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Research Article

Preparation and *In-Vitro* Evaluation of Guar Gum Based Extended Release Matrix Tablets of Aceclofenac

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Abstract

Aceclofenac is one of the emerging NSAID molecules for arthritis treatment with less GIT complications. Guar-gum is a natural galactomannan selected for this study because of its non-toxicity and easy availability. The present study was designed to study the effect of Guar-gum on the release rate of Aceclofenac for the preparation of extended release formulations. Tablets were prepared by wet-granulation method. The tablets were subjected to physico-chemical, swelling index and in-vitro release studies. The release profiles were compared with marketed product. Other excipients like Hydroxy Propyl Methyl Cellulose, Micro Crystalline Cellulose were added to achieve a extended release product with drug release as uniform as possible with marketed product. The best fit release kinetics was achieved with zero-order followed by first-order and Higuchi equation. The results concluded that Guar-gum may be successfully used in the preparation of extended release formulations of Aceclofenac in combination with Hydroxy Propyl Methyl Cellulose and with other excipients like Micro Crystalline Cellulose and Lactose.

1. INTRODUCTION

Non-steroidal anti-inflammatory drugs are considered to be first line drugs in the symptomatic treatment of rheumatoid arthritis, osteoarthritis, alkylosing spondylitis. Aceclofenac is one of the emerging NSAID molecules for arthritis. It is a newer derivative of diclofenac and has less gastrointestinal complications [1]. The successful treatment of arthritis depends on the maintenance of effective drug concentration level in the body for which a constant and uniform supply of drug is required. Sustained release dosage forms deliver the drug at a slower rate over an extended period of time and achieve this objective.

Reservoir and matrix tablets are common sustained release dosage forms in part due to their apparent simplicity of formulation and production. Synthetic polymers and Natural gums are used as matrix formers and coating materials. Guar gum, a natural Galactomannan, selected for this study because of its non-toxicity, low cost and free availability as compared to cellulose derivatives. Guar gum is stable over a wide pH range and the non-ionic nature of the molecule is responsible for the almost constant viscosity of its solutions in the pH range 1-10.5 [2]. The present study was designed to prepare and evaluate the extended release matrix tablets of Aceclofenac by using Guar-gum as a carrier.

2. MATERIALS AND METHODS

Aceclofenac was obtained as gift sample from Ipca Laboratories, Mumbai, Guar-gum and Lactose Monohydrate were puurchased from Central Drug House,New Delhi. HPMC K100LV and MCC were obtained from Colorcon Asia Pvt Ltd and JRS Pharma, NY, USA respectively.

The collected gift sample of drug was subjected to preformulation studies like solubility, micromeritic properties and drug – excipient compatibility studies.

2.1 Solubility Studies of Aceclofenac

The solubility of Aceclofenac was studied in buffers of different pH range (pH 1.2, pH 6.8 and pH 7.4) at room temperature, by shake flask method. An excess quantity of Aceclofenac was taken in 10 ml of different solutions in a shaking water bath (100 agitations/min) for 24 h at room temperature. The solution was then passed through a whatmann filter paper (No.1) and the mount of the drug dissolved was analyzed spectrophotometrically (UV-117, Systronics) after suitable dilutions[3].

2.2 Drug-Excipient Compatibility Studies by FT-IR Analysis

The IR absorption spectra of the pure drug and physical admixtures of drug with various excipients were taken in the range of 4000-400 cm^{-1} using KBr disc method (Schimadzu IR – Prestige-21) and observed for characteristic peaks of drug.

2.3 Preparation of Tablets

Tablets were prepared by Wet Granulation method.Accurately weighed quantity of Aceclofenac , Guar gum , Lactose(and if any other excipients like HPMC, Microcrystalline cellulose)were taken in a Mortar, mixed well and sifted through 40-mesh screen.The materials were granulated with water.Wet mass was sieved through 16 mesh screen and granules obtained were air-dried in oven at 50°c for 2 hrs. Dried granules were sifted through 20-mesh screen. Moisture contents of dried granules was controlled and maintained between 2-3 %. (If it was not within the limit then the granulation was further reprocessed) Above blend with the target weight of 500mg was compressed by using 11 mm normal concave punches and 2% Talc was used as a lubricant.

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Table 1: Ingredients used in the Formulations F1 – F7

S. No	Ingredients	F1 (Weight in mg)	F2 (Weight in mg)	F3 (Weight in mg)	F4 (Weight in mg)	F5 (Weight in mg)	F6 (Weight in mg)	F7 (Weight in mg)
1	Aceclofenac	200	200	200	200	200	200	200
2	Guar Gum	200	100	100	100	100	100	90
3	HPMC K100 LVCP	-	-	100	-	100	75	75
4	MCC	-	-	-	100	50	50	60
5	Lactose anhydrous	100	200	100	100	50	75	50
6	Purified water	q.s	q.s	q.s	q.s	q.s	q.s	q.s
7	Talc (2%)	10	10	10	10	10	10	10
8	Total Weight	510	510	510	510	510	510	510

2.4 Evaluation of Physical Characteristics

The prepared tablets were subjected to various tests to measure the various parameters like Weight variation, Hardness, Friability and Thickness. The tests were carried out as per Indian Pharmacopoeia and the observed values were checked for the pharmacopoeial limits where applicable.

2.5 Drug Content Determination

About 3 tablets were powdered in a mortar and powder equivalent to 100 mg of Aceclofenac was taken in a 100 ml volumetric flask. The powder was dissolved in a minimum volume of methanol and then volume was further adjusted with methanol. The solution was filtered through Whatman filter paper (No.1).Then the solution was further diluted as per requirement and analysed spectrophotometrically at 275 nm (UV-117, Systronics) [3].

2.6 Swelling-Index Determination

The extent of Swelling was measured in terms of % weight gain by the tablet[4]. Three tablets from each formulation were kept in Petri dishes containing pH 6.8 phosphate buffer. At the end of one hr tablets were withdrawn, soaked with tissue paper, and weighed. At the end of second hr the process was repeated and weights of tablets were noted. Then for every 2 hr. weights of tablets were noted, and the process was continued till the end of 12 hrs. Percent weight gain by tablet was calculated by using the following formula;

Swelling Index (SI) = {(Mt-Mo)/Mo} x 100

Where, S.I = Swelling Index
Mt= weight of tablet at time t
Mo= weight of tablet at time t=0

2.7 *In-Vitro* Dissolution Test

The in vitro dissolution study was carried out using USP Type 2 dissolution apparatus. The study was carried out in 900 ml of 1% SLS in 0.1N HCl buffer (pH 1.2) for first 2 hours and then 900 ml of phosphate buffer (pH 6.8) from 3 to 12 h. The dissolution medium was kept in thermostatically controlled water bath, maintained at 37+0.5°c. The pre-weighed tablet was then introduced into the dissolution jar and the paddle was rotated at 75 rpm. At different time intervals, 5 ml sample was withdrawn and analyzed spectrophotometrically at 274 nm for the drug release. At each time of withdrawal, 5 ml of fresh corresponding medium was replaced into the dissolution flask [3].

2.8 Comparison of Drug Release Profiles

The release profiles of various batches are compared by three methods. They are (1) Statistical methods, (2) Model independent methods, (3) Model dependent methods[5].

Model independent methods are used to compare the dissolution profiles of reference product and test product. A simple model independent approach uses a difference factor (f1) and a similarity factor (f2) to compare the dissolution profiles.

The difference factor (f1) was calculated by using the formula

$$f1 = \frac{\sum_{f=1}^{n} |Rj - Tj|}{\sum_{j=1}^{n} Rj} \times 100$$

The similarity factor (f2) was calculated by using the formula

$$f2 = 50 \times \log\left\{\left[1 + (1/n)\sum_{j=1}^{n} |Rj - Tj|^2\right]^{-0.5} \times 100\right\}$$

Where, n is the sampling number

Rj and Tj are the percent dissolved of the reference and test products at each time point j

In general, f1 values lower than 15 (0-15) and f2 values higher than 50 (50-100) show the similarity of the dissolution profiles.

2.9 Drug Release Kinetics

Drug dissolution from solid dosage forms has been described by kinetic models in which the dissolved amount of drug (Q) is a function of the test time ,t or Q(t). Some analytical definitions of the Q(t) function are commonly used, such as zero order, first order, Higuchi, Korsmeyer-Peppas, Hixson-Crowell models, Weibull models. These models are used to characterize drug dissolution/release profiles[5].

3. RESULTS AND DISCUSSION

3.1 Solubility Studies of Aceclofenac

The results of Aceclofenac solubility in various media were shown in Table 2.

Table 2: Solubility of Aceclofenac in different solvents

S. No	Solvents	λmax	Solubility(mg/ml)*
1	0.1 N HCl buffer (pH 1.2)	274 nm	0.066±0.021
2	0.1 N HCl buffer (pH 1.2) + 0.5%w/v SLS		0.312±0.033
3	0.1 N HCl buffer (pH 1.2) +1.0%w/v SLS		0.814±0.043
4	Phosphate buffer (pH 6.8)		7.922±0.074
5	Phosphate buffer (pH 7.4)		6.112±0.055

*All values are expressed as Mean ± S.D, n=3

At lower pH, the solubility was less and as the pH was raised from acidic to pH 6.8, the solubility was increased. However beyond pH 6.8, the solubility again decreased. The solubility was very less in 0.1 N HCl and to increase the solubility in acidic medium Sodium Lauryl Sulphate (SLS) was used. 1% w/v SLS showed sufficient solubility of Aceclofenac in 0.1 N HCl.

Hence media containing 0.1 N HCl with 1% SLS for first 2 hours and phosphate buffer (pH 6.8) from 3 to 12 hours was selected for dissolution studies. Similar results were observed in previous studies[6].

3.2 Drug-Excipient Compatibility Studies by FT-IR Analysis

Drug-Excipient compatibility was carried out by FT-IR analysis. Initially the IR spectrum of pure drug was obtained with major peaks at 3333.10, 2935.76, 1770.56, 1523.82, 1313.57, 850.64.After that various admixtures of drug with other excipients like Guar gum, HPMC, MCC, SLS and Lactose were prepared and IR Spectra were obtained. The obtained spectra of physical admixtures were observed for major peaks of drugs. The results of this observation were concluded that there is no interaction between the drug (Aceclofenac) and other excipients.

3.3 Evaluation of Physical Characteristics and Drug Content

All the formulated tablets met the pharmacopoeial standard of uniformity of the weight, percentage friability, thickness and drug content. The values were tabulated (table 3) and all the values were within the limit.

Table 3: Physical Parameters and Drug Content of Aceclofenac matrix tablets

Formulations	Average weight (mg)	Hardness (Kg/cm^2)	Friability (%)	Thickness (mm)	Drug Content (%)*
F1	511.2 ± 2.263	6	0.33	4.3	99.93 ± 0.87
F2	509.35 ± 3.372	6	0.21	4.3	99.88 ± 0.52
F3	510.53 ± 2.192	6	0.13	4.2	100.79 ± 0.33
F4	511.13 ± 1.311	6	0.18	4.3	101.69 ± 1.24
F5	512.11 ± 1.863	6	0.23	4.2	99.29 ± 0.76
F6	509.66 ± 2.312	6	0.17	4.2	101.34 ± 1.15
F7	510.73 ± 2.341	6	0.12	4.2	100.51 ± 0.74

**All values were expressed as Mean ± S.D, n=3*

3.4 Swelling-Index Determination

The results of swelling behavior study of Aceclofenac matrix tablets were shown in the Table 4.

Table 4: Swelling Index of Aceclofenac matrix tablets

Time (in hrs)	Swelling Index*						
	F1	F2	F3	F4	F5	F6	F7
0	0	0	0	0	0	0	0
1	55.64±1.21	48.11±2.26	46.11±2.40	49.16±1.50	52.11±2.71	50.52±1.44	52.11±3.13
2	71.35±0.856	63.85±1.63	65.66±2.18	70.18±1.33	72.54±2.69	71.31±1.41	73.61±2.97
4	89.21±1.56	76.17±0.791	84.17±1.81	91.23±1.18	89.22±1.97	92.22±1.77	95.17±2.91
6	105.71±1.31	91.25±1.10	103.15±1.92	112.34±2.33	105.11±2.13	111.51±1.60	114.31±3.11
8	119.78±2.12	106.47±2.21	119.31±1.15	124.21±1.73	120.21±2.12	125.21±2.52	128.33±3.27
10	128.43±1.76	120.51±1.56	123.32±2.14	116.12±2.31	126.15±1.56	128.56±2.88	123.21±2.11
12	132.51±1.51	118.83±1.13	119.18±2.11	110.34±1.88	121.57±1.70	124.12±1.47	118.61±2.24

**All values are expressed as Mean±S.D, n=3*

Except in the case of F1 (Drug: Polymer used in the ratio of 1:1), the swelling was reduced after 8 hrs (F4, F7) or after 10 hrs (F2, F3, F5 and F6). In case of F1 there was no reduction in swelling index even up to 12 hrs. This may be due to the fact that the gum content is higher in it and hence a thicker rigid swollen matrix layer. In case of other formulations (F2-F7) depending upon the quantity of microcrystalline cellulose and lactose, the swelling index was reduced, due to the erosion of swollen gel layer.From these data it appears that if we can achieve either gastric retention or muco-adhesion in the intestine, formula of F1 & F2 may be used for controlling drug release for a period beyond 12 hrs.

3.5 *In-Vitro* Dissolution Test

The results of in-vitro release studies were shown in the Figure 1. All the formulations showed a low drug release in 0.1N HCl buffer (3-9% of drug) due to low solubility of Aceclofenac in the acid medium (pH 1.2).But the drug release in third hour was more when the dissolution medium was changed to phosphate buffer (pH 6.8) from acid buffer. This may be due to the fact that the drug released from the matrix may get accumulated in the surface of tablet in first two hours because of low solubility of drug in the acid medium and when the medium was changed to phosphate buffer, the drug may get released suddenly because of high solubility or high sink condition obtained. Similar results have been reported in the previous studies[6]. After that a sustained and drug release in the range of 50% to 72% was displayed by all the formulations.

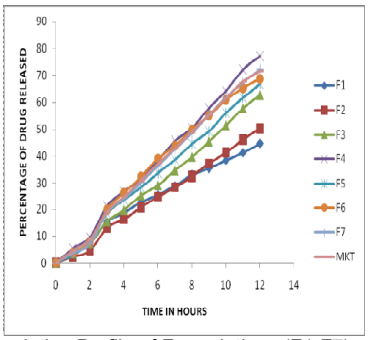

Figure 1: Dissolution Profile of Formulations (F1-F7) and Marketed Product (MKT)

The release profiles were compared with that of marketed product. Initially up to 3 hrs the release profile was same as that of marketed product. The overall drug release of F3 was higher than F2 due to faster hydration rate of HPMC[7] but lesser than marketed product. In the case of F4 the overall release profile was higher than marketed product, due to faster erosion of swollen gel layer. The overall releases profiles of F5, F6 and F7 were compared with marketed product. The release profiles of F5 and F6 was found to be nearly matching with marketed product, but cumulative amount of drug released was less. But formulation F7, which was formulated with 45% of Guar gum was found to be matching with marketed product in release profile as well as cumulative amount of drug released. The results were further supported by statistical analysis.

From the student–t test it was found that there was no significant difference among the dissolution profiles of F5, F6 & F7 at 5% level of significance (For F5 & F6, t=1.321,t<0.05 : For F6 & F7, p=1.412,t<0.05 : For F5 & F7, t=1.532,t<0.05). From model independent approach it was found that the dissolution profiles of F4,F5 and F6 were found to be matching with that of marketed product (For formulation-5, f1=9.06 and f2=69.0 : For formulation-6, f1=5.16 and f2=82.0 : For formulation-7, f1=3.26 and f2=87.0). In general, f1 values lower than 15 (0-15) and f2 values higher than 50 (50-100) show the similarity of the dissolution profiles[5].

3.6 Drug Release Kinetics

Zero-Order, First-Order, Higuchi and Peppas models were used to explain the release kinetics of Aceclofenac matrix tablets.The calculated R^2 and k values were shown in the table 5.From the results it was concluded that all formulations except F1 follow zero-order than first order. It is acceptable from any extended release formulation to fit more in zero order than first order. And from Peppas model, n value was used to describe the release mechanism of drug from modified release dosage forms. n value was greater than 1 in all the cases , the release of drug may be due to erosion and relaxation of the swollen matrix layer than diffusion[5].

Table 5: Descriptive statistics of regression and parameters of the mathematical models for the dissolution data of formulations

Kinetic models	Statistical parameter	F1	F2	F3	F4	F5	F6	F7	MKT
Zero-Order	**R^2**	0.985	0.996	0.997	0.997	0.996	0.990	0.996	0.997
	P	<0.01	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	K	3.729	4.288	5.290	6.501	5.662	6.042	6.270	6.194
First-Order	**R^2**	0.996	0.986	0.971	0.955	0.977	0.990	0.972	0.976
	P	<0.001	<0.01	<0.01	<0.01	<0.01	<0.001	<0.01	<0.01
	K	0.048	0.057	0.080	0.117	0.089	0.099	0.106	0.104
Higuchi	**R^2**	0.952	0.909	0.904	0.915	0.919	0.931	0.909	0.921
	P	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
	K	14.09	15.82	19.46	24.07	21.01	22.64	23.29	22.99
Peppas	**R^2**	0.974	0.979	0.994	0.989	0.979	0.975	0.977	0.991
	P	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.001
	K	3.811	2.449	3.776	5.395	3.698	4.255	3.656	4.776
	n	1.033	1.253	1.142	1.083	1.204	1.181	1.241	1.121

4. CONCLUSION

Extended release matrix tablets of Aceclofenac were prepared by wet granulation method. All the formulated tablets met the pharmacopoeial standard of uniformity of weight, percentage friability, thickness and drug content.The swelling behavior of all formulated tablets, was found to be uniform, that is the swelling index increased with increasing the time. As the rate of swelling increases, the overall release of drug was also increased. Neither microcrystalline cellulose nor HPMC (Methocel K100LV CP) were included in the formulations F1 and F2, where the drug release was nearer to 50% even up to 12 hours. HPMC (Methocel K100LV CP) was included in F3 and release rate was increased due to rapid hydration of polymer and then relaxation of swollen gel layer. After including microcrystalline cellulose, the release rate was increased due to further penetration of medium and resulting in erosion of guar-gum matrices. Lactose is the most useful filler for tablet formulations. It is freely water soluble and would modify the drug release for undergoing solution. From the above results, it was concluded that guar-gum may be used as a matrix former for the preparation of extended release matrix tablets of Aceclfenac, either alone or in combination with HPMC (Methocel K100LV CP) and with other excipients like microcrystalline cellulose and lactose.

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