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FORMULATION DEVELOPMENT AND EVALUATION OF SUSTAINED RELEASE TABLETS OF ACECLOFENAC

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ABSTRACT

The study was undertaken with an aim to formulate develop and evaluation of Aceclofenac sustained release tablets using different polymers(hpmc, carbomer) as release retarding agent. Preformulation study of Aceclofenac was done initially and results directed for the further course of formulation. Based on preformulation studies different batches were prepared using selected excipeints. Granules were evaluated for tests LOD, Bulk density, tapped density, compressibility index, Hausner ratio before being punched as tablets. Tablets were tested for weight variation, thickness, hardness and friability as per official procedure. Dissolution of batch T-8 was carried out in 6.8 pH media and compared with marketed preparation. Based on dissolution tests and F-2 values in pH 6.8 phosphate buffer as release medium, it was concluded that T-8 satisfactory performs in the same manner as that of marketed formulation. F-2 (similarity factor) value of T-6 was found to be 73.90.

Keywords: Aceclofenac, Granules, Weight variation, Hardness.

INTRODUCTION[1-7]

For many decades treatment of an acute disease or a chronic illness has been mostly accomplished by delivery of drugs to patients using various pharmaceutical dosage forms, including tablets, capsules, pills, suppositories, creams, ointments, liquids, aerosols, and

injectables, as drug carriers. This type of drug delivery system is known to provide a prompt release of drug or immediate release product. Such immediate release products result in relatively rapid drug absorption and onset of accompanying pharmacodynamic effects. An alternative to administering another dose is to use a dosage form that will provide sustained drug release, and therefore, maintain plasma drug concentrations, beyond what is typically seen using immediate release dosage forms. In recent years, various modified release and/ or the time for drug release The basic rationale of a sustained drug delivery system is to optimize the Biopharmaceutic, Pharmacokinetic and Pharmacodynamic 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.

1.1 Modified Release Dosage Form and Drug Delivery[3, 8]

Drug products designed to reduce the frequency of dosing by modifying the rate of drug absorption have been available for many years. Early modified release products were often intramuscular/subcutaneous injection of suspensions of insoluble drug complexes, e.g. Procaine penicillin, protamine zinc insulin, insulin zinc suspension or injections of the drug in oil, e.g. Fluphenazine decanoate. Advance in technology have resulted in novel modified release dosage form. In contrast to conventional (immediate release) forms, modified release products provide either delayed release or extended release of drug.

1.1.1 Sustained Release

The U.S. Food and Drug Administration (FDA) defines an “sustained release dosage form is one that allows a reduction in dosing frequency from that necessitated by a conventional dosage form, such as a solution or an immediate release dosage form”.

Sustained release tablets and capsules are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to take three or four times daily to achieve the same therapeutic effect.

1.1.2 Pharmacokinetic Simulation Of Sustained Release Products[8,3]: The plasma drug concentration profiles of many sustained release products fits an oral one compartment model assuming first order absorption and elimination. Compared to an immediate release product, the sustained release product typically shows a smaller absorption rate constant, because of the slower absorption of the sustained release product.

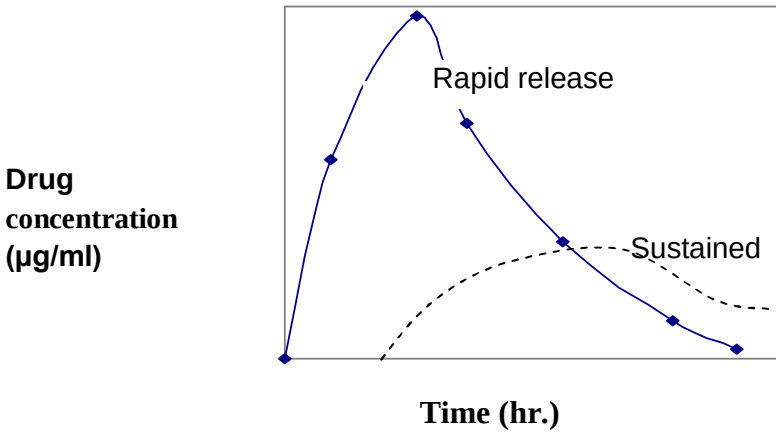


Fig 3. Plasma drug concentration of a SR and a regular release product.

1.1.3 Terminology And Sustained Release Concept[3,9-15]:

Over the years, many terms (and abbreviations), such as sustained release(SR), sustained action (SA), prolonged action (PA), controlled release (CD), extended release (ER), timed release (TR), and long acting (LA), have been used by manufactures to describe product types and features. These are terms used to identify drug delivery systems that are designed to active a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. In the case of injectable dosage form, this period may vary from days to months. Although these terms often have been used interchangeably, individual products bearing these descriptions may differ in design an performance and must be examined individually to as certain their respective features.

Sustained release

In case of sustained release (SR) dosage forms the release of the active agent, although, is lower than in the conventional formulations, however, it is still substantially affected by the external environments into which it is going to be released.

Controlled release

Controlled release (CR) systems provide drug release in an amount sufficient to maintain the therapeutic drug level over extended period of time, with the release profiles of predominantly controlled by the special technological construction and design of the system itself. The release of the active constituent is therefore, ideally independent of exterior factors.

Prolonged action

Prolonged or long action products are dosage forms containing chemically modified therapeutic substances in order to prolong biological half life

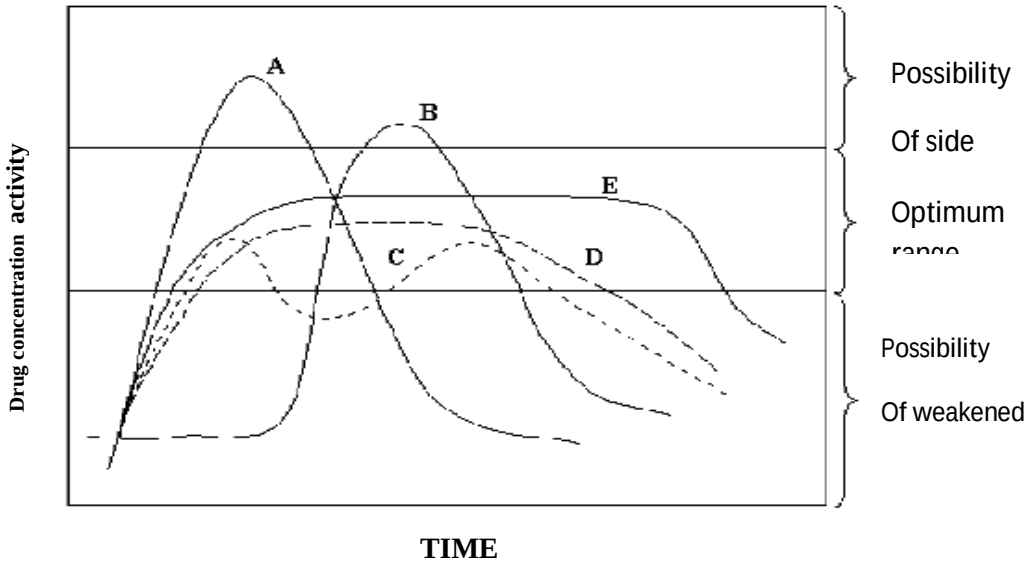


Fig. 6 : Relationship between drug concentration and time for Products Possessing Various Release Profiles

A -Immediate release B -Delayed action C - Repeat action D - Prolonged release

E - Controlled, sustained release

1.1.4 CLASSIFICATION[10]:

Modified Release dosage form may be classified as

A .Delayed release

B. Extended release

B.1: Sustained release

B.2: Controlled release

A. Delayed release: [3]

The drug is released at a later time after administration. The delayed action is achieved by the incorporation of a special coat, such as enteric coating, or other time barriers such as the formaldehyde treatment of soft and hard gelatin capsules. The purposes of such preparations are to prevent side effects related to the drug presence in the stomach, protect the drug from degradation in the highly acidic pH of the gastric fluid.

B. Extended release: B-1): Sustained Release System[13-17]:

The idealized objective points to the two aspects most important to drug delivery, namely, spatial placement relates to targeting a drug to a specified organ or tissue, while temporal delivery refers to controlling the rate of drug delivery to the target tissue. An appropriately designed sustained release drug delivery can be a major advance towards solving these two problems. The bulk of research has been directed at oral dosage forms that satisfy the temporal aspect of drug delivery, but many of the new approaches under investigation may allow for spatial placement as well.

ADVANTAGES OF SUSTAINED RELEASE DRUG DELIVERY:[17-21]

The improvement in drug delivery is represented by several potential advantages as below.

1. It improves patient compliance.
2. It employs lesser quantity of the drug.
3. It may improve the pathophysiology of the diseases.

(a) It minimizes or eliminates local side effects.
(b) It minimizes or eliminates systemic side effects.
(c) It obtains less potentiation or reduction in drug activity with chronic use.
(d) It minimizes drug accumulation with chronic dosing.

4. It improves the efficiency in treatment.

(a) It cures or controls the condition more promptly.
(b) It improves the control of condition i.e. reduces fluctuation in the drug level.
(c) It improves bioavailability of some drugs.
(d) Make use of special effects, e.g., sustained release aspirin for morning relief of arthritis by dosing before bedtime.

5. Economy:

(a) In comparison with conventional dosage forms the average cost of treatment over an extended period may be less.
(b) Economy also may results from a decrease in nursing time and hospitalization. Also

- ❖ Reduce blood level oscillation characteristic of multiple dosing of conventional dosage forms.
- ❖ Reduce amount of drug administration
- ❖ Maximizing availability with a minimum dose.

- Control of drug absorption; high peak level peaks that may be observed after administration of high availability drug can be reduced.
- Safety margin of high potency drugs can be increased.
- Increased reliability of therapy

1.2 CONVENTIONAL DRUG THERAPY [4, 22]

In most cases of conventional dosage form the dosing interval is much shorter than the half-life of the drug resulting in a number of limitations.

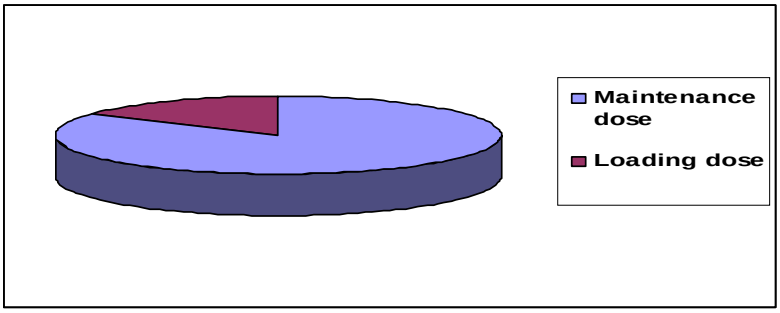
1. Unless the dosing interval is relatively short, depending on biological half-life of the drug, large peaks and valleys (Fig.7) in the drug level will occur.
2. Success by this approach is dependent on patient compliance with the dosing regimen. Numerous studies have documented that lack of compliance is an important reason for drug therapy inefficiency or failure.

1.3 THEORY OF SUSTAINED RELEASE:[23,17]

Sustained release dosage form may contain:

a) Maintenance dose, and

b) Loading dose



The maintenance dose or slowly available portion will release the drug slowly and maintain the therapeutic level for an extended period of time. While the loading dose or immediately available portion will held obtaining the therapeutic level quickly after administration.

1.4 ORAL CONTROLLED RELEASE SYSTEM [10]

Oral route has been the most popular and successfully used for controlled delivery of drug because of convenience and ease of administration, greater flexibility in dosage form design(possible because of versatility of GI anatomy and physiology) and ease of production and low cost of such a system.

The controlled release systems for oral use are mostly solids and based on dissolution, diffusion or a combination of both mechanisms in the control of release rate of drug.

A. Continuous release systems

These systems release the drug for a prolonged period of time along the entire length of GIT with normal transit of the dosage form.

The various systems under this category are:

1. Dissolution controlled release system
2. Diffusion controlled release system
3. Dissolution and diffusion controlled release system
4. Ion exchange resin – drug complexes
5. Slow dissolving salts and complexes
6. pH – dependant formulation
7. Osmotic pressure controlled systems
8. Hydrodynamic pressure controlled system

B. Delayed transit and continuous release system

These systems are designed to prolong their residence in the GIT along with their release systems included in this category are;

1. Altered density systems
2. Mucoadhesive systems
3. Size- based systems

C. Delayed release systems

The design of such systems involves release of drug only at a specific site in the GIT. The two types of delayed release systems are;

1. Intestinal release systems
2. Colonic release systems

The drugs contained in this system are those that are:

i. Destroyed in the stomach or intestinal site.
ii. Known to cause gastric distress
iii. Absorbed from a specific intestinal site, or
iv. Meant to exert local effect at a specific GI site.

3. PLAN OF WORK

The following experimental protocol was therefore designed to all systematic approach to the study.

1) Drug selection
2) Literature Survey:
3) Preformulation study: Compatibility evaluation was carried out between drug and polymers in physical observation and by using FT- IR spectral study.
4) Preparation of standard curve for Aceclofenac in phosphate buffer pH 6.8 .
5) Formulation development of sustained release matrix tablets of using different release retardant.
6) The following evaluation parameters were studied based on laboratory experiments.

i) Evaluation of granules

- Angle of repose
- Apparent bulk density
- Tapped bulk density
- Percent compressibility
- Loss on drying
- Hausner Ratio

ii) Evaluation of tablets

- Tablet dimensions
- Hardness
- Friability
- Weight variation
- Content uniformity of active ingredient
- *In-vitro* dissolution study

7) Stability study of optimized batch

5.1 Materials Used in study

Sr.No	MATERIALS USED
1.	Aceclofenac
2.	Microcrystalline cellulose (Avicel pH 101)
3.	PVP k 30
4.	HPMC K 4M
5.	HPMC K 15M
6.	Acrypol 934 P
7.	Aerosil
8.	Isopropyl Alchol

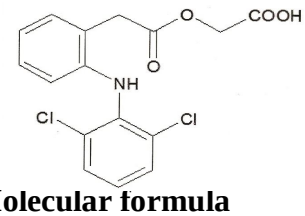
5.2. Instruments Used in study

Sr. No	INSTRUMENTS	MANUFACTURER
1	Electronic Balance & Top loading Balance,	Shimadzu Corporation, AW 220 and BX 6205
2	Tray Dryer	Erweka Pvt. Ltd.
3	Coating machine	Erweka Pvt. Ltd.
4	Dissolution Apparatus (USP) Auto Sampler	Electrolab Pvt. Ltd.
5	Shaking Water Bath	Equitron
6	Tablet Hardness tester	Monsanto
7	Friability test apparatus	Electrolab Pvt. Ltd. EF 2 USP
8	Ultra Violet Visible spectro photometer	Shimadzu Corporation UV-1700
9	FT-IR Spectrophotometer	Shimadzu Corporation, 8400S
10	Tap density Appratus	Erweka Pvt. Ltd.
11	Granulate Flow Tester	Erweka Pvt. Ltd.
12	Vernier Caliper	Digimatic
13	pH Meter,	Systronics (335)
14	LOD apparatus	Sartorius
15	Tablet punching machine	CADMACH 16 station

5.3 DRUG PROFILE [85-88]

ACECLOFENAC

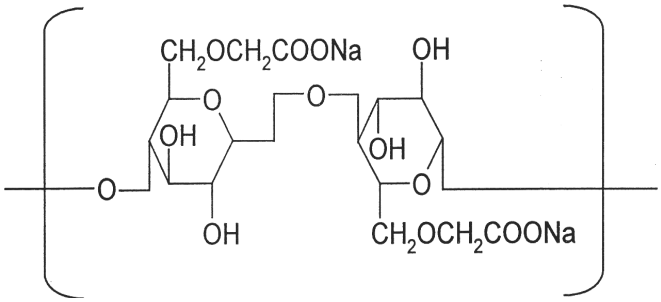
Aceclofenac is one of the emerging NON STEROIDAL ANTI INFLAMMATORY DRUG molecules for arthritis treatment. it is a newer derivative of diclofenac and has less gastrointestinal complications. the successful treatment of arthritis depends on the maintenance of effective drug concentration level in the body for which a constant and uniform supply of drug is desired. Sustained release dosage forms deliver the drug at a slow release rate over an extended period of time and achieve this objective. the short biological half-life 9about 4 h) and dosing frequency more than one per day make aceclofenac an ideal candidate for sustained release.



Molecular formula $C_{16}H_{13}C_{12}N0_4$

5.4 POLYMER PROFILE [89-92,61]

HYDROXYPROPYL METHYLCELLULOS



Empirical Formula: $C_8H_{15}O_6 – (C_{10}H_{18}O_6)$ n – $C_8H_{15}O_5$

Viscosity: 2% solution

HPMC K100M –80000-120000 cps

HPMC K15M-11250-21000 cps

HPMC K4M-3000-5000 cps

Carbomer 934 P

It is a high molecular weight polymer of acrylic acid cross linked with allyl ethers of sucrose.

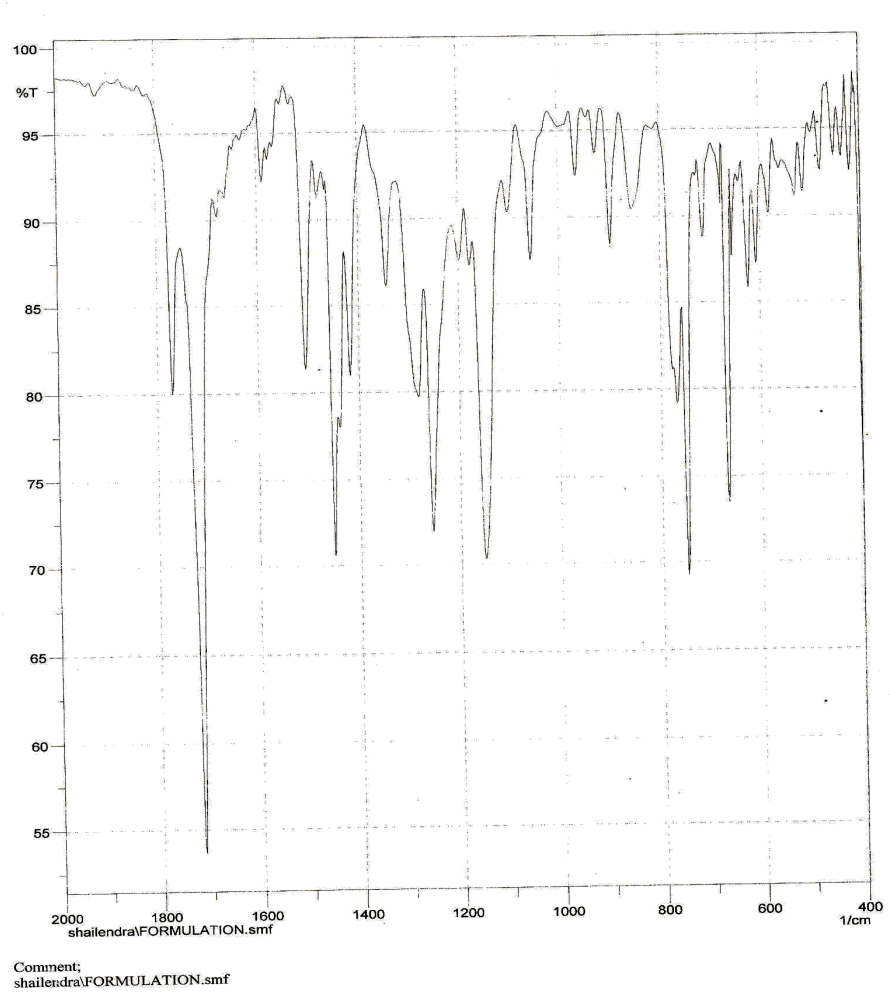
5.5 PREFORMULATION STUDY[93-94]

Preformulation stability studies are usually the first quantitative assessment of chemical stability of a drug as well as stability in presence of other excipients.

Identification of Drug

The identification of drug was done by FT-IR Spectroscopy

Method: Triturate 1-2 mg of the substance to be examined with 300-400 mg, unless otherwise specified, of finely powdered and dried potassium bromide or potassium chloride . These quantities are usually sufficient to give a disc of 10-15 mm diameter and a spectrum of suitable intensity. Infrared spectrophotometers are used for recording spectra in the region of 4000 – 650.



Drug – Excipient Compatibility Study

Compatibility studies were conducted to investigate and predict physicochemical interaction between drug substance and excipents and therefore to select suitability of chemically compatible excipients.

Drug & Excipients (Ratio 1 : 1)	**Observation**			**Result**
	Initial	**30°C±2/65%±5 RH after 30 days**	**40°C±2/75%±5 RH after 30 days**	
Aceclofenac	White to off White powder	White to off White powder	White to off White powder	Compatible
Aceclofenac+ HPMC K 15 M	White to off White powder	White to off White powder	White to off White powder	Compatible
Aceclofenac + HPMC K 4 M	White to off White powder	White to off White powder	White to off White powder	Compatible
Aceclofenac + Carbomer 934P	White to off White powder	White to off White powder	White to off White powder	Compatible
Aceclofenac+ PVP K 30	White to off White powder	White to off White powder	White to off White powder	Compatible
Aceclofenac+ Mg. Stearate	White to off White powder	White to off White powder	White to off White powder	Compatible
Aceclofenac+ Mcc	White to off White powder	White to off White powder	White to off White powder	Compatible

Physical observation of compatibility study:

5.6 STANDARD CURVE OF ACECLOFENAC

Preparation of phosphate buffer pH 6.8

Accurately weighed quantity of 27.218 g of potassium dihydrogen phosphate was dissolved in distilled water and diluted with distilled water upto 1000 ml. 50ml of above solution was taken in a 200 ml of volumetric flask, 22.4 ml of 0.2 M NaOH was added to the solution and then diluted with distilled water upto volume.

Preparation of standard curve in 6.8 pH buffer

100 mg equivalent weighed of Aceclofenac was dissolved in 100 ml of phosphate buffer pH 6.8. The 10 ml of above solution was further diluted upto 100 ml with phosphate buffer pH 6.8. The resulting solution was serially diluted with phosphate buffer pH 6.8. to get drug concentration 5,10,15,20,25 µg/ml. The absorbance of the solutions was measured against phosphate buffer pH 6.8 as a blank at 274.0 nm using double beam UV visible spectrophotometer.. The plot of absorbance v/s concentration (µg/ml) was plotted and data was subjected to obtain linear regression analysis.

Observation

The standard calibration curve of drug in phosphate buffer pH 6.8 depicted as Figure. The data of absorbance was shown in Table . The data had correlation coefficient of 0.9992.

6.1 Manufacturing procedure of sustained release tablet of Aceclofenac

Wet Granulation Method

Weight accurately Drug + HPMC K15M + PVP K-30 and Microcrystaline cellulose pass through 40 no sieves and mix properly for 3-5 minutes in a steel tub.

Prepare binder solution by dispersing PVP K30 in isopropyl alcohol.

Granulation of above mixture is done by prepared binder solution by kneading up to granulation end point is obtained(Dough mass) .Pass the dough mass through 12 mess and keep it in a tray dryer for drying and finaly keep the loss on drying(LOD) up to 2-3 %.Remove the dried granules from oven and pass through 20 mess sieve to get optimum size granules.Lubrication is done by using Mg.stearate and passed through 60 mesh of the granules for 3 to 4 min. in a steel tub and then in polybag.

6.2 DESIGN AND DEVELOPMENT OF ACECLOFENAC SR MATRIX TABLETS

Formulation of Batch T-1 to T-5

Formulation Ingredients	TRIAL BATCHES				
	ASR - 01	ASR - 02	ASR - 03	ASR - 04	ASR – 05
Aceclofenac	200	200	200	200	200
MCC	67	63	62	74	72

PVP K – 30	10	9	10	8	10
I.P.A	Q.S	Q.S	Q.S	Q.S	Q.S
HPMC K4M	-	20	15	10	10
HPMC K 15	15	10	15	10	-
ACRYPOL 934 P	10	-	-	-	10
MAG STEARATE	5	5	5	5	5
AEROSIL	3	3	3	3	3
TOTAL WEIGHT	310 mg	310 mg	310 mg	310 mg	310 mg

6.2.1 DESIGN AND DEVELOPMENT OF ACECLOFENAC SR MATRIX TABLETS

Table No. 4.1 Formulation of Batch T-6 to T-10

Formulation Ingredients	**TRIAL BATCHES**				
	ASR - 06	**ASR - 07**	**Final**	**ASR - 09**	**ASR - 10**
Aceclofenac	200	200	200	200	200
MCC	71	67	49	53	42
PVP K – 30	11	10	10	10	10
I.P.A	Q.S	Q.S	Q.S	Q.S	Q.S
HPMC K4M	-	10	-	20	25
HPMC K 15	5	10	23	-	-
ACRYPOL 934 P	15	5	20	19	25
MAG STEARATE	5	5	5	5	5
AEROSIL	3	3	3	3	3
TOTAL WEIGHT	310 mg	310 mg	310 mg	310 mg	310 mg

6. EVALUATION STUDIES [93,95-98]

Characterization of Trial Blends

B.No	Bulk density*	Tapped density*	Loss on Drying in %*	Compressibility Index*	Hausner Ratio*	Angle of Repose(^{o})*
T1	0.442 ±. 0.024	0.506 ± 0.014	1.7 ± 0.011	12.65 ± 0.015	1.14 ± 0.014	34^{o}±2
T2	0.486 ± 0.018	0.556 ± 0.026	1.2 ± 0.014	12.59 ± 0.022	1.14 ± 0.016	31^{o}±3
T3	0.529 ± 0.016	0.593 ± 0.021	1.5 ± 0.018	10.79 ± 0.021	1.12 ± 0.014	31^{o}±2
T4	0.512 ± 0.019	0.574 ± 0.025	1.4 ± 0.016	10.80 ± 0.019	1.12 ± 0.018	28^{o}±3
T5	0.544 ± 0.022	0.601 ± 0.022	1.4 ± 0.011	9.48 ± 0.014	1.10 ± 0.019	28^{o}± 2
T6	0.539 ± 0.017	0.586 ± 0.021	1.3 ± 0.013	8.02 ± 0.016	1.09 ± 0.021	26^{o}±3
T7	0.499 ± 0.018	0.564 ± 0.016	1.8 ± 0.017	11.52 ± 0.024	1.13 ± 0.022	32^{o}±2
T8	0.523 ± 0.018	0.602 ± 0.017	2.2 ± 0.012	13.12 ± 0.021	1.15 ± 0.017	35^{o} ±2
T9	0.524 ± 0.014	0.596 ± 0.024	1.5 ± 0.016	10.74 ± 0.019	1.14 ± 0.015	31^{o} ± 2
T10	0.527 ± 0.019	0.587 ± 0.024	1.2 ± 0.016	11.59 ± 0.017	1.13 ± 0.018	31^{o} ± 3

7.2 EVALUATION OF TABLET

All the prepared sustained release tables were evaluated for following official and unofficial parameters.

7.2.1 Weight Variation

7.2.2 Dimensions

7.2.3 Hardness Test

7.2.4 Friability Test

7.2.5 Drug content

7.2.6 Dissolution study

Physical parameters of tables of each batch

B.No	Weight Variation (mg)*	Thickness (mm)*	Hardness (kg/cm2)*	Friability (%)	Drug Content (%)
T1	310±1.97	4.66±0.2	6	0.62±0.03	101.65
T2	310±1.68	4.63± 0.0	4	0.62±0.02	98.22
T3	310±3.05	4.37±0.3	4	0.42±0.05	103.99
T4	310±3.01	4.72±0.2	5	0.49±0.04	100.83
T5	310±1.84	4.69±0.3	6	0.65±0.03	96.98
T6	310±2.36	4.66±0.2	6	0.59±0.04	96.89
T7	310±3.14	4.60±0.3	4	0.67±0.02	96.42
T8	310±2.15	4.66±0.2	4	0.53±0.03	99.25
T9	310±3.14	4.60±0.3	6	0.65±0.03	99.73
T10	310±1.87	4.69±0.2	4	0.45±0.02	100.75

* Each value represents the mean ± standard deviation (n = 10)

7.2.5 Drug Content of Aceclofenac by HPLC

Column : µ bonda pack C_{18} (1-30 cm; d = 4mm) Waters

Eluent : Add to 900 ml of water, 4 ml of ammonia 25% and 5ml of conc. Phosphoric acid. Shake and to bring on pH = 2.1 with phosphoric acid. Add 100ml acetonitril. Filtrate under vacuum

Flow rate : 1.0 ml/min

Detection : 2.70 nm

Injection : 20 µl. Autosampler Spark Holland.

Temperature : room temperature (15-25^{o}C)

Solutions

Standard : Accurately weigh 100 mg of **Aceclofenac** reference standard into a 100.0 ml volumetric flask, dissolve in methanol and dilute to volume.

Sample to : Accurately weigh an amount of tablet powder, equal 100mg of **Aceclofenac** into a 100.0 ml volumetric flask, and add methanol to volume. Stir during one night to allow the Aceclofenac to dissolve. Centrifuge and inject the clear solution.

Calculation

$$\frac{\text{area Sa x th.wgh.S x wgh.St}}{\text{area St X th. wgh. St x wgh. sa}} \times 100\% = \text{assay \%}$$

Where :

area Sa	=	The area of the sample solution
area St	=	The area of the standard solution
th.wgh.St	=	The theoretical weight of the sample solution
th.wgh.st	=	The theoretical weight of the standard solution
wgh.Sa	=	The real weight of the sample solution
wgh.St	=	The real weight of the standard solution

7.2.6 Dissolution Study

Medium	:	6.8 pH phosphate buffer
Volume	:	900ml
Apparatus	:	Paddle
Rotation	:	75 rpm
Time	:	24 hours
Detection	:	UV, 274nm
St. stock solution	:	Weigh an amount of **Aceclofenac,**

reference standard equal to 103.27 mg **Aceclofenac** into a 100.0 ml volumetric flask which was dissolve in medium

Std. solution : Dilute 10.00 ml St, Stock solution to 100ml with medium

Sample Solution : Take 10ml solution of sample from each

vessel and filtered and take absorbance at 274 nm on double beam UV spectrophotometer and replace the volume with dissolution medium maintaining the temperature.

Calculation

$$\frac{\text{Ex. S x th.wgh.St x 10 x 900 x purity}}{\text{Ex.St x wgh. St x 100 x 1 x 100}} \times 1000$$

Where :

Ex.S = The extinction of the sample solution

Ex.St = The extinction of the standard solution

th.wgh.St = The theoretical weight of the reference standard calculated on the assay of the reference standard

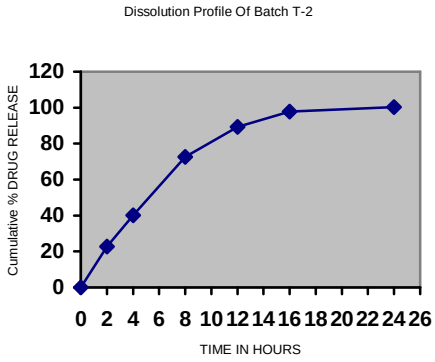
wgh.St = The real weight of the reference solution

Table No.8 Dissolution Profile of batch No. T-1 to T-10 and marketed sample in 6.8 pH phosphate buffer

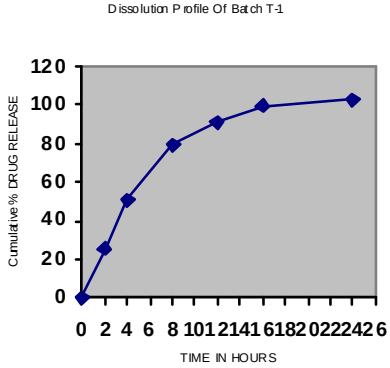
B.No	Time in Hours (cumulative % drug release)						
	6.8 PH buffer						
	0	**2**	**4**	**8**	**12**	**16**	**24**
T1	0	25.65	50.48	79.25	91.25	99.52	102.69
T2	0	22.68	40.17	72.58	89.24	97.77	100.25
T3	0	18.85	39.45	65.95	90.58	99.01	100.25
T4	0	20.65	40.25	72.56	92.68	99.67	102.58
T5	0	26.98	49.65	75.82	95.62	101.24	101.98
T6	0	24.98	42.78	70.98	85.24	92.57	101.69
T7	0	25.64	45.65	75.58	90.14	99.65	102.97
T8	0	15.56	25.63	69.85	82.46	92.05	99.56
T9	0	17.56	30.64	75.52	80.97	95.41	101.28
T10	0	14.69	22.57	65.24	75.68	88.52	97.24
Market Sample	0	11.41	21.63	71.64	78.46	89.27	100.35

Dissolution Profiles

T2



T1



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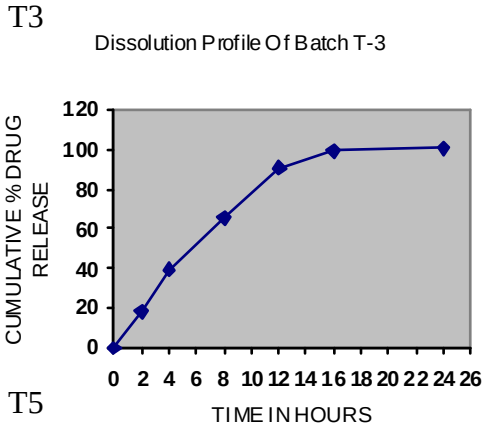

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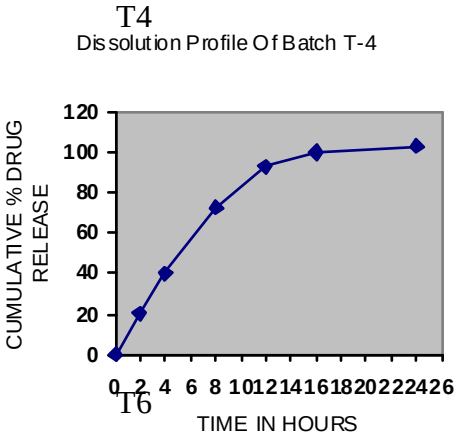
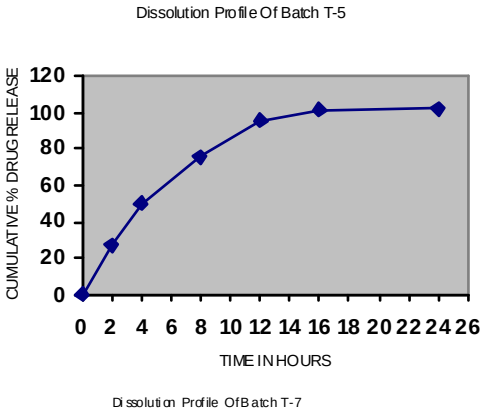
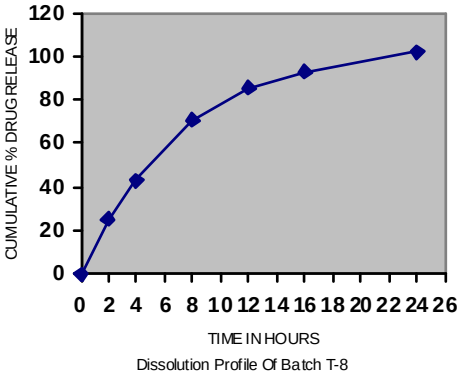


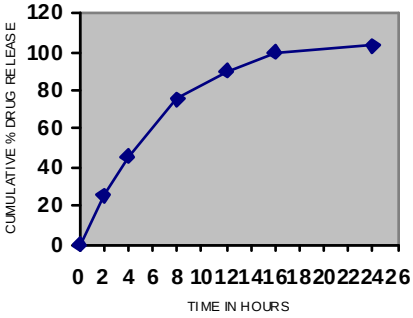
T5



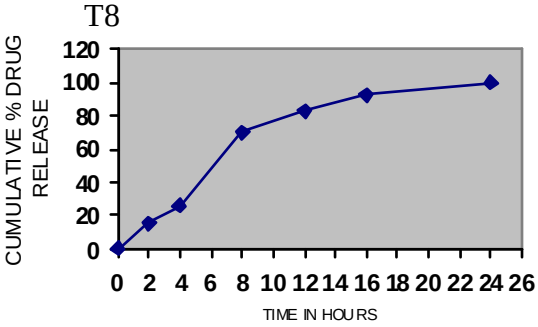
T6



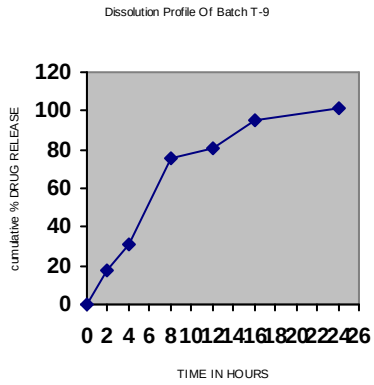
T7



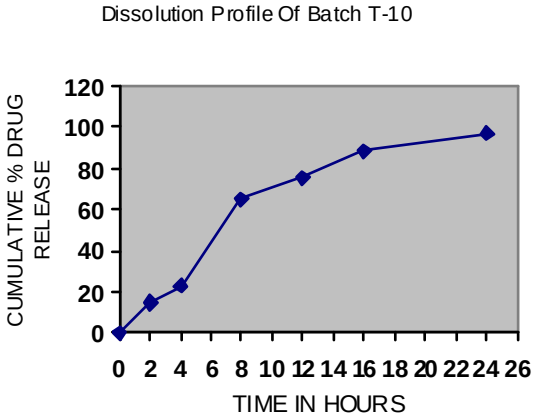
T8

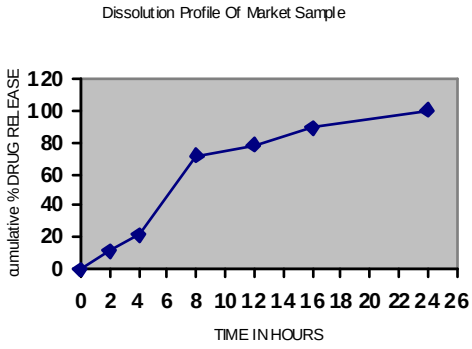


T9



T10





MARKET SAMPLE

Determination of Similarity & Disimilarity Factor

Table No.9 Disimilarity Factor

Time (hours)	R	T	R-T	SQR	MOD (sqrt)	Cumulative MOD	Cumulative R	F1
0	0	0	0	0	0	0	0	0
2	11.41	15.56	-4.15	17.22	4.15	4.15	11.41	36.37
4	21.63	25.63	-4	16	4	8.15	33.04	24.66
8	71.64	69.85	1.79	3.20	1.79	9.94	104.68	9.49
12	78.46	82.46	-4	16	4	13.94	183.14	7.61
16	89.27	92.02	-2.75	7.56	2.75	16.69	272.41	6.12
24	100.35	99.56	0.79	0.62	0.79	17.48	372.76	4.68

Table No.10 Similarity Factor

Time in (hours)	R	T	R-T	(R-T)2	Cumulative (R-T)2	Cum(R-T)2*1/N	Cum(R-T)2*1/N +1	SQRT	1/SQRT	100*1/SQRT	F2
0	0	0	0	0	0	0	1	1	1	100	100
2	11.41	15.56	-4.15	17.22	17.22	2.87	3.87	1.96	0.50	50.83	85.30
4	21.63	25.63	-4	16	33.22	5.53	6.53	2.55	0.39	39.11	79.61
8	71.64	69.85	1.79	3.20	36.43	6.07	7.07	2.65	0.37	37.60	78.76
12	78.46	82.46	-4	16	52.42	8.73	9.73	3.12	0.32	32.04	75.28
16	89.27	92.02	-2.75	7.56	59.98	9.99	10.99	3.31	0.30	30.15	73.96
24	100.35	99.56	0.79	0.62	60.61	10.10	11.10	3.33	0.30	30.01	73.9

STABILITY STUDY OF TABLETS OF BATCH T8[94]

The batch T8 was selected as an optimum batch and the stability study was carried out at accelerated condition. of 40°C/75 % RH condition for a period of two month.

Drug content of batch T 8 kept for stability

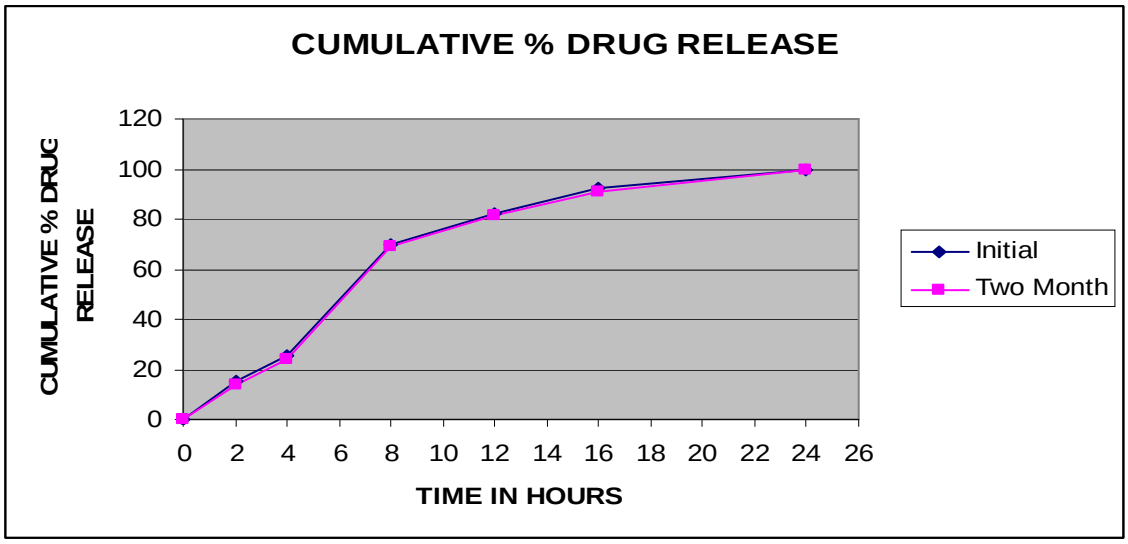
Time	Drug Content (%)
Zero month	99.25
Two month	99.14

Dissolution profile of batch T-8 kept for stability

Dissolut- ion Medium	Time (hrs)	Cumulative % release	
		Initial	Two month
	0	0	0
	2	15.56	14.12
	4	25.63	23.69
6.8pH buffer	8	69.85	69.12
	12	82.46	81.78

	16	92.02	91.23
	24	99.56	99.31

Dissolution profile of batch T-8 kept on stability at 40°C /75% RH



RESULTS AND DISCUSSION

The procured sample of Aceclofenac was tested for its identification. The manufacturer also was confirmed of quality and purity of sample.

The drug – excipients compatibility was done at accelerated temperature 40°C/75% ± 5% and 30° C/65% ± 5% relative humidity. Opened and closed vial methods were used. The result doesn't show any physical change to the mixture after 30 days. This fact concluded that the drug and Excipient are compatible with each other.

The sustained release tablets of Aceclofenac were prepared by wet granulation method, They were evaluated for weight variation, drug content, friability, hardness, and thickness for all batches (T-1 – T-10).

No significant difference was observed in the weight of individual tablets from the average weight. Tablet weights of all batches were found with in recommended pharmacopoeia limits. The data of uniformity of content indicated that tablets of all batches had drug content within pharmacopoeia limits. The hardness of tablets of all batches are in acceptable limits, as shows in the literature. All the formulation showed % friability less then 1% that indicates ability of tablets to withstands shocks, which may encounter. Standard calibration curve of Aceclofenac was prepared in phosphate buffer medium 6.8pH.Correlation coefficient

values indicate the linear correlation between concentration and absorbance and following lamberts beers law.

The release of Aceclofenac from sustained release tablet of various formulations varied according to the ratio and degree of the polymer. In case of tablet of T1containing drug & HPMCK15M (quantity in mg). 200: 15 : the release profile, was showing the release 102.69%. In case of tablets of T2 containing drug and HPMC K15M & HPMC K4M (in mg). 200:10:20 it was showing 100.25% release in 24 hours. In case of tablets of T3 containing drug polymer's (HPMCK15M, HPMCK4M in mg) 200 : 15 : 15 : prepare to be seen in the effect of combination of polymers in release of drug but it was showing same release given 100.25% upto 24 hour. In case of tablets T4 containing drug and HPMC K15M & HPMCK 4M (in mg) 200: 10: 10 the release profile was showing drug release more than 100% .In case of tablets of T5 containing drug and HPMC K 4M & HPMC K15M PVP K30 (in mg) 200: 10: 10:10 . Prepared the tablets. But it cannot maintain the release with in 100%. In case of tablets of T6 containing drug and HPMC K 15M (in Mg) 200 : 5 . It was seen the increase in release of drug and shown more than 100% drug release in 24 hour profile. In case of tablets T7, containing drug. HPMCK4M & HPMCK15m (in mg) 200:10:10 the release profile was showing drug release more than 100%. In case of Tablets T8 containing drug. HPMCK15M (in mg) 200 : 23. The release profile was showing drug release with in 24 hours. With very slower release than all formulations containing % drug release 99.56.

In case of tablets T9, containing drug. HPMCK4M (in mg) 200:20 the release profile was showing drug release more than 100%. In case of tablets T10, containing drug. HPMCK4M (in mg) 200:25 the release profile was showing drug release less than 100%.

For similarity, F2 calculation was done in 6.8 pH phosphate buffer showing the value of similarity factor (F2) i.e., 73.9

Results of stability studies of batch T-8 indicates that it was stable at $40^{o}C/75\%$ + 5% relative humidity as there was no significant difference was observed for dissolution and average drug content data after two months.

CONCLUSION

The study was undertaken with an aim to formulate develop and evaluation of Aceclofenac sustained release tablets using different polymers as release retarding agent. Preformulation study of Aceclofenac was done initially and results directed for the further course of

formulation. Based on preformulation studies different batches were prepared using selected excipeints. Granules were evaluated for tests LOD, Bulk density, tapped density, compressibility index, Hausner ratio before being punched as tablets. Tablets were tested for weight variation, thickness, hardness and friability as per official procedure. Dissolution of batch T-8 was carried out in 6.8 pH media and compared with marketed preparation. Based on dissolution tests and F-2 values in pH 6.8 phosphate buffer as release medium, it was concluded that T-8 satisfactory performs in the same manner as that of marketed formulation. F-2 (similarity factor) value of T-6 was found to be 73.90. From the above results and discussion it is concluded that formulation of sustained release tablet of Aceclofenac containing HPMC K 15M & 200 : 23 (in mg) T8 can be taken as an ideal or optimized formulation of sustained release tablets for 24 hour release as it fulfills all the requirements for sustained release tablet and our study encourages for the further clinical trials on this formulation.

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