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Formulation and Evaluation of Sustained Release Matrix Tablets of Aceclofenac

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***Abstract*: The objective of the present study was to study the effect of polymers on sustained release of Aceclofenac from tablets. Compatibility was studied by Fourier transform infrared spectroscopy and DSC. The tablets were prepared by melt granulation method using Ricebran wax. The prepared matrix tablets were evaluated for their physicochemical parameters such as weight variation, hardness, friability, content uniformity and in-vitro dissolution. Pre and post compression parameters were evaluated and all the parameters were found within the limit. The drug release data were subjected to different models in order to evaluate release kinetics and mechanism of drug release. Formulation F9 was selected as best formulation. The dissolution of formulation F9 can be Shows Non-fickian drug release mechanism.**

***Keywords*: Matrix tablets, Aceclofenac, Ricebran wax, DSC.**

1. Introduction

Sustained release technology is relatively new field and as a consequence, research in the field has been extremely fertile and has produced many discoveries. The basic rationale of a sustained drug delivery system is to optimize the Biopharmaceutical, Pharmacokinetic and Pharmacodynamics properties of a drug in such a way that its utility is maximized through reduction in side effects and cure or control of condition in the shortest possible time by using smallest quantity of drug, administered by the most suitable route. The novel system of drug delivery offer a means of improving the therapeutic effectiveness of incorporated drugs by providing sustained, controlled delivery and / or targeting the drug to desired site. The goal of any drug delivery 1 Department of Pharmaceutics Introduction system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then maintain the desired drug concentration.

Aceclofenac is an oral non-steroidal anti-inflammatory drug (NSAID) with marked anti-inflammatory and analgesic properties used to treat osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. It is reported to have a higher anti-inflammatory action or at least comparable effects than conventional NSAIDs in double-blind studies. Aceclofenac potently inhibits the cyclo-oxygenase enzyme (COX) that is involved in the synthesis of prostaglandins, which are inflammatory mediators that cause pain, swelling, inflammation, and fever. Aceclofenac belongs to BCS Class II as it possesses poor aqueous solubility.

A matrix system consists of active and inactive ingredients that are homogeneously dispersed and mixed in the dosage form. It is by far the most commonly used oral controlled release technology and the popularity of the matrix systems can be attributed to several factors which will be discussed in the later section. The release from matrix type formulations governed by Fick's first law of diffusion.

$$J = dQt/dt = - D\, dC/dx$$

J is flux, or rate of diffusion, while Q is the amount diffused per unit of time t, and D is diffusion coefficient**.**

2. Materials and Methods

A. Materials

Aceclofenac was purchased from Modern industries, HPMC K4, Ricebran wax, purchased from Research lab fine chemical industries, Talc and Microcrystalline cellulose are from Modern Industries.

B. Method of preparation of matrix tablets

Matrix tablets of Aceclofenac were prepared by melt granulation method using varying proportions of polymers in combination. The composition of matrix tablets is given in table -1. For each formulation required quantities of Aceclofenac, polymer (Ricebran wax and Microcrystalline cellulose), were accurately weighed according to the composition and wax are melt then gradually adding drug. Then cool the mixture and added microcrystalline cellulose. The solidified mixture is passed through sieved no 20. The added are HPMC K4 and the obtained blend was lubricated with talc. For another 5 minutes. The appropriate amount of the mixture was weighed and then compressed using 8 station rotary tablet press (CEMACH machineries ltd Ahmedabad, India) equipped with 10 mm flat faced punches at a constant compression force required to produce hardness of tablets about 2-4 kg/ cm^2. All the tablets were stored in airtight containers for further use.

Table 1
Formulation code for each Batch

Sr.no.	Excipients (mg)	F1	F2	F3	F4	F5	F6	F7	**F8**	**F9**
1	Drug	100	100	100	100	100	100	100	100	100
2	Rice bran wax	200	200	200	250	250	250	300	300	300
3	MCC	30	30	30	20	20	20	10	10	10
4	HPMC K4M	20	20	20	20	20	20	20	20	20
5	Talc	10	10	10	10	10	10	10	10	10
9	Total weight	360	360	360	360	360	360	360	360	360

3. Pre-compression parameters

A. *Angle of repose (θ)*

Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and horizontal plane. The frictional force in a loose powder or granules can be measured by the angle of repose.

$$\tan\theta = h / r$$

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

Where, θis the angle of repose
h is height of pile
r is radius of the base of the pile

B. *Carr's compressibility index*

The compressibility index of the granules was determined by the Carr's compressibility index. (%) Carr's Index can be calculated by using the following formula,

$$\text{Carr's Index (\%)} = \frac{\text{TBD - LBD}}{\text{TBD}} \times 100$$

4. Post-compression parameters

The prepared matrix tablets were evaluated for their physical properties like, hardness and friability, swelling index and drug content.

A. *Hardness test*

Tablets require a certain amount of strength, or hardness and resistance to friability, to withstand mechanical shocks of handling during manufacture, packaging and shipping. The hardness of the tablets was determined using Digital Hardness tester. It is expressed in Kg/cm^2. Three tablets were randomly picked from each formulation and the mean and standard deviation values were calculated.

B. *Friability test*

It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition.

The friability of tablets was determined by using Electro lab, USP EF 2 friabilator. It is expressed in percentage (%). Ten tablets were initially weighed ($W_{initial}$) and transferred into friabilator. The friabilator was operated at 25 RPM for 4 minutes. The tablets were weighed again (W_{final}). The percentage friability was then calculated by,

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} x100$$

% Friability of tablets less than 1% is considered acceptable.

C. *Swelling index*

The swelling behavior of a dosage unit was measured by studying its weight gain. The swelling index of tablets was determine by placing the tablets in a petridish using dissolution medium as 0.1N HCL (pH 1.2) and pH 7.4 phosphate buffer. After 1, 2, 4, 6, and 8 hours. Each tablet was withdrawn carefully, blotted with tissue paper to remove for each time interval.

The swelling index was calculated by the following equation:
Swelling index (SI) = (Wt – W0)/WO × 100
Where, Wt= Weight of tablet at time t.
W0 = Initial weight of tablet

D. *In vitro dissolution study*

In vitro drug release studies of matrix tablets were done in eight-station USP XXII type II dissolution test apparatus (Electro lab TDT-08, India) at 37°C (± 0.5°C) and 50 rpm speed in 900 mL of dissolution medium. Dissolution medium consisted of 0.1N hydrochloric acid for the first 2 hours and phosphate buffer pH 7.4 from 3 to 8 hours. Five millitre (5ml) samples were taken by filtration at predetermined time intervals and after each sampling the volume of dissolution medium was replaced with 5ml of phosphate buffer (pH 7.4). The amount of drug released is determined spectrophotometrically.

In- Vitro Drug Release Kinetic Study

Zero Order Kinetics

A Zero order release would be predicted by the following equation,

$$Qt-Q0=K^0t$$

Where
Qt =Amount of drug release dissolved in time 't'
Co=Initial amount of drug concentration in solution.
K^{o}t=Zero order rate constant.

When the data were plotted as cumulative % drug release versus time, if the plot is linear then data obeys zero order kinetics with slope equal to K0. This model represents an ideal release profile in order to achieve the prolonged pharmacological action.

First Order Kinetics:

A first order release would be predicted by the following

equation

$$\text{Log } Qt = \text{Log } Q0 - Klt/2.303$$

Where,

Qt=Amount of drug released in time 't'

Co=Initial amount of drug concentration in solution.

Klt=first order rate constant

When data were plotted as log cumulative% drug remaining versus time yields a straight line indicating that the release follows first order kinetics. The constant K can be obtained multiplying slope values.

Higuchi's Model:

Drug release from the matrix device by diffusion has been described by Higuchi's diffusion equation

$$Ft = Q = VD5/T(2C - 5Cs)Cst$$

Where,

Q=Amount of drug release dissolved in time 't'.

Co=diffusion coefficient of drug in the release matrix.

Cs=Solubility of drug in the matrix.

5=porosity of matrix

t=Tortuosity

T=Time (h)

The equation may be simplified then the equation becomes,

$$Ft = Q = KhX\ t1/2$$

Where,

Kh=Higuchi dissolution constant

When data were plotted according to this equation, i.e. cumulative drug released versus square root of time, yields a straight line, indicating that the drug was released by diffusion mechanism.

Peppas Korsmeyer Equation:

In 1983 korsmeyer et.al developed a simple, semiempirical model, when diffusion is the main drug release mechanism, relating exponentially the drug release to the elapsed time (t)

$$At/Ao = Kt/n$$

Where,

K=Constant

n=Release

t=Time

At and Ao=Absolute cumulative amount of drug released at times.

This is used when the release mechanism is not well known or when more than one type of a release phenomenon could be involved.

5. Results and Discussion

A. *Pre-compression parameters*

The powder mixture of all the formulations were evaluated for angle of repose, bulk density, tapped density, compressibility index and their values were shown in table 2. The bulk density 0.54 to 71 g/ml and Powder blend indicated good flow properties with an angle of repose values ranging from 30.9to 36.5. The compressibility index for all the formulations were found to be less than 11.4 %, which indicates that the powder mixture has good flow properties. Hausner's ratio was also calculated, the ration was ranged between 1.08 and 1.12.

B. *Evaluation of post-compression parameters*

Sustained release matrix tablets of Aceclofenac were prepared by direct compression technique. Total nine formulations were prepared. The tablet weight variation, hardness, friability and content uniformity for each formulation are shown in table 3. The weight variation test indicated that the percentage deviation of all tablet formulations was found to be within pharmacopoeial acceptable limit. The hardness of all the tablets was within the range of 4±5.4kg/cm. The drug content

Table 2
Pre-compression parameters: (Granules)

Sr. No.	Formulation Code	Bulk Density (gm/ml)*	Tapped Density (gm/ml)*	Angle of Repose (°)*	Carr's Index (%)	Hausner's Ratio
1	F1	0.54±0.03	0.61±0.12	36.5±0.05	11.29±0.12	1.12
2	F2	0.48±0.07	0.51±0.01	33.02±0.01	5.8±0.03	1.06
3	F3	0.61±0.12	0.66±0.15	32.6±0.02	7.5±0.07	1.08
4	F4	0.57±0.05	0.61±0.12	34.21±0.03	6.5±0.06	1.15
5	F5	0.54±0.03	0.61±0.12	33.42±0.02	6.5±0.06	1.12
6	F6	0.61±0.12	0.66±0.15	33.4±0.01	7.5±0.07	1.08
7	F7	0.71±0.22	0.77±0.25	33.4±0.02	7.7±0.07	1.08
8	F8	0.61±0.12	0.66±0.15	33.42±0.02	7.5±0.07	1.08
9	F9	0.54±0.03	0.61±0.12	30.9±0.01	11.4±0.10	1.12

Table 3
Post-compression parameters: (Tablet)

Sr. No.	Formulation code	Weight variation (mg)*	Diameter (mm)	Thickness (mm)*	Hardness (kg/cm^2)*	Friability (%)
1	F1	200±2.86	10	4.3±0.03	4.5±0.12	0.89
2	F2	196±4.01	10	4.1±0.01	5±0.15	0.90
3	F3	198±3.90	10	4.1±0.01	4.5±0.12	0.90
4	F4	197±2.89	10	4.3±0.03	4.7±0.13	1.8
5	F5	195±4.05	10	4.3±0.03	5.2±0.17	0.90
6	F6	199±2.89	10	4.2±0.02	5±0.15	0.88
7	F7	194±4.15	10	4.1±0.01	5.5±0.19	0.88
8	F8	198±3.90	10	4.3±0.03	5.1±0.15	0.90
9	F9	199±2.89	10	4.2±0.02	5.3±0.018	0.90

Table 4
Swelling index of formulations (F1-F9)

Time (hrs.)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	33.3	31	28	33.3	33.3	28	28	25	33.3
2	42.8	41	39	41	45	39.1	35.4	39	42
4	50	45	44	48	51	45	50	44	48
6	54	51	47	52	52	50	51	47	50
8	57	59	57	58	59	58	60	61	62

Table 5
In-vitro dissolution study of Aceclofenac

Sr. no.	Time (h)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	0	0	0	0	0	0	0	0	0	0
2	1	27.15±0.599	44.42±0.580	54.94±0.732	9.34±0.330	7.84±0.440	8.53±0.582	6.46±0.576	40.84±0.116	8.76±0.911
3	2	11.1±0.762	12.61±0.336	12.03±0.336	22.89±0.521	14.81±0.504	17.23±0.196	18.03±0.459	15.95±0.574	17.12±0.136
4	3	21.4±0.735	24.99±0.392	22.68±0.124	33.01±0.838	24.3±0.500	26.98±0.629	29.52±0.672	28.35±0.495	24.09±0.118
5	4	33.23±0.128	38.79±0.746	36.01±1.73	53.84±0.573	40.05±0.659	45.84±0.739	49.54±0.170	43.19±0.401	44.55±0.598
6	5	45.99±0.941	49.25±0.521	47.62±1.028	71.37±0.509	52.6±0.737	58.52±0.706	65.46±0.615	54.93±0.595	64.4±0.635
7	6	57.48±0.599	60.04±0.876	62.34±0.506	91.97±0.567	69.29±0.532	78.9±0.976	83.66±0.259	73.45±0.726	86.66±0.851
8	7	57.47±0.357	60.21±0.401	64.42±0.495	92.21±0.358	69.26±0.615	79.47±0.582	83.68±0.366	72.52±0.582	81.89±0.521
9	8	59.57±0.582	60.31±0.459	64.73±0.336	93.47±0.389	71.05±0.629	80.21±0.215	85.78±0.402	75.26±0.502	88.42±0.285

in all the batches was determined by measuring absorbance of sample at 274 nm using double beam UV spectrophotometer (LABINDIA).

C. *Swelling index*

The swelling behavior of a dosage unit was measured by studying its weight gain. The swelling index of tablets was determine by placing the tablets in a petridish using dissolution medium as 0.1N HCL(pH 1.2) and pH 7.4 phosphate buffer. After 1, 2, 4, 6, and 8 hours. Each tablet was withdrawn carefully, blotted with tissue paper to remove for each time interval.

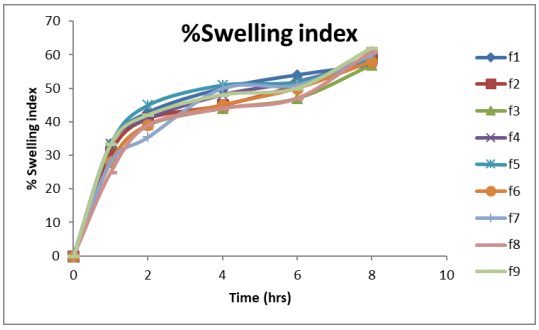

Fig. 1. Swelling index of aceclofenac tablet

D. *In vitro dissolution study*

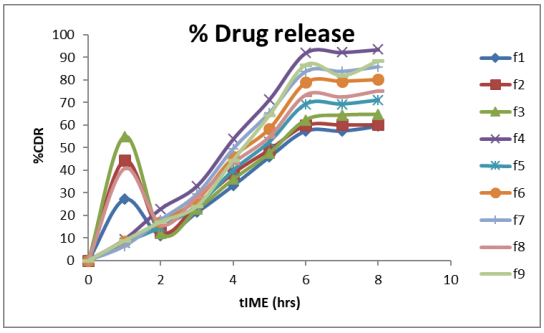

Fig. 2. % drug release of aceclofenac tablet

E. *Compatibility study: (at 40 ℃/ 75% RH)*

Table 6
Compatibility study of drug with different excipients

Sr. No.	Ingredients	Observation (After 30 Days)
1	Aceclofenac	No change
2	Aceclofenac + Rice bran wax	No change
3	Aceclofenac + Carnuba wax	No change
4	Aceclofenac+ Talc	No change
5	Aceclofenac + Microcrystalline sodium	No change
6	All mixture	No change

F. *DSC Study*

Thermal analysis of drug was carried out using DSC. The DSC curve of aceclofenac profile a sharp exothermic peak at C corresponding to its melting, and indicating its crystalline nature and purity of sample. The DSC thermogram is shown in figure 3.

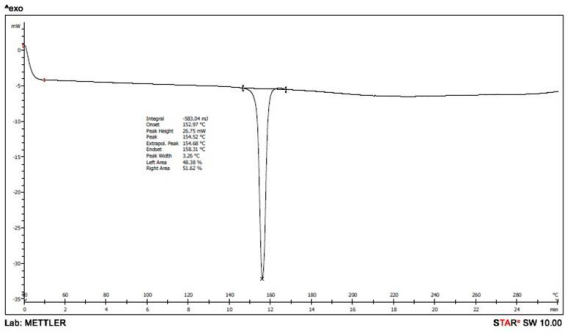

Fig. 3. DSC Thermogram of Aceclofenac

G. *FT-IR Study*

Infrared spectrum of Aceclofenac was recorded. The observed peaks are match with the peaks given in pharmacopoeia which confirms that the supplied samples was of Aceclofenac.

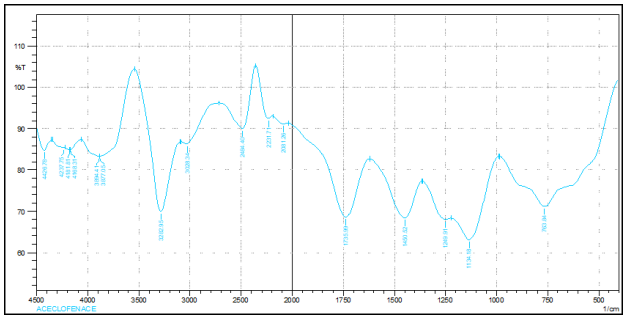

Fig. 4. IR spectrum of Aceclofenac

The observed peaks along with functional groups assigned to them are given below:

Table 7
IR interpretation

Peak (cm^{-1})	Functional group
3282	O-H Stretching
3028	N-H Bending
1735	C=O Stretching
1134	C-O Bending
763	C-Cl Stretching

6. Conclusion

Sustained release matrix tablets of Aceclofenac were prepared using different ratios of Ricebran wax and Microcrystalline cellulose by melt granulation method. The results of the present study demonstrates that the Ricebran wax and Microcrystalline cellulose control the Aceclofenac release effectively for 8 hrs. It is concluded that sustained release of Aceclofenac over a period of 8 hours was obtained with formulation (F-9) containing high amount of Ricebran wax and Microcrystalline cellulose.

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