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FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLET OF ACECLOFENAC

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ABSTRACT

Aceclofenac is a widely prescribed NSAID for the treatment of osteoarthritis, rheumatoid arthritis, and pain-related inflammatory conditions. Owing to its short elimination half-life of nearly 4 hours, frequent administration is required, which may lead to gastrointestinal irritation and fluctuating plasma drug levels. The present research aims to develop sustained release (SR) matrix tablets of aceclofenac using a combination of hydrophilic polymer Hydroxypropyl Methylcellulose (HPMC K15M) and hydrophobic natural resin rosin oil to achieve controlled drug release. Formulations were prepared by wet granulation using PVP K30 as binder. Pre-compression parameters such as flow properties were evaluated, followed by post-compression evaluation including hardness, friability, weight variation, thickness, and drug content. In-vitro drug release was performed in pH 7.4 phosphate buffer for 12 hours. FTIR confirmed compatibility between drug and excipients. Results showed that increasing rosin oil concentration reduced the release rate, while HPMC provided matrix swelling and diffusion control. The optimized formulation (F5) containing a balanced ratio of HPMC and rosin oil released 94.2% drug in 12 hours, following zero-order kinetics with non-Fickian diffusion. The study concludes that HPMC combined with rosin oil resin is effective in modulating the sustained release of aceclofenac, offering a cost-effective and stable SR dosage form.

KEYWORDS: sustained release, Rosin oil as Resin, HPMC, Acelcofenac.

INTRODUCTION

Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient acceptance, and cost-effective manufacturing process.

Pharmaceutical products designed for oral delivery are mainly immediate release type or conventional drug delivery systems, which are designed for immediate release of drug for rapid absorption. These immediate release dosage forms have some limitations such as.

1) Drugs with short half-life requires frequent administration, which increases chances of missing dose of drug leading to poor patient compliance.

2) A typical peak-valley plasma concentration-time profile is obtained which makes attainment of steady state condition difficult.

3) The unavoidable fluctuations in the drug concentration may lead to under medication or overmedication as the CSS values fall or rise beyond the therapeutic range.

4) The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index, whenever overmedication occurs.

In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of controlled drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits.

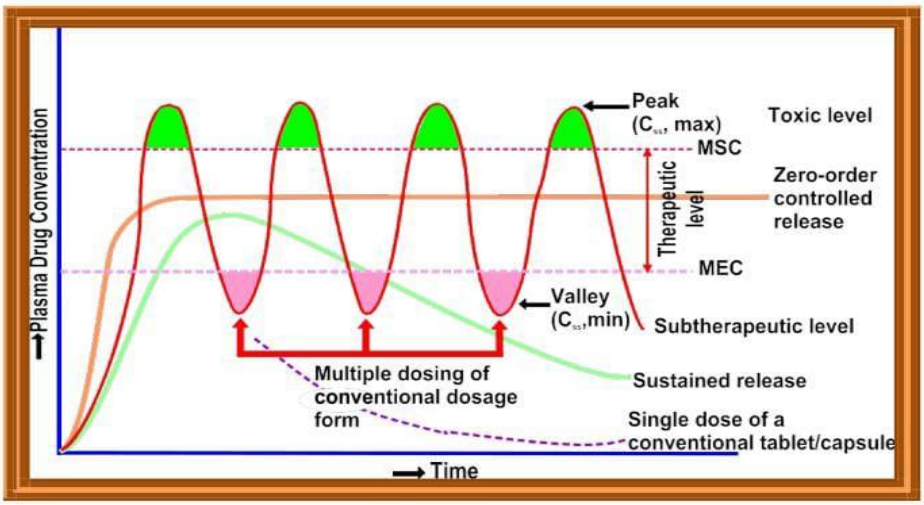


Fig. No: 1- A hypothetical plasma concentration-time profile from conventional multiple dosing and single doses of sustained and controlled delivery formulations.

Controlled Drug Delivery Systems

Controlled drug delivery systems have been developed which are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/or targeting the delivery of drug to a tissue.

Controlled drug delivery or modified drug delivery systems are conveniently divided into four categories.

1) Delayed release
2) Sustained release
3) Site-specific targeting
4) Receptor targeting
5) More precisely,

1) Sustained drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects.
2) Localized drug action by spatial placement of a controlled release system adjacent to or in the diseased tissue.
3) Targeted drug action by using carriers or chemical derivatives to deliver drug to a particular target cell type.
4) Provide a physiologically/therapeutically based drug release system. In other words, the amount and the rate of drug release are determined by the physiological/ therapeutic needs of the body.

A controlled drug delivery system is usually designed to deliver the drug at particular rate. Safe and effective blood levels are maintained for a period as long as the system continues to deliver the drug. Controlled drug delivery usually results in substantially constant blood levels of the active ingredient as compared to the uncontrolled fluctuations observed when multiple doses of quick releasing conventional dosage forms are administered to a patient.

Advantages of Controlled Drug Delivery System

1. Avoid patient compliance problems.
2. Employ less total drug

a) Minimize or eliminate local side effects
b) Minimize or eliminate systemic side effects
c) Obtain less potentiation or reduction in drug activity with chronic use.

d) Minimize drug accumulation with chronic dosing.

3. Improve efficiency in treatment

a) Cures or controls condition more promptly.

b) Improves control of condition i.e., reduced fluctuation in drug level.

c) Improves bioavailability of some drugs.

d) Make use of special effects, E.g. Sustained-release aspirin for morning relief of arthritis by dosing before bed time.

4. Economy i.e. reduction in health care costs. The average cost of treatment over an extended time period may be less, with less frequency of dosing, enhanced therapeutic benefits and reduced side effects. The time required for health care personnel to dispense and administer the drug and monitor patient is also reduced.

Disadvantages

1) Decreased systemic availability in comparison to immediate release conventional dosage forms, which may be due to incomplete release, increased first-pass metabolism, increased instability, insufficient residence time for complete release, site specific absorption, pH dependent stability etc.

2) Poor in vitro – in vivo correlation.

3) Possibility of dose dumping due to food, physiologic or formulation variables or chewing or grinding of oral formulations by the patient and thus, increased risk of toxicity.

4) Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reactions.

5) Reduced potential for dosage adjustment of drugs normally administered in varying strengths.

6) Stability problems.

7) Increased cost.

8) More rapid development of tolerance and counselling.

9) Need for additional patient education and counselling.

MATERIALS AND METHODS

Materials	Grade	Company
Aceclofenac	Pharma	Mirco Labs Pvt.Ltd.Hosur.
Rosin oil as resin	Pharma	Twilinght Litaka Pvt.Ltd. Pune
HPMC	A.R.	Twilinght Litaka Pvt.Ltd. Pune
Pvp K_{30}	L.R	SD Fine Chemicals, Boisar
Di-Calcium Phosphate	A.R	SD Fine Chemicals, Boisar
Talc and magnesium Stearate	A.R	SD Fine Chemicals, Boisar

INSTRUMENTS AND EQUIPMENTS USED

S.NO.	INSTRUMENTS /EQUIPMENT	COMPANY
1.	Electronic balance	Shimadzu
2.	Hardness tester	Monsanto
3.	Friability test apparatus	Roche friabilator
4.	Hydraulic press	Rimek mini press-1
5	Dial caliper	Mitutoyo , japan.
6.	Tablet dissolution tester (USPXXIII)	Electro lab
7.	Density tap tester	Electro lab
8.	UV Spectrophotometer	Shimadzu
9.	FTIR Spectrophotometer	Shimadzu
10.	pH meter	Hanna instruments, Italy.
11.	Humidity chamber	Thermo Lab.
12.	Magnetic stirrer	Remi Equipments Pvt Ltd
13.	Cyclo mixer	Remi Equipments Pvt Ltd
14.	Hot air oven	Tempo instruments and Equipments (1) Pvt . Ltd

METHODS

I. Preparation of calibration curve.

1) Preparation of standard graph of Aceclofenac using 0.1N HCl

2) Preparation of standard graph of Aceclofenac using phosphate buffer pH 6.8

II. Evaluation of Pre-compression parameters.

III. Formulation of tablets of Aceclofenac.

Preparation of sustained release matrix tablets of Aceclofenac with Xanthan gum.

IV. Evaluation of the prepared formulation for Physico-Chemical characteristics.

V. In-vitro drug release studies using 0.1N HCl and phosphate buffer pH 6.8.

I. PREPARATION OF CALIBRATION CURVE

1) Preparation of Standard graph of Aceclofenac using 0.1 N HCl. Beer's law is obeyed in the concentration range of 0 – 20 mcg/ml.

Method:- 100 mg of Aceclofenac was accurately weighed into 100ml volumetric flask and dissolved in 0.1 HCl. The volume was made up to 100ml to get a concentration of (1 mg/ml.) stock solution- I. From this, 10 ml was withdrawn and diluted to 100 ml to get a concentration of (100 µg/ml) stock solution -II.

Calibration curve in 0.1 N Hydrochloric acid:- From the standard stock solution-II (SS-II) 0.4ml, 0.8 ml, 1.2 ml, 1.6 ml and 2 ml were withdrawn and volume ware made up to 10 ml with 0.1 HCl to give a concentration of 4 µg, 8 µg, 12 µg, 16 µg, and 20 µg/ml. Absorbance of these solutions ware measured against a blank of 0.1 HCl at 275 nm for Aceclofenac and the absorbance values ware summarized in Table 2. Calibration curve was plotted, drug concentrations versus absorbance given in the Fig. 4

2). Preparation of standard graph of Aceclofenac using phosphate buffer pH 6.8.

Beer's law is obeyed in the concentration range of 0 – 20 mcg/ml.

METHOD

100 mg of Aceclofenac was accurately weighed into 100ml volumetric flask and dissolved in phosphate buffer pH 6.8. The volume was made up to 100ml to get a concentration of (1 mg/ml.) stock solution- I. From this, 10 ml was withdrawn and diluted to 100 ml to get a concentration of (100 µg/ml) stock solution -II.

Calibration curve in phosphate buffer pH 6.8:- From the standard stock solution-II (SS-II) 0.4 ml, 0.8 ml, 1.2 ml, 1.6 ml and 2 ml were withdrawn and volume ware made up to 10 ml with phosphate buffer pH 6.8 to give a concentration of 4 µg, 8 µg, 12 µg, 16 µg, and 20 µg/ml. Absorbance of these solutions ware measured against a blank of phosphate buffer pH 6.8 at 275 nm for Aceclofenac and the absorbance values ware summarized in Calibration curve was plotted, drug concentrations versus absorbance was given in the Fig. 5

III. EVALUATION OF PRE-COMPRESSION PARAMETER

1) Angle of Repose (θ):- This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane. The powders were allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of granules formed.

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

Where,

θ = angle of repose

h = height of the heap

r = radius of the heap

The relationship between Angle of repose and powder flow is as follows.

Angle of repose	Powder flow
< 25	Excellent
25-30	Good
30-40	Passable
> 40	Very poor

2) Compressibility Index

The flow ability of powder can be evaluated by comparing the bulk density (Do) and tapped density (D f) of powder and the rate at which it packed down.

Compressibility index is calculated by –

$$\text{Compressibility index (\%)} = \frac{D_f - D_o}{D_f} \times 100$$

Where

Do = Bulk density

D f = Tapped density

Percent compressibility	Type of flow
5-15	Excellent
12-16	Good
18-21	Fare-passable
23-25	Poor
33-38	Very poor
>40	Extremely poor

3) Hausner's Ratio

It is the ratio of tapped density to bulk density.

Hausner's ratio = D f/ Do

Where

Do = Bulk density

D f = Tapped density

4) Content Uniformity

The granules were crushed and power containing 100 mg of Aceclofenac was dissolved in 100 ml of 0.1N HCl. The solution was passed through a whatmann (No. 1) filter and analyzed spectrophotometrically at 275 nm after sufficient dilution with 0.1N HCl.

IV. FORMULATION OF MATRIX TABLETS OF ACECLOFENAC

1 Preparation of sustained release matrix tablets of Aceclofenac with Xanthane Gum as retarding material

- Accurately weighed quantity of Aceclofenac, Xanthane Gum Dicalcium Phosphate & Pvp K30 were taken in mortar and mixed. Sufficient quantity of iso propylene alcohol was added to the dry blend gradually with constant kneading to ensure a homogenous mass.
- The dough mass was passed through a # 16 mesh sieve. Then granules were dried at 500C and dried granules again passed through #22 and were lubricated with talc (1 %) and

magnesium stearate (1 %) and compressed into tablets on a 10-station rotatory punching machine using 10 mm concave punches. Each tablet contains 200 mg of Aceclofenac.

- The drug matrix ratio was varied to obtain the matrix tablets of varying polymer concentration.

V. Table No. 3. Composition of Matrix tablets of Aceclofenac

Ingredients(mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Aceclofenac	30	30	30	30	30	30	30	30	30
Rosin oil as resin	20	40	60	-	-	-	-	-	-
HPMC	-	-	-	20	40	60	-	-	-
Xanthan gum: Resin	-	-	-	-	-	-	20	40	60
Di – Calcium Phosphate	136	116	96	136	116	96	136	116	96
PvpK30	10	10	10	10	10	10	10	10	10
Talc	2	2	2	2	2	2	2	2	2
Magnesium stearate	2	2	2	2	2	2	2	2	2
Total weight	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**

VI. EVALUATION OF THE PREPARED FORMULATION FOR PHYSICO-CHEMICAL CHARACTERISTIC

All prepared matrix tablets were evaluated for the following parameters.

1) Shape of Tablets: - Tablets were examined under the magnifying lens for the shape of the tablet.

2) Tablet Dimensions: - Thickness and diameter were measured using a calibrated vernier caliper. Three tablets of each formulation were picked randomly and thickness was measured individually.

3) Weight variation: - The causes for weight variation can be divided into granulation and mechanical problems. If the granule size is large, the dies will not be uniformly filled. Similarly mechanical problems can be traced of lower punches of non-uniform length.

Method: - Uncoated tablets complies this test. The average weight is determined by weighing 20 tablets. Not more than two tablets deviate from the average weight by a percentage greater than that given and no tablet deviates by more than double that percentage. Weight variation tolerances for uncoated tablets.

Average Weight of Tablets (mg)	Maximum Difference Allowed (%)
130 or less	10
130-324	7.5
More than 324	5

4) Hardness: - Hardness was measured using Monsanto Hardness tester that measures the pressure required to break diametrically placed matrix tablets by applying pressure with coiled spring.

5) Friability: - The friability of tablets was determined by using Roche friabilator. It is expressed in percentage (%). 6 tablets were initially weighed (Winitial) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (Wfinal). The % friability was then calculated by- %F = 100 (1-W0/W) % Friability of tablets less than 1% was considered acceptable.

6) Drug Content: - The drug content, 1 tablet was crushed and powder containing 100 mg of Aceclofenac was dissolved in 100 ml of 0.1N HCl. The solution was passed through a whatmann (No. 1) filter and analysed spectrophotometrically at 275 nm after sufficient with 0.1N HCl.

7) Swelling Study: The swelling behaviour of a dosage form was measured by studying its weight gain or water uptake. The dimensional changes could be measured in terms of the increase in tablet diameter and/or thickness over time. Water uptake was measured in terms of percent weight gain, as given by the equation.

$$WU = \frac{(Wt - W0) \times 100}{W0}$$

Where,

Wt = Weight of dosage form at time t.

W0 = Initial weight of dosage form

VII. IN-VITRO DRUG RELEASE STUDIES USING 0.1N HCL AND PHOSPHATE BUFFER pH 6.8

For the present work in-vitro dissolution studies were carried out in simulated G.I fluid (0.1N HCl & phosphate buffer of pH 6.8 using dissolution test apparatus USP XXIV rotating basket assembly.

Determination of Dissolution Pattern: - Freshly prepared test media of 900 ml was placed in dissolution vessels of dissolution test apparatus USP XXIV model. Samples of the matrix tablet of Aceclofenac (after weighing) was placed in basket by holding it above the solution layer immediately, basket was immersed in dissolution media and maintained at 37.5 ±10C and was rotated at the speed of 50 rpm. 5 ml of samples were withdrawn at fixed time intervals, and this was immediately replaced with same volume of test media.

The samples withdrawn were filtered and estimated spectrophotometrically at 275 nm. Cumulative amount of the drug release at each interval was calculated by using standard graph of Aceclofenac.

Dissolution studies were performed for all formulations. The mean values and standard deviations were calculated.

Dissolution Test Apparatus USP XXIV Model

VIII) Data Analysis (Curve Fitting Analysis)

To analyse the mechanism of the drug release rate kinetics of the dosage form, the data obtained were graphed as:

1) Cumulative percentage drug released Vs Time (In-Vitro drug release plots)
2) Cumulative percentage drug released Vs Square root of time (Higuchi's plots)
3) Log cumulative percentage drug remaining Vs Time (First order plots)
4) Log percentage drug released Vs Log time (Peppas plots)

• **Higuchi release model**: - To study the Higuchi release kinetics, the release rate data were fitted to the following equation.

$F = K .t1/2$

Where,

'F' is the amount of drug release,

'K' is the release rate constant, and

't' is the release time.

When the data is plotted as accumulative drug released versus square root of time, yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to 'K'.

• **Korsmeyer and Peppas release model:** - The release rate data were fitted to the following equation,

$Mt /M\infty = K. tn$

Where,

$Mt /M\infty$ is the fraction of drug release,

'K' is the release constant,

't' is the release time, and

'n' is the diffusional exponent for the drug release that is dependent on the shape of the matrix dosage form.

When the data is plotted as Log of drug released versus Log time, yields a straight line with a slope equal to 'n' and the 'K' can be obtained from Y- intercept. For non-Fickian release the 'n' values falls between 0.5 and 1.0, while for Fickian (case I) diffusion n=0.5 and zero order release (case II transport) n=1.0.

• **Zero order release rate kinetics**: - To study the zero–order release kinetics the release rate data are fitted to the following equation.

$F= Kt$

Where

'F' is the fraction of drug release,

'K' is the release rate constant and

't' is the release time.

When the data is plotted as cumulative percent drug release versus time, if the plot is linear then the data obeys zero-order release kinetics, with a slope equal to K.

• **First Order Kinetics**: A first order release would be predicated by the following equation.

Kt Log C = log Co – 2.30

Where;

C = Amount of drug remained at time 't'

Co = Initial amount of drug

K = First order rate constant (hr-1)

When the data is plotted as cumulative percent drug remaining versus time yields a straight line, indicating that the release follows First-order kinetics. The constant 'k' can be obtained by multiplying 2.303 with slope values.

IX. Stability Studies

1. Introduction:- In any rational drug design or evaluation of dosage forms for drugs ,the stability of the active component must be a major criteria in determining their acceptance or rejection Stability of a drug can be defined as the time form the day eif manufacturing and the packaging of the formulation, until it's chemical or biological activity is not less than a predetermined level of labeled potency and it's physical characteristics have not changed appreciably or deleteriously.

2) Objective of the study

The purpose of the stability testing is to provide evidence on how the quality of a drug substance varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf- lives.

The international conference on harmonization (ICH) Guidelines titled "Stability Testing of new drug substance and products"(QIA) describes the stability test requirements for drug registration application in the European u Union, Japan and the United States of America.

ICH specifies the length of study and storage conditions.

Long term testing: 25°C±2°C/60% RH ± 5% for 12 months.

Accelerated testing: 40°C±2°C /75% RH ±5% for 6 months.

Stability studies were carried out at 25°C/60% RH and 40°C/75% RH for the selected formulation for the period of 6 months.

- **METHOD**

The selected formulation was packed in amber-coloured bottles, which were tightly plugged with cotton and capped. They were then stored at 25°C/60 % RH AND 40°C/75% RH for 6 months and evaluated for their physical appearance, drug content and drug excipients compatibility at specified internals of time.

RESULT AND DISCUSSION

I. CALIBRATION CURVE

Standard Calibration Curve of Aceclofenac in pH 1.2

Standard calibration curve of Aceclofenac was drawn by plotting absorbance v/s concentration. The absorbance values are tabulated in Table 2. Standard calibration curve of Aceclofenac in the Beer's range between 0-20 µg/ml is shown in.

SL. No.	Concentration (µg/ml)	Absorbance*
1	0	0.075
2	4	0.124
3	8	0.186
4	12	0.248
5	16	0.305
6	20	0.075

Fig. 4. Table No. 4. Calibration data of Aceclofenac in pH 1.2 at 266 nm.

*Average of 3 determinations

The linear regression analysis for standard curve in pH 1.2

The linear regression analysis was done on absorbance data points. The results are as follows**:**

The Slope = 0.0124

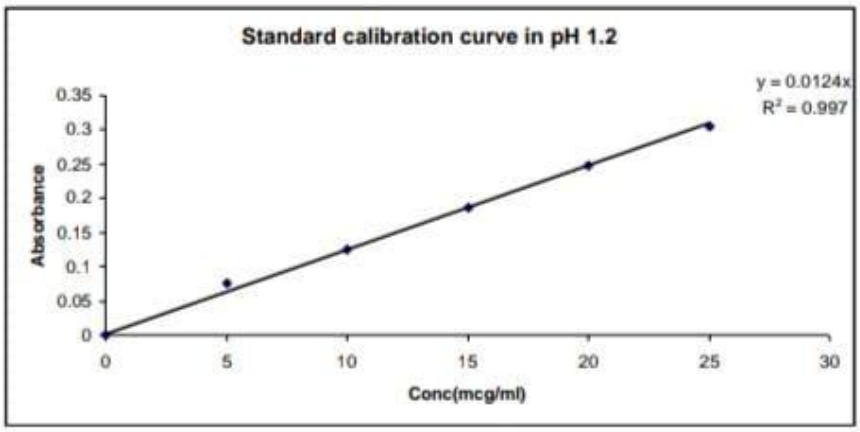
The intercept = 0.00

The correlation coefficient = 0.997

A straight-line equation (y = mx + c) was generated to facilitate the calculation for amount of drug. The equation is as follows.

Absorbance = 0.0124 x Concentration

Standard calibration curve for Aceclofenac in pH 1.2 at 266nm



Standard Calibration Curve of Aceclofenac in phosphate buffer pH 6.8

Standard calibration curve of Aceclofenac was drawn by plotting absorbance v/s concentration. The absorbance values are tabulated in Table 3. Standard calibration curve of Aceclofenac in the Beer's range between 0-20 µg/ml is shown in Fig.5.

Table No. 5: Calibration data of Aceclofenac in phosphate buffer pH 6.8 at 266nm.

SL. No.	Concentration (µg/ml)	Absorbance*
1	0	0
2	4	0.121
3	8	0.256
4	12	0.383
5	16	0.536
6	20	0.612

*Average of 3 determinations

The linear regression analysis for standard curve in phosphate buffer pH 6.8

The linear regression analysis was done on absorbance data points. The results are as follows.

The Slope = 0.0318

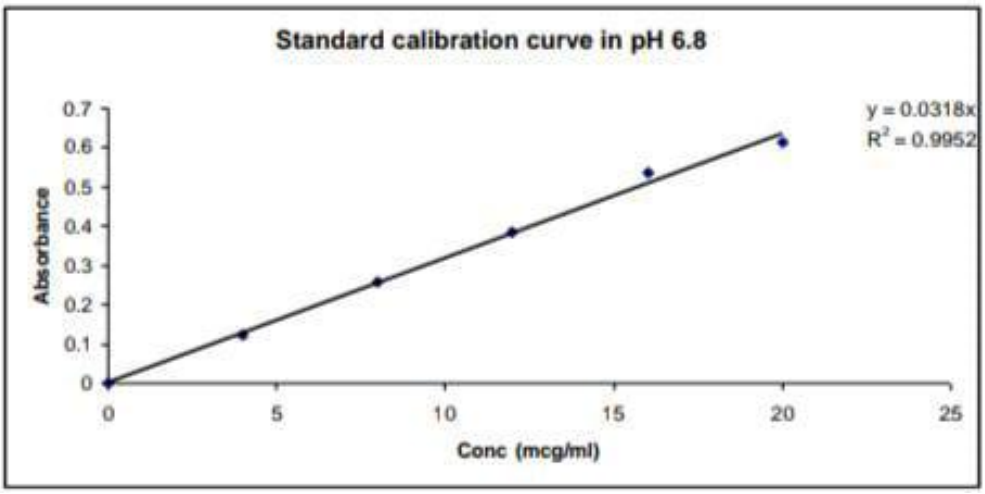
The intercept = 0 .00

The correlation coefficient = 0.9952

A straight-line equation (y = mx + c) was generated to facilitate the calculation for amount of drug. The equation is as follows.

Absorbance = 0.0318x Concentration

Standard calibration curve for Aceclofenac in phosphate buffer pH 6.8 at 266 nm



III. EVALUATION FOR PRE-COMPRESSION PARAMETER

The blended granules of different formulation were evaluated for angle of repose, loose bulk density, tapped bulk density, compressibility index and Hausner ratio. The results of these evaluations were as follows.

Angle of repose

Angle of repose ranged from 21.52° ± 1.03 to 24.92° ± 0.78. The results were found to be below 25o and hence the blend was found to have excellent flowability.

Loose bulk density and tapped density

Bulk and tapped densities are used for the measurement of Compressibility index. The LBD and TBD ranged from 0.455 ± 0.00 to 0.500 ± 0.00 g/ml; and 0.526 ± 0.00 to 0.588 ± 0.00 g/ml respectively.

Flow properties of granules

Formulation code	Angle of repose (°)*	Loose bulk density (g/ml)*	Tapped bulk density (g/ml)*	Hausner's ratio*	Carr's index (%)*
F1	21.52±1.03	0.476±0.00	0.556±0.00	1.17±0.00	14.286±0.00
F2	22.34±0.49	0.500±0.00	0.588±0.00	1.18±0.00	15.000±0.00
F3	24.72±0.51	0.455±0.00	0.526±0.00	1.16±0.00	13.636±0.00
F4	24.92±0.78	0.500±0.00	0.588±0.00	1.18±0.00	15.000±0.00
F5	22.27±2.30	0.476±0.00	0.556±0.00	1.17±0.00	14.286±0.00
F6	24.04±1.62	0.476±0.00	0.556±0.00	1.17±0.00	14.286±0.00
F7	24.72±0.51	0.500±0.00	0.588±0.00	1.18±0.00	15.000±0.00
F8	24.04±1.62	0.455±0.00	0.526±0.00	1.16±0.00	13.636±0.00
F9	22.42±2.40	0.500±0.00	0.588±0.00	1.18±0.00	15.000±0.00

Compressibility index (Carr's index)

The compressibility index (%) ranged from 13.636 ± 0.00 to 15.000 ± 0.00 (Table 8.9). The blend was found to have excellent flowing property as the result were found to be below 15%.

Hausner ratio

The Hausner ratio ranged from 1.16 ± 0.00 to 1.18 ± 0.00, (Table 8.9). The result indicates the free-flowing properties of the granules.

Evaluation of sustained release matrix tablets

Appearance

The tablets were observed visually and did not show any defect such as capping, chipping and lamination.

Physical characteristics

The physical characteristic of Aceclofenac sustained release matrix tablets (F1 to F9) such as thickness, diameter, hardness, friability, weight variation and drug content were determined and results of the formulations (F1 to F9) found to be within the limits specified in official books.

Dimension (Thickness and Diameter)

Thickness and diameter specifications may be set on an individual product basis. Excessive variation in the tablet thickness and diameter can result in problems with packaging as well as consumer acceptance. The size (diameter) of the tablets of all formulations was found to be 4.39±0.06 to 4.48±0.08 mm.

Tablet Hardness

A difference in tablet hardness reflects difference in tablet density and porosity. In which turn are supposed to result in different release pattern of the drug by affecting the rate of penetration of dissolution fluid at the surface of the tablet and formation of gel barrier. The hardness of tablets was found to be in the range of 7.65±0.58 kg/cm2 to 8.05±0.50kg/cm2. This indicates good tablet strength.

Percent Friability

Percentage friability of all the formulations was found between 0.043 to 0.100%. This indicated good handling property of the prepared SR tablet.

Weight Variation

A tablet is designed to contain a specific amount of drug. When the average mass of the tablet is 350 mg the pharmacopoeial limit for percentage deviation is ± 5 %. The percentage deviation from average tablet weight for all the tablet was found tobe within the specified limits and hence all formulations complied with the test for weight variation according to the pharmacopeial specifications.

Physico-Chemical Characterization of Aceclofenac SR

Tablets

F. Code	Thickness (mm)*	Hardness (kg/cm^2)*	Friability (%)	Weight variation (mg)	Drug content (%w/w)*
F1	4.42±0.06	7.80±0.59	0.057	351.40±2.26	99.48±0.45
F2	4.41±0.04	7.75±0.63	0.071	352.15±2.92	99.22±0.56
F3	4.42±0.07	7.70±0.54	0.085	350.10±2.77	99.61±0.69
F4	4.48±0.08	8.05±0.50	0.100	352.05±2.39	100.21±1.09
F5	4.39±0.06	7.85±0.34	0.057	353.05±2.84	99.78±1.05
F6	4.41±0.02	7.65±0.58	0.071	351.55±3.02	99.83±1.41
F7	4.44±0.08	7.80±0.48	0.071	352.60±2.39	100.61±0.35
F8	4.43±0.07	7.95±0.55	0.043	352.75±2.92	99.88±0.87
F9	4.46±0.02	7.85±0.41	0.043	351.75±2.95	98.90±0.65

*All the values are expressed as mean± SE, n=3

Drug content of Aceclofenac

The content of active ingredients in the formulation was found to be between 98.90±0.65 to 100.61±0.35 % w/w, which is within the specified limit as per Indian Pharmacopoeia 1996 (i.e. 90-110% w/w).

In-Vitro Dissolution Studies

In-vitro release drug profile of aceclofenac formulation F1 (Rosin oil as Resin)

Time (hours)	Percentage drug released*	Amount (mg)	% DE	MDT
0	0.00±0.00	0.00	0.00	0.00
1	08.07±1.03	16.14	4.00	0.50
2	15.13±0.90	30.26	7.75	0.97
3	27.85±0.57	55.70	12.27	1.67
4	43.80±1.59	87.60	18.14	2.35
5	58.16±0.82	116.32	24.71	2.87
6	74.15±1.64	148.30	31.61	3.44
7	88.21±1.20	176.42	38.69	3.93
8	99.25±0.77	198.50	45.59	4.34

In-vitro release drug profile of aceclofenac formulation F2(Rosin oil as Resin)

Time (hours)	Percentage drug released*	Amount (mg)	% DE	MDT
0	0.00±0.00	0.00	0.00	0.00
1	07.19±0.74	14.37	3.54	0.50
2	14.64±1.06	29.28	7.21	1.02
3	25.25±0.33	50.50	11.36	1.62
4	40.07±1.07	80.13	16.54	2.33
5	55.89±0.69	111.78	22.68	2.93
6	71.04±1.29	142.09	29.39	3.52
7	85.06±2.12	170.13	36.36	4.02
8	96.61±0.98	193.21	43.16	4.41

*All values are expressed as mean ±SD, n=3.

In-vitro release drug profile of aceclofenac formulation F3 (Rosin oil as Resin)

Time (hours)	Percentage drug released*	Amount (mg)	% DE	MDT
0	0.00±0.00	0.00	0.00	0.00
1	06.21±0.61	12.41	3.09	0.50
2	12.19±0.90	24.38	6.38	1.03
3	24.12±0.38	48.23	10.34	1.67
4	39.44±0.63	78.87	15.55	2.40
5	53.63±0.44	107.25	21.67	2.97
6	70.67±1.42	141.33	28.37	3.58
7	82.80±0.88	165.60	35.25	4.01
8	92.41±0.57	184.82	41.74	4.36

*All values are expressed as mean ±SD, n=3.

In-vitro release drug profile of aceclofenac formulation F4 (HPMC)

Time (hours)	Percentage drug released*	Amount (mg)	% DE	MDT
0	0.00±0.00	0.00	0.00	0.00
1	09.25±1.51	18.49	4.61	0.50
2	16.11±1.06	32.22	8.66	0.93
3	25.84±0.38	51.67	12.71	1.50
4	41.03±0.44	82.06	17.81	2.25
5	54.63±0.38	109.27	23.75	2.81
6	70.04±0.57	140.07	30.21	3.44
7	86.41±0.51	172.81	37.15	4.00
8	96.82±0.57	193.63	44.01	4.38

*All values are expressed as mean ±SD, n=3.

In-vitro release drug profile of formulation F5

Time (hours)	Percentage drug released*	Amount (mg)	% DE	MDT
0	0.00±0.00	0.00	0.00	0.00
1	07.48±1.03	14.96	3.49	0.50
2	14.15±1.19	28.30	7.04	1.01
3	23.61±0.25	47.22	10.92	1.59
4	39.44±0.72	78.87	15.98	2.37
5	52.79±0.38	105.57	21.97	2.91
6	69.83±0.58	139.66	28.53	3.55
7	84.64±0.32	169.29	35.52	4.07
8	92.28±0.82	184.57	42.18	4.36

All values are expressed as mean ±SD, n=3

In-vitro release drug profile of formulation F6

Time (hours)	Percentage drug released*	Amount (mg)	% DE	MDT
0	0.00±0.00	0.00	0.00	0.00
1	06.11±0.88	12.21	3.04	0.50
2	13.07±1.19	26.14	6.30	1.03
3	22.77±0.63	45.54	10.09	1.64
4	38.89±0.44	77.78	15.17	2.43
5	47.33±0.51	94.65	20.72	2.80
6	66.05±0.50	132.10	26.70	3.58
7	81.24±0.63	162.49	33.43	4.13
8	89.05±0.51	178.10	39.94	4.43

*All values are expressed as mean ±SD, n=3

In-vitro release drug profile of formulation F7

Time (hours)	Percentage drug released*	Amount (mg)	% DE	MDT
0	0.00±0.00	0.00	0.00	0.00
1	08.17±0.88	16.33	4.05	0.50
2	15.03±0.90	30.07	7.82	0.96
3	24.29±0.38	48.57	11.80	1.55
4	37.76±0.63	75.51	16.58	2.23
5	49.47±0.51	98.94	21.94	2.78
6	62.65±0.83	125.30	27.62	3.36
7	78.77±0.45	157.54	33.79	4.01
8	91.49±0.50	182.97	40.24	4.49

*All values are expressed as mean ±SD, n=3.

In-vitro release drug profile of formulation F8

Time (hours)	Percentage drug released*	Amount (mg)	% DE	MDT
0	0.00±0.00	0.00	0.00	0.00
1	06.50±0.90	13.00	3.24	0.50
2	13.37±1.03	26.73	6.58	1.02
3	21.60±0.83	43.19	10.24	1.59
4	31.38±0.76	62.75	14.28	2.16
5	46.74±0.32	93.48	19.18	2.94
6	58.45±0.84	116.90	24.73	3.46
7	75.03±0.57	150.06	30.74	4.14
8	87.67±0.44	175.33	37.10	4.63

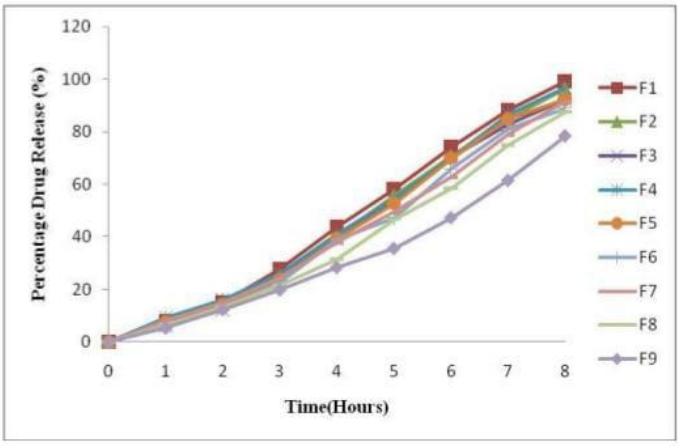
*All values are expressed as mean ±SD, n=3.

In-vitro release drug profile of formulation F9

Time (hours)	Percentage drug released*	Amount (mg)	% DE	MDT
0	0.00±0.00	0.00	0.00	0.00
1	05.33±0.74	10.64	2.63	0.50
2	12.29±1.18	24.57	5.72	1.07
3	19.79±1.27	39.58	9.20	1.62
4	28.40±0.58	56.79	12.90	2.16
5	35.58±0.38	71.15	16.65	2.64
6	47.25±0.69	94.49	20.73	3.36
7	61.43±0.51	122.87	25.52	4.09
8	78.31±0.38	156.61	31.08	4.84

*All values are expressed as mean ±SD, n=3.

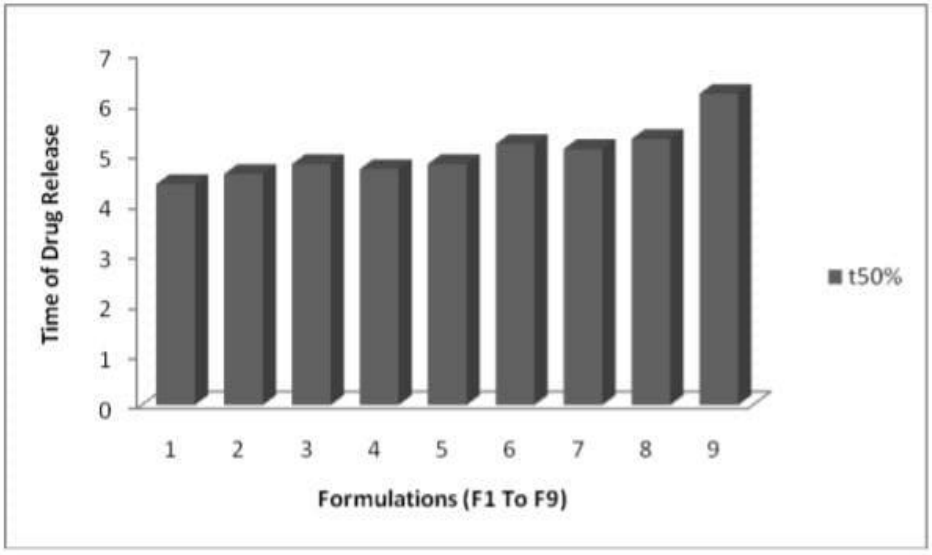
Comparative study of Cumulative In-vitro % Drug release curve of formulation F1 to F9.



Time of in vitro drug released for aceclofenac t50% values of F1 to F9.

Formulation code	Time of drug released (hours) ($t_{50\%}$)
F1	4.4
F2	4.6
F3	4.8
F4	4.7
F5	4.8
F6	5.2
F7	5.1
F8	5.3
F9	6.2

In vitro drug release for t50% values of F1 to F9.



Aceclofenac is a water insoluble drug; its release from the matrix is largely dependent on the polymer swelling, drug diffusion and matrix erosion. The concentration of polymer in the sustained release layer was a key factor in controlling the drug release. Various sustained release formulations were formulated with HPMC K15M, Carboxy methyl cellulose, Xanthan gum polymer alone; polyvinyl pyrrolidone as binder and microcrystalline cellulose was used as diluents.

In vitro release studies of formulations F1, F2 and F3 prepared by HPMC K15M with concentrations of 20%, 30% & 40% respectively. The drug released from formulation F1 to F3 were found to be 99.25 ± 0.77, 96.61 ± 0.98, and 92.41 ± 0.57% for aceclofenac respectively.

In vitro release studies of formulations F4, F5 and F6 prepared by Carboxy methyl cellulose with concentrations of 20%, 30% & 40% respectively.

The drug released from formulation F4 to F6 were found to be 96.82 ± 0.57, 92.28 ± 0.82, and 89.05 ± 0.51% for aceclofenac respectively. In vitro release studies of formulations F7, F8 and F9 prepared by Xanthan gum with concentrations of 20%, 30% & 40% respectively. The drug released from formulation F7 to F9 were found to be 91.49 ± 0.50, 87.67 ± 0.44, and 78.31 ± 0.38% for aceclofenac respectively. The release rate of F9 was found to be higher when compared to other formulations this is due to increase in the concentration of polymer (Xanthan gum). In vitro release studies of formulations F3, F6 and F9 prepared by with

concentrations of 30% HPMC K15M, Carboxy methyl cellulose and Xanthan gum shows sustained release effects. The result of t50% was shown in Table 8.20 and Figure 8.21, according to the time of drug release values of t50%, the formulation F9 was selected as the best formulation. The overall release rate of aceclofenac from carboxy methyl cellulose and HPMC K15M matrices are significantly higher than that from xanthan gum matrices; were shown in Figure 8.20 and which is confirmed by smaller MDT (4.38, 4.36, 4.43 and 4.34, 4.41, 4.36) respectively for carboxy methyl cellulose and HPMC K15M and higher MDT for xanthan gum matrices. These results are indicating that xanthan gum has higher drug retarding ability for long duration than carboxy methyl cellulose and HPMC K15M. Xanthan gum also showed the least %DE while carboxy methyl cellulose and HPMC K15M also showed the greatest %DE among the tablets with just one of the retarding polymers. Based on the in-vitro drug release data, MDT, %DE and t50%, the formulation F9 was selected as the optimized formulation. Hence the formulation F9 was selected for the further stability study.

Data Analysis (Curve Fitting Analysis)

Korsemeyer-Peppas model indicates that the release mechanism is not well known or more than one type of release phenomena could be involved. The „n‟ value could be used to characterize different release mechanisms as.

Different drug release mechanisms of kinetic model.

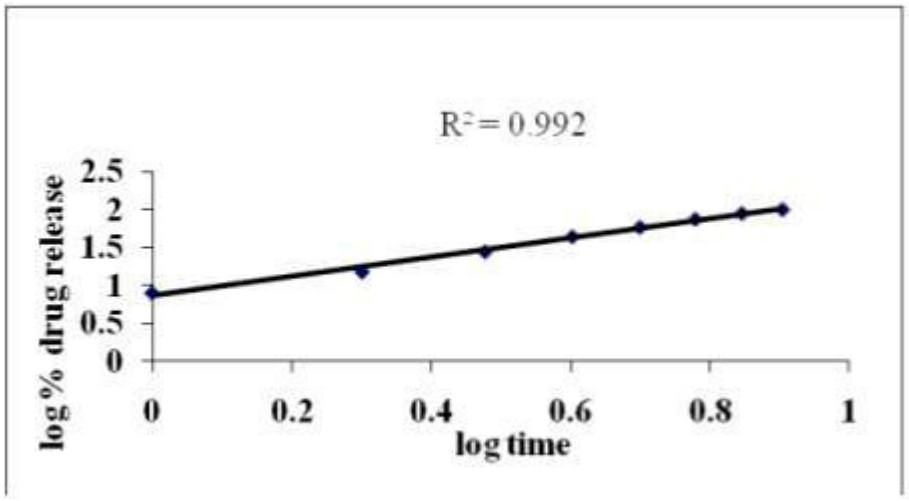
Release exponent (n)	Drug Transport Mechanism
0.5	Fickian diffusion
0.45< n=0.89	Non- Fickian diffusion
0.89	Case II transport
Higher than 0.89	Super case II transport

It ranges between 0.5 to 1, so it was concluded that the drug release occurred via non-fickian diffusion, which shows that the release from initially dry, hydrophilic glassy polymers that swell when added to water and become rubbery show anomalous diffusion as a result of the rearrangement of macro molecular chains.

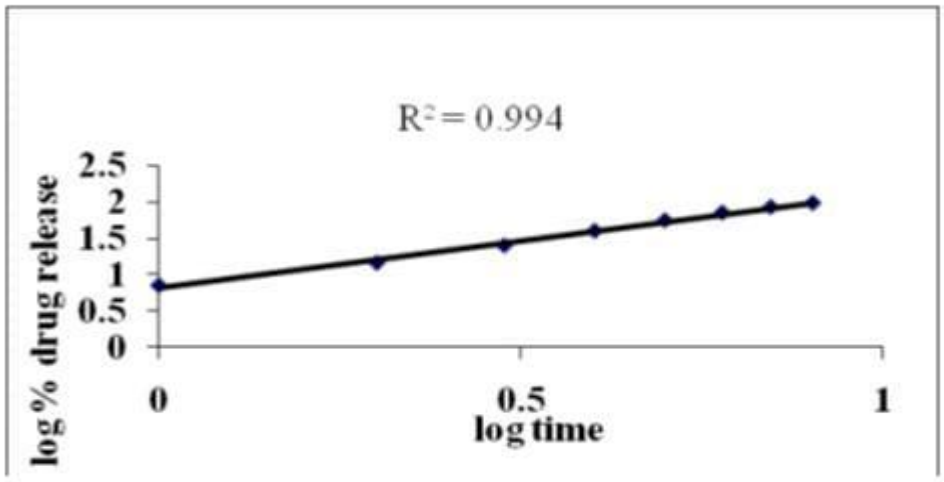
In-vitro Release Kinetic models for Aceclofenac sustained release Matrix tablets of formulations.

(F1 to F9)

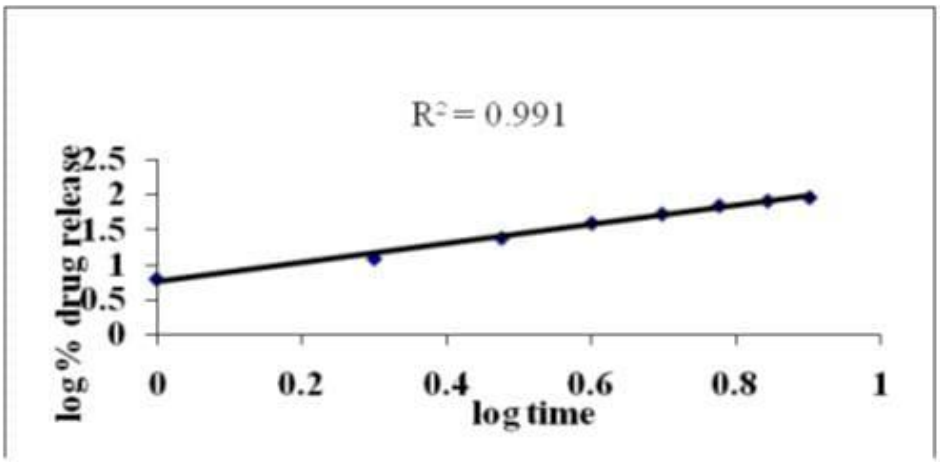
F. Code	Zero order	First order	Higuchi	Korsemeyer- Peppas		Best fit model
	R^2	R^2	R^2	R^2	Slope(n)	
F1	0.989	0.623	0.857	0.992	1.268	Peppas
F2	0.986	0.725	0.846	0.994	1.302	Peppas
F3	0.984	0.805	0.842	0.991	1.376	Peppas
F4	0.986	0.719	0.850	0.987	1.186	Peppas
F5	0.983	0.803	0.843	0.989	1.279	Peppas
F6	0.981	0.817	0.838	0.994	1.342	Peppas
F7	0.986	0.778	0.846	0.991	1.197	Peppas
F8	0.977	0.792	0.825	0.993	1.279	Peppas
F9	0.967	0.803	0.813	0.995	1.262	Peppas



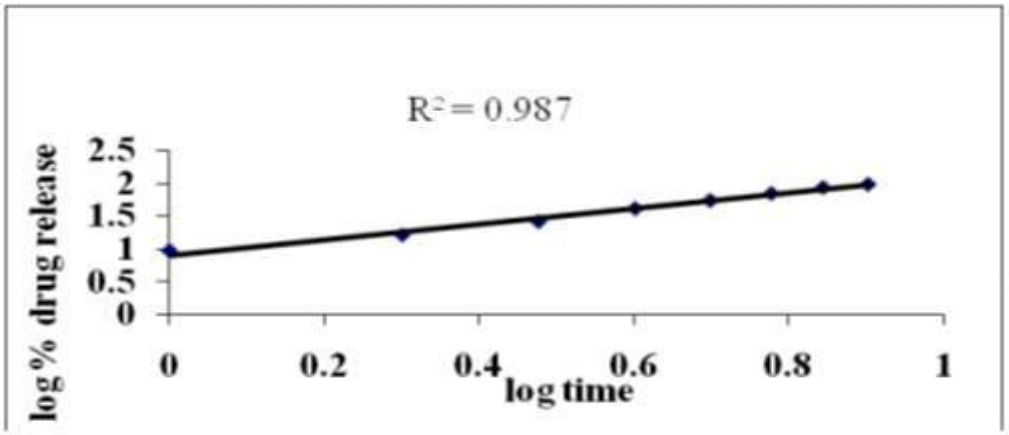
Best fit model (Peppas) of formulation F1



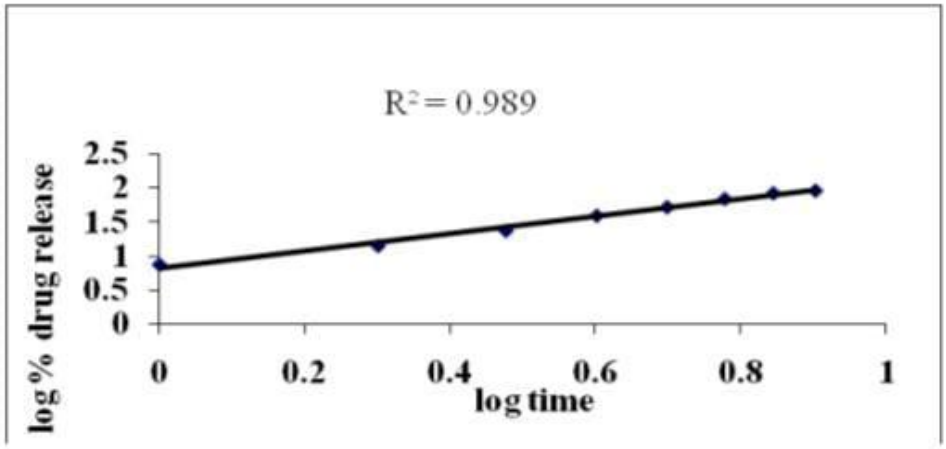
Best fit model (Peppas) of formulation F2



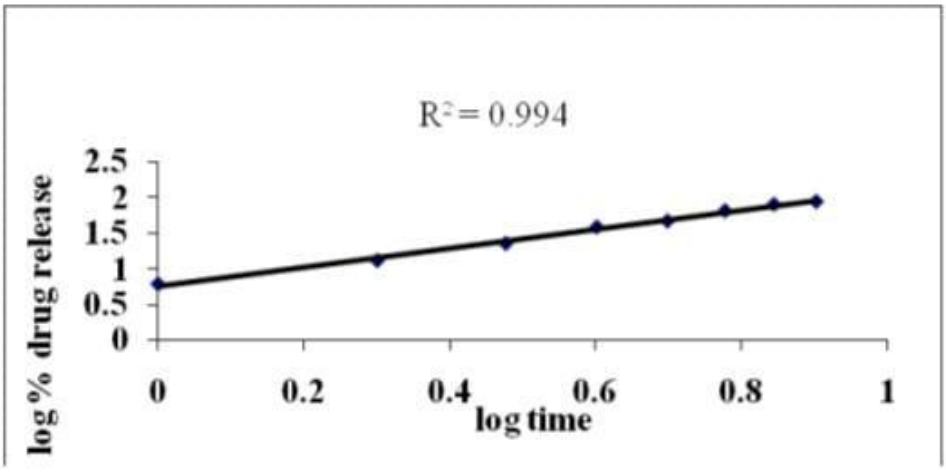
Best fit model (Peppas) of formulation F3



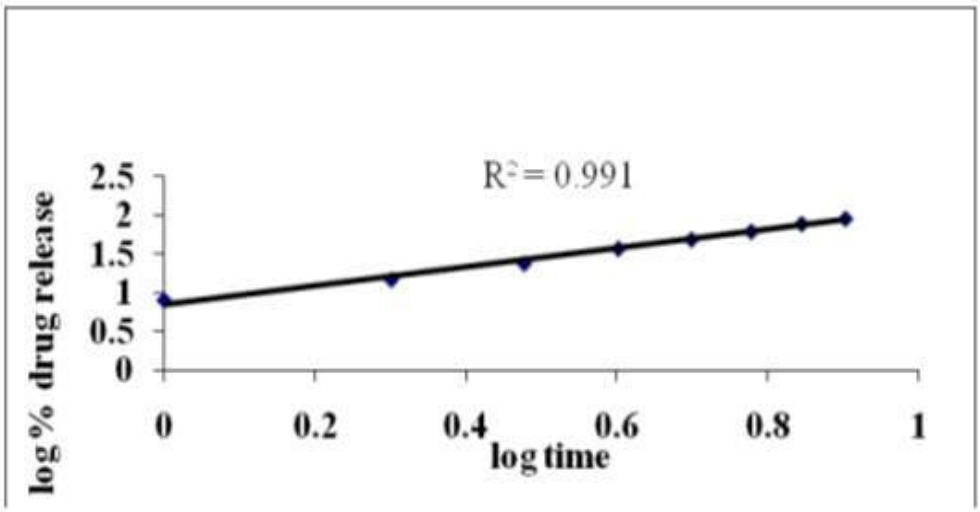
Best fit model (Peppas) of formulation F4



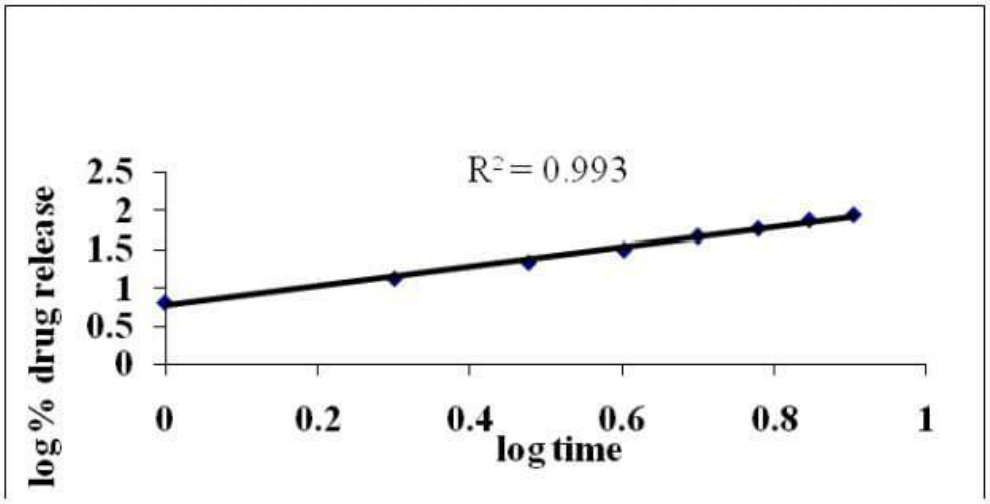
Best fit model (Peppas) of formulation F5



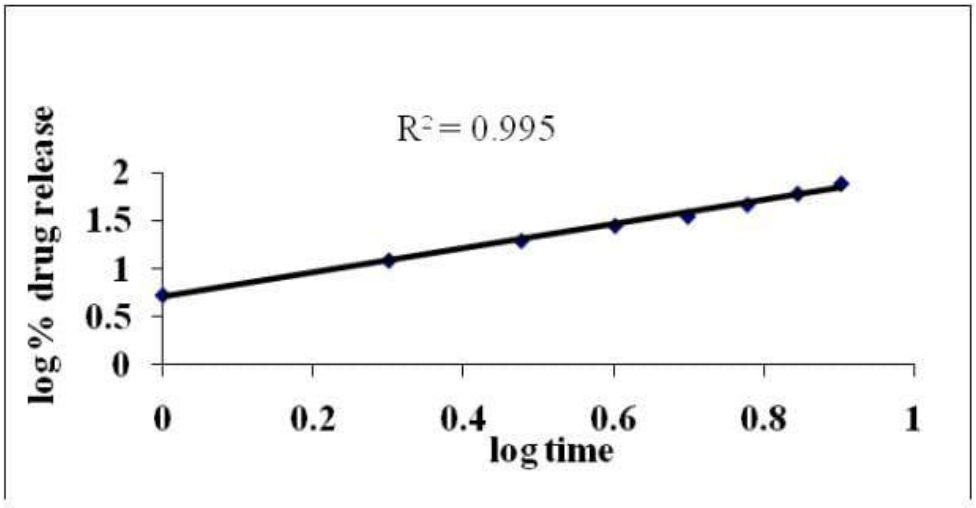
Best fit model (Peppas) of formulation F6



Best fit model (Peppas) of formulation F7



Best fit model (Peppas) of formulation F8



Best fit model (Peppas) of formulation F9

To know the kinetics of the best formulations, the release data was treated according to different models. Drug release data of tablets was fitted in peppas equation and found release mechanism to be diffusion.

Stability Study

After storage the formulation was analysed for various physical parameters, results are showed in Table.

Stability date of F6 Formulation

Time in Months	Formulation F6 Stored at 40^0C/75%RH	
	Physical appearance	% Drug Content
1	+++	98.75
2	+++	98.36
3	++	97.99

+++= same as on Zero Day, ++=Slight change in colour

VI) In-vitro Dissolution Study

The in-vitro drug release of the entire matrix tablets were carried in 0.1N HCl for first 2 hrs followed by phosphate buffer pH 6.8 from 2 to 24 hrs by USP XXIV type-II apparatus and the values are shown. The plot of % Cumulative drug release v/s time (hrs) was plotted and depicted as shown. From the in-vitro dissolution data, it was found that the drug release from formulations containing pure drug (PD) without polymer is 97.28% in 3 hrs, Xanthan gum 30% (F) 98.94% in 24 hrs. From the results it was observed that increasing the amount of gum in the formulations, resulted in slower rate and decreased amount of drug release from the tablet. This slow release is because of the formation of more thick gel like structure around the matrix HPMC & Rosin oil as Resin that delays release from tablet matrix. The maximum drug release was found to be 98.94%. This indicates that the minimum quantity of maximum quantity of HPMC & Rosin oil as Resin (30%) required to prepare the sustain release matrix tablets of Aceclofenac.

VII) Curve Fitting Analysis.

The kinetic treatment reflected that release data of HPMC & Rosin oil as Resin formulation showed higher r2 values for Zero order plot indicating that release of drug follows zero order kinetic, further Korsmeyer and peppas equation resulted into the value of n between 0.5 and 1 with all the tablets indicating non-fickian diffusion as the release mechanism.

Stability studies

The selected formulation F6& F7 were evaluated for stability studies which were stored at 400 C at 75% RH tested for 3months and were analyses for their drug content at the monthly interval. The residual drug contents of formulation were found to be within the permissible

limits and the results of 3 months duration are shown in the table no 00 & 00 which was estimated by seeing drug content uniformity.

CONCLUSION

In present investigation an attempt has been made to design and develop Aceclofenac sustained release matrix tablets using, Rosin oil as resin and HPMC as release retarding polymers. Aceclofenac is widely used as a centrally acting muscle relaxant; therefore, have been selected to prepare sustained release dosage forms. An ideal matrix formulation prepared with different polymers and diluents concentrations should release its content in a sustained profile a reasonable length of time and preferably with Korsmeyer-peppas kinetic. The active pharmaceutical ingredient Aceclofenac was evaluated for its physical characteristics, analytical profiles and drug polymer compatibility study. The granules were prepared by wet granulation method. The prepared granules were evaluated for Angle of repose, Bulk density, Tapped density and Carr‟s index. The results obtained were found to be satisfactory and within the specified limits. After compression parameters like Thickness, Hardness, Weight variation, Friability, content uniformity and In-Vitro release studies were evaluated. Result of the present study demonstrated that hydrophilic polymers could be successfully employed for formulating sustained release matrix tablets of Aceclofenac. The investigated sustained release matrix tablet was capable of maintaining constant plasma concentration upto 8 hours. This can be expected to reduce the frequency of administration and decrease the dose dependent side effects.

The efficacy and safety of Aceclofenac tablet dosage form are expected to offer optimum therapeutic efficacy and improved patient compliance. In the present study the effect of types and concentration of polymer were studied on In-Vitro drug release. It shows that increase in concentration of polymer results in the sustained drug release for 8 hours. The study has revealed that by increasing concentration of polymer, release rate of drug was retarded and results confirmed that the release rate from hydrophilic matrix tablets depends on type and concentration of polymer. In present studies, matrix formulation containing Rosin oil as resin 40% is probably showing release up to 78% within 8 hrs. According to stability study it was found that there was no significant change in hardness, drug content and in vitro dissolution of optimized formulation (F9). In present investigation an attempt has been made to design and develop some aceclofenac matrix tablets using Rosin oil as resin, HPMC etc, as release

retarding polymers. Aceclofenac Is a centrally acting muscle relaxant drug substance have been selected to prepare dosage forms.

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