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FORMULATION AND EVALUATION OF DICLOFENAC SODIUM SUSTAINED RELEASE MATRIX TABLETS USING AEGLE MARMELOS GUM

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ABSTRACT
The present study is to investigates the effect of acacia gum with drug of diclofenac sodium tablets. Acacia gum is used as synthetic polymer It was characterized for physicochemical properties like solubility, loss on drying, ash content, angle of repose, density, compressibility index etc. Diclofenac sodium matrix tablets were prepared by wet granulation with four formulations (AM-1 to AM-4) containing 100 mg drug and gum in different ratios (1:0.25 to 1:2). Tablets were evaluated for properties like thickness, hardness, friability, drug content, disintegration time. Drug release was studied in 0.1N HCl for 2 hrs and phosphate buffer pH 7.4 for 10 hrs using USP Type II dissolution apparatus. Among the formulations, AM-4 with drug:gum ratio of 1:2 showed slowest drug release of 98.86% over 12 hrs. The results indicate that acacia gum is suitable for use as a release retardant in diclofenac sodium sustained release matrix tablets.. The prepared formulations were evaluated for pre-compression parameters relevant to granules like angle of repose, bulk density, tapped density, hausner's index and carr's index while tablets were evaluated for various post-compression parameters like tablet thickness, hardness, weight variation, friability, content uniformity, disintegration time, swelling behaviour and in-vitro drug release study.

KEYWORDS: HPMC K4M, Acacia, Matrix Tablet, Diclofenac Sodium, *In vitro* drug release.

INTRODUCTION

Oral route is the most preferred method for drug administration due to various advantages such as ease of ingestion, pain avoidance, flexibility in formulation etc. Tablets are the most common oral dosage forms due to benefits like precise dosing, portability, tamper resistance, ease of manufacturing, good stability and patient compliance. Sustained release tablets provide prolonged, continuous release of drug over an extended period of time resulting in constant plasma concentration compared to immediate release dosage forms. This improves patient compliance, reduces dose frequency and minimizes side effects associated with fluctuation in drug levels. Polymers play an important role in modulating drug release from sustained release dosage forms. Both synthetic and natural polymers have been explored for developing sustained release formulations. Natural gums and mucilages have gained interest as release retarding materials owing to their non-toxicity, easy availability, cost effectiveness and biocompatibility. Oral route is a preferred and convenient route for drug administration. It has been used for both conventional and novel drug delivery systems. In modern pharmaceuticals, sustained release dosage forms are gaining popularity over conventional dosage forms. A sustained release tablet provides uniform drug release over an extended period. Controlled release dosage forms provide continuous release of the drug at a predetermined rate and time. The goals of sustained/controlled release systems include reducing dosing frequency, increasing effectiveness through localization at the site of action, reducing dose requirement, providing continuous drug delivery, reducing side effects, and maintaining adequate systemic drug levels. Matrix tablets serve as an important oral extended release dosage form. Hence, conventional dosage forms are limited by issues like patient compliance, drug targeting, local side effects, frequent administration, and fluctuations in blood drug levels. A matrix tablet is an oral solid dosage form in which the drug is homogenously dispersed in hydrophilic or hydrophobic matrices that act as release rate retardants. Polymers are high molecular weight compounds derived from natural and synthetic sources. Hydrophilic polymers like HPMC K4M form a hydrogel matrix which satisfies the key criteria for controlled release patterns by swelling. HPMC is a partly O-methylated and O-(2-hydroxypropylated) cellulose with a molecular

weight of 10,000-1,500,000. Hydrophobic polymers like acacia gum reduce the rate and extent of drug release due to reduced matrix porosity. Acacia is an acidic polysaccharide containing D-galactose, L-arabinose, L-rhamnose, D-glucuronic acid with a molecular weight of approximately 240,000-500,000. Both HPMC K4M and acacia gum are cellulose-based polymers that form hydrogels by simultaneous inward diffusion. Diclofenac sodium is 2-[2,6-dichlorophenyl)amino]phenyl acetate and is soluble in water. It is a non-steroidal anti-inflammatory drug with analgesic activity, inhibiting PG synthesis with some COX-2 selectivity. It is well absorbed orally, 99% protein bound, and metabolized and excreted in both urine and bile.

MATERIALS

Diclofenac sodium was procured from Yarrow Chem Products, Mumbai. Acacia were collected locally, authenticated and the gum was extracted using standard procedures. Direct compression grade microcrystalline cellulose, magnesium stearateandtalc were obtained from Central Drug House, New Delhi. All other chemicals and reagents used were of analytical grade.

METHOD

Sustained release tablets of diclofenac sodium using varying concentration of Acaciaand HPMC K4M polymers were prepared by direct compression method. Other ingredients like lactose was used as diluent, and magnesium stearateas a lubricant and talc as glidant. All the excipients along with API weighed as shown in Table 1 and passed through sieve no.20. Then, all ingredients were mixed following geometric mixing excluding glidant and lubricant for 15 minutes.7 The powder blend was thoroughly mixed with talc and magnesium stearate and compressed into a 400 mg tablet using a single rotatory punching machine.

Table 1: Formulation table of matrix tablet for 400 mg.

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Diaclofenac sodium	50	50	50	50	50	50
HPMC(K4M)	12	20	28	-	-	-
Acacia	-	-	-	12	20	28
Lactose	328	320	312	328	320	312
Talc	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5

Preparation of Diclofenac Sodium Sustained Release Matrix Tablets

Oral sustained release matrix tablets each containing 100mg of Diclofenac sodium were prepared by wet granulationmethod using different drug: gum ratios viz. 1:0.25, 1:0.5, 1:1 and 1:2 for various formulations containing *Acacia*gum. Microcrystalline cellulose was used as filler to maintain the tablet weight. The compressed tabletwere stored in a closed container for 15 days, no significant evidenceof chemical change was observed.

Evaluation

The prepared formulations were evaluated for the following parameters.

Pre-compressional studies of powder blend

A preformulation study is the first step in sane drug development. All studies which are performed prior to the development of dosage form to reduce error and provide a remunerative data to carry out dosage form development for the treatment of various diseases.

1. Pre-compression evaluation

i. Angle of Repose

The angle of repose of granules was determined by the funnel method. The accurately weight granules weretaken in the funnel. The granules were allowed to flow through the funnel freely on to the surface. Thediameter of the granules cone was measured and angle of repose was calculated using the followingequation

$\tan \theta = h/r$

or $\theta = \tan^{-1}(h/r)$

Where, θ = angle of repose,
h = height of the conc, and
r = radius of the cone base

ii. Bulk Density

It is the ratio of bulk mass of powder to the bulk volume. It is calculated by this formula

Bulk density = weight of powder bulk/Bulk volume

iii. Tapped Density

It is the ratio of the weight of blend to the minimum volume occupied in measuring cylinder by powder. Measuring cylinder containing the porous mass of powder was tapped using tapped density apparatus.8

Tapped density = weight of powder blend/Tapped volume

iv. Hausner's Index

It is an indirect index of ease of measuring of powder flow. Lower Hausner's ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Hausner's ratio = Tapped density/Bulk density

Where,
Dt is the tapped density and Db is the bulk density.

v. Carr's Index

The Carr's index (% compressibility) of the granules was calculated from the difference between the tappedand bulk densities divided by the tapped density and the ratio expressed as a percentage.

Carr's Index (%) = Dt - Db X 100/ Dt

Carr's index = Tapped density-bulk density× 100 Tapped Density

Where,

Dt is the tapped density and Db is the bulk density.

2. Post-compression evaluation

i. Tablet Thickness

The thickness of the tablets was determined by using vernier caliper. Five tablets were used, and averagevalues were calculated.It is expressed in mm.

ii. Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness ofthe tablets was determined using Monsanto hardness tester. It is expressed in kg/cm2. Three tablets wererandomly picked and hardness of the tablets were determined.

iii. Weight Variation

The weight of 20 tablets was measured and average weight was calculated. The individual weight of each tablet was measured to determine its variation. Weight variation was determined by comparison of individual tablet weight with average weight.

iv. Friability

It is calculated by Roche friability apparatus. Pre-weighed six tablets were subjected to the device which provided combined effect of shock and abrasion from height of six inches with each rotation, at 25 rpm speed and operated for 100 revolutions. Tablets were dusted and re-weighed. Compressed tablets that lose less than 0.5-1.0% of their weight were generally considered acceptable. It is expressed in percentage (%) and calculated by the following formula

Friability (%) = *Initial weight – final weight* × 100
Initial weight

V. Content Uniformity

The prepared formulation of Diclofenac sodium was weight and crushed. Powder equivalent to 50 mg of diclofenc sodium was weighed and shaken with 10 ml of methanol in 100 ml volumetric flask and filtered. The aliquot (1 ml) was taken and make up its volume up to 100 ml with methanol and absorbance was taken at 285 nm using UV spectrophotometer (UV- 1601, Shimadzu, Japan). Drug content was determined by using standard curve of diclofenac sodium.

vi. Disintegration Time

Disintegration time test was carried out according to USP specification. 6 tablets were placed in adisintegration tester filled with distilled water at 37±0.20C. The tablets were considered completelydisintegrated when all the particles passed through the wire mesh. Disintegration times recorded are meanof two determinations.

vii. Swelling Behaviour of Formulations

The swelling index of all the tablet formulations was studied. The extent of swelling was measured in terms of percent weight gain by the tablet. To study the swelling behavior, one tablet from each formulation waskept in a petri dish containing 20 ml phosphate buffer pH 7.4. At the end of 1 hr, the tablet was withdrawn, kept on tissue paper and weighed. The process was continued for every 2 hr, till the end of 12 hr.

The % weight gain by the tablet was calculated by formula

S.I. = {(Mt-M0) / M0} x 100

Where,

S.I. = swelling index

Mt = weight of tablet at the time (t)

Mo = weight of tablet at time 0.

Table 2: Micrometrics properties of pre-compressional powder blend.

Formulation code	Angle of repose (θ)	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index	Hausner's ratio
F1	33.41±0.21	0.4889±0.22	0.4814±0.22	17.82±0.09	1.18±0.07
F2	30.24±0.20	0.4279±0.05	0.4554±0.11	16.81±0.08	1.20±0.09
F3	21.22±0.11	0.3861±0.21	0.4281±0.05	12.09±0.04	1.14±0.06
F4	34.22±0.22	0.4047±0.03	0.4462±0.21	13.02±0.11	1.12±0.09
F5	29.11±0.10	0.4147±0.05	0.4782±0.34	16.01±0.10	1.16±0.06
F6	30.22±0.65	0.4035±0.23	0.4841±0.06	14.51±0.08	1.15±0.03

***In vitro* drug release study**

In vitro drug release studies were carried out using USP type II (paddle type) apparatus (Lab India Dissolution apparatus D5 8000). Dissolution medium was 900 ml phosphate buffer saline (pH 6.8) with paddle rotation at 75 rpm and temperature was maintained at 37 ± 1°C.

Aliquots of 5 ml were withdrawn after each hour and equivalent amount of fresh buffer maintained at same temperature was replaced to maintain sink conditions. The samples were analyzed for diclofenac sodium content at 276 nm by UV-spectrophotometer and calculated the drug release using calibration curve of diclofenac sodium.

RESULTS

Pre compression parameters

The prepared formulations were evaluated for pre compression parameters and their results were given in table 2 and 3. The powder blend was evaluated for various parameters like angle of repose, tapped density, bulk density, Carr's index and Hausner's ratio respectively. The value of angle of repose of all formulations ranges between 21.22 ± 0.11 to 34.22 ± 0.22 (θ) which shows very good powder flow property. The result of bulk density and tapped density ranges from 0.3861 ± 0.21 to 0.4889 ± 0.22 g/ml and 0.4281 ± 0.05 to 0.4841 ± 0.06 g/ml respectively. The values of compressibility indices, including Carr's index and Hausner's ratio ranged from 12.09 ± 0.04 to 17.82 ± 0.09 and 1.12 ± 0.09 to 1.20 ± 0.09 respectively.

Post compression parameters

The weight of diclofenac loaded matrix tablets was found to be in the range of 0.389 ± 0.004 to 0.399 ± 0.002 gm. Thickness was observed as 1.2 ± 0.1mm and % friability of various formulations was found to be in between 0.06 ± 0.009 to 0.81 ± 0.011. The hardness of tablet was found to be 5.5 ± 0.2 to 7.2 ± 0.2 kg/cm2. The *in vitro* drug release that was performed for HPMC andacacia containing formulations were given in figure 2. The % *in vitro* drug release from formulations F1, F2, F3, F4, F5 and F6 at the end of 10 h was found to be 79.22 ± 0.032%, 83.22 ± 0.01%, 88.20 ± 0.056%, 77.00 ± 0.013%, 81.02 ± 0.067% and 85.22 ± 0.045% respectively. Drug release kinetics parameters with n, R2 value are provided in (Table 4). The regression coefficient value of zero order was observed R2 value 0.949 to 0.994. So, the drug release was found to be zero orderkinetics.

DISCUSSION

The powder blends showed good flow properties. The post-compression parameters were within acceptable limits. In vitro release showed that the synthetic polymer provided more sustained release compared to the natural polymer due to its higher viscosity and hydration rate. Drug release decreased with increased polymer levels. Formulation F3 with 7% HPMC K4M followed zero order release and non-Fickian diffusion. It showed better sustained release compared to the marketed formulation in dissolution testing.

Table 3: Post-compressional studies of Diclofenac loaded matrix tablets.

Formulation code	Weight variation	Hardness (kg/cm^2)	Thickness (mm)	% Friability	% Drug release
F1	0.389±0.004	5.5±0.2	1.2±0.1	0.12±0.002	79.22±0.032
F2	0.397±0.005	6.0±0.3	1.2±0.1	0.28±0.08	83.22±0.012
F3	0.399±0.002	7.2±0.2	1.2±0.1	0.06±0.009	88.20±0.056
F4	0.396±0.005	5.8±0.2	1.2±0.1	0.81±0.011	77.00±0.013
F5	0.397±0.004	6.2±0.3	1.2±0.1	0.69±0.018	81.02±0.067
F6	0.398±0.003	6.8±0.2	1.2±0.1	0.38±0.032	85.22±0.045

Table 4: Release kinetics profile of Diclofenac loaded sodium matrix tablets.

Formulation code	Zero order (R2)	First order (R2)	Higuchi (R2)	Korsmeyerpeppas (R2)	Value of (n)
F1	0.9746	0.6231	0.9749	0.7080	1.100
F2	0.9925	0.6460	0.9880	0.7408	1.299
F3	0.9954	0.7247	0.9347	0.7644	1.159
F4	0.949	0.6023	0.9897	0.6384	1.008
F5	0.9807	0.6813	0.9755	0.6901	1.073
F6	0.9947	0.7186	0.9518	0.7474	1.134
Marketed	0.9951	0.7268	0.9401	0.7589	1.142

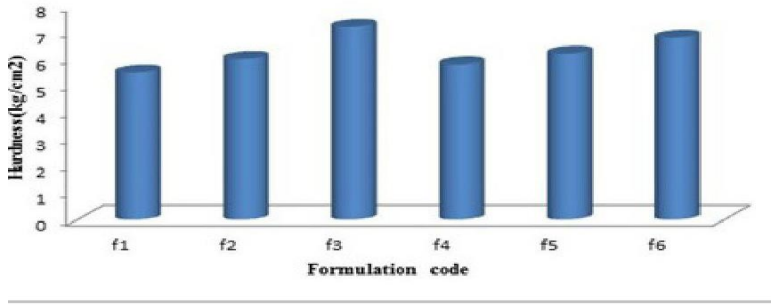

Figure 1: Graphillustrating the hardness profile of differents us tained release formulations.

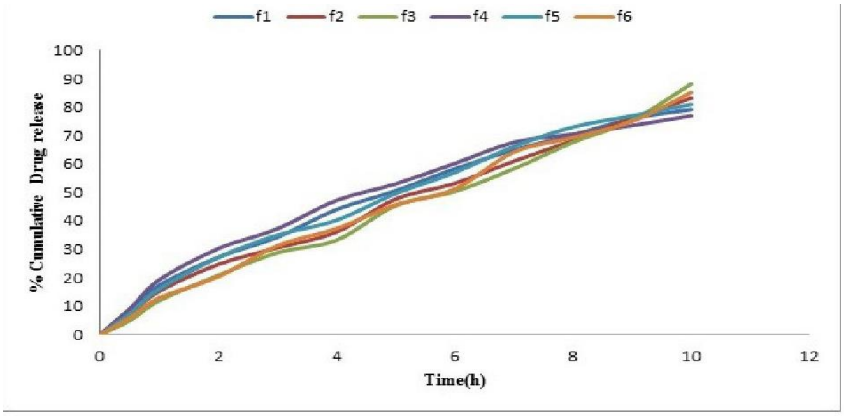

Figure 2: *Invitro* drug release profile of Diclofenac sodium containing matrix tablets for all formulation.

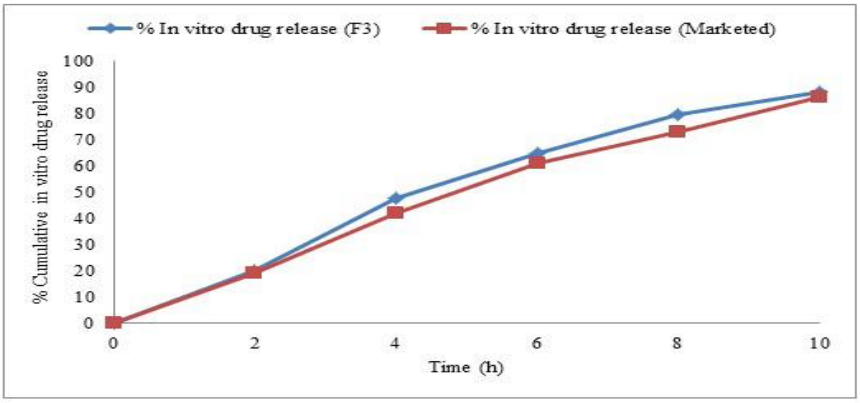

Figure 3: % Comparative In vitro drug release of optimised formulation F3 and marketed preparation.

Stability Studies

Stability studies were performed for optimized formulation and marketed formulation at various temperature conditions as room temperature (RT=30 ± 50), freezing temperature (FT=2-4 ± 20), and accelerated temperature (AT=45 ± 50) for 60 days. For F3 slight colour change was seen after 45 days at accelerated condition, but no further defects were seen till 60 days. Marketed preparation was also tested for stability in similar conditions for 60 days. After 45 days slight colour change was observed at room temperature and accelerated conditions. And mottling was also observed after 60 days at accelerated conditions. The stability studies of optimized and marketed preparation were showed in (Table 5, 6).

Table 5: Stability Studies at different Temperature for the Formulation F3.

Days	Optimized Formulation (F3)					
	Physical appearance			Drug content (%)		
	RT	FT	AT	RT	FT	AT
0	+	+	+	88.20±0.056	88.20±0.056	88.20±0.056
7	+	+	+	88.20±0.14	88.20±0.78	88.20±0.92
14	+	+	+	88.17±0.20	88.12±0.44	88.16±0.19

28	+	+	++	88.09±0.11	88.07±0.79	88.04±0.34
35	+	+	++	88.01±0.02	87.84±0.56	87.80±0.06
45	+	++	++	87.72±0.13	87.11±0.37	87.42±0.36
60	++	-	-	87.28±0.05	86.89±0.28	86.78±0.01

No colour change (+), slightly colour change (++), mottling (-); RT- Room Temperature - (30±50); FT- Freezing Temperature - (2-4±20)

Table No. 6: Stability Studies at different Temperature for the Marketed preparation.

Days	Marketed					
	Physical appearance			Drug content (%)		
	RT	FT	AT	RT	FT	AT
0	+	+	+	86.17±0.12	86.17±0.12	86.17±0.12
7	+	+	+	86.17±0.17	86.17±0.18	86.17±0.61
14	+	+	+	86.14±0.11	86.03±0.44	86.06±0.29
28	+	+	++	86.02±0.32	85.99±0.19	85.64±0.24
35	+	+	++	85.77±0.91	85.24±0.66	85.87±0.01
45	+	++	++	85.39±0.15	85.21±0.17	85.53±0.11
60	++	-	-	85.78±0.01	84.88±0.28	84.46±0.02

CONCLUSION

The drug polymer ratio was found to influence the drug release, as the polymer level increased, the drug release rates were found to be decreased. The release of drug after a study of the release kinetics model follows zero order and the mechanism of drug release was found to be non- fickian diffusion super case II. Concentration of natural and synthetic polymer also affects the hardness and drug release profile. Amongst different formulations, F3 (HPMC) was found to be an optimized formulation which gives better results than the marketed formulation on the basis of *in vitro* release. Thus, it can be concluded that the formulation F3 can be more efficient and potential in comparison with marketed formulation for the development of sustained drug delivery system. The percentage of drug release for F6 is 85.22%.

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