

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 6 and 7, as there is no marked difference between these values.

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 4 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.

Table 4: Similarity (*f2*) and dissimilarity (*f1*) 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 – *f1* [Acceptance Criteria: 0 - 50]			2.44
Similarity Factor - *f2* [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.

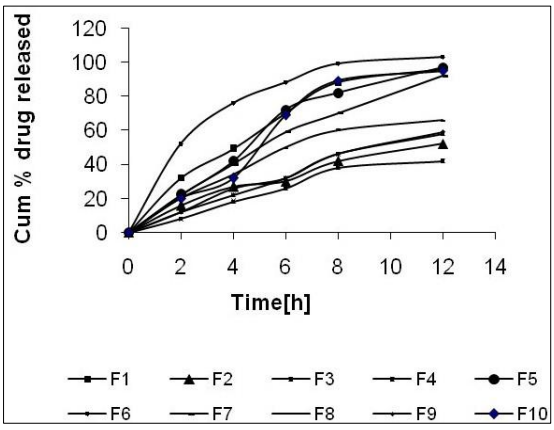

Figure 1: Release profile of aceclofenac from the various formulations

Table 5: *In vitro* profile of aceclofenac various trial formulations based on t50 and t90

Formulation code	t50a	t90b
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^{a} = time for 50% drug release (in h); t_{50}b= time for 90% drug release (in h)

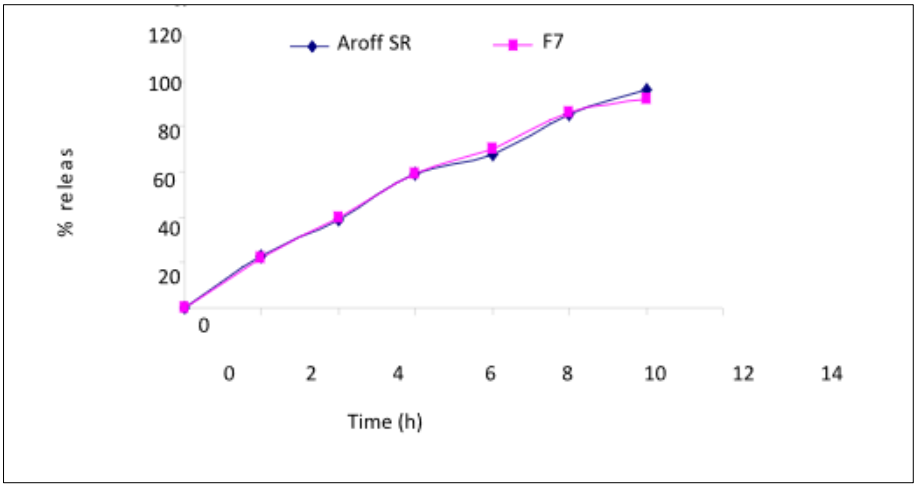

Figure 2: Dissolution comparison graph between AROFF SR tablet and Batch No. F7

Table 6: 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	Hixson-Crowell	Korsmeyer-Peppas	Korsmeyer-	Korsmeyer-	Hixson-Crowell
best fit	cube root	model	Peppas model	Peppas model	cube root

Table 7: 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	Higuchi	Korsmeyer-	Korsmeyer-	First order release
	cube root	model	Peppas model	Peppas model	model

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 [16, 17].

CONCLUSION

In this study, the prepared matrix aceclofenac tablet showed significant drug release property. It maintains the constant concentration for a long time means that it increases the half-life and bioavailability of the drug.

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