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# Development and *in-vitro* evaluation of sustained release matrix tablets of Acelofenac using different grade of Methocel K100m Cr polymer

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## ABSTRACT

*In the present study, an attempt has been made to evaluate the effect of hydrophilic polymers on the release profile of drug from matrix system. Acelofenac, a non-steroidal anti-inflammatory drugs agent, was used as a model drug to evaluate its release characteristics from different matrices. Matrix tablets of Acelofenac were prepared by direct compression process using Methocel K100m CR polymer. Release kinetics of Acelofenac from these sustained release matrices in distilled water using USP paddle method with sinker for 8 hours was studied. Statistically significant differences were found among the drug release profile from different formulations. Higher polymer content (70%) in the matrix decreased the rate of the drug due to increased tortuosity and decreased porosity. At lower polymeric level (30%), the rate of drug release was elevated. The release mechanism was explored and explained with zero order, first order, Higuchi and Korsmeyer equations. The results generated in this study showed that the profile and kinetics of drug release were functions of polymer type, polymer level and physico-chemical properties of the drug.*

**Key Words:** Acelofenac, Hydroxypropyl Methyl Cellulose E-5, Hydroxypropyl Methyl Cellulose E-50 LV, Hydroxypropyl Methyl Cellulose K4M, matrix tablets, sustained release.

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## INTRODUCTION

Oral administration of drugs has been the most common and preferred route for delivery of most therapeutic agents. It remains the preferred route of administration investigated in the discovery and development of new drug candidates and formulations. The popularity of the oral route is attributed to patient acceptance, ease of administration, accurate dosing, cost-effective manufacturing methods, and generally improved shelf-life of the product. Traditionally patient only takes medication during the day time hours. Plasma levels can therefore fall to sub-

therapeutic levels overnight. So to overcome this problem sustains release of formulation is required [1].

Aceclofenac is a newer non-steroidal anti-inflammatory drug having potent analgesic and anti-inflammatory properties. Aceclofenac is newer derivative of diclofenac and having less GIT complication. Aceclofenac is widely used in the treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. Half life of Aceclofenac is 4 - 4.3 hrs.[2] Aceclofenac is rapidly eliminated from the body and unable to maintain therapeutic concentration at site of action. Conventionally Aceclofenac is available as 100 mg tablet given by mouth required multiple daily doses twice or thrice daily to maintain adequate plasma drug concentration. Hence there is need of sustained release formulation of aceclofenac.

Advantages of sustain release

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

## MATERIALS AND METHODS

Acelofenac was obtained from Amoli organics pvt. Ltd, Mumbai.Pvt.Ltd., India. HPMC (Methocel K100M CR) was a gift sample received from Colorcon Asia Pvt.Limited Magnesium stearate and talc were procured from Hanua Chemicals Limited, (Japan). Colloidal Silicon Dioxide (Aerosil 200) Degussa Evonik AG, Germany

### Preformulation studies

### Scanning of drug [3]:

Accurately weighed 50.0 mg of drug was dissolved in methanol and diluted it upto 100.0 ml. Then 2.0 ml of above solution was diluted upto 50.0 ml with methanol and examined between 220 nm and 370 nm.

### Compatibility Studies [4]

A physical mixture (1:1) of drug and polymers was prepared and mixed with suitable quantity of IR grade potassium bromide and prepared transparent pellets. They were scanned from 4000 to 400 cm^sup -1^ in a Perkin Elmer FTIR spectrophotometer.

### Preparation of matrix tablets

Tablets were prepared by direct compression process. In all cases, the amount of the active ingredient was 9.650 mg and the total weight of the tablet was 150 mg (Table-1). During granulation process matrix-forming agents, talc, methocel, magnesium stearate, avicel pH 102 and the active ingredient were weighed properly. Firstly active ingredient, talc and Methocel

were mixed for 10 minutes properly. Dried granules were sieved through 20 mesh SS screen to get compressible particle. Lubricants are added during blending part.

During blending total mass was taken in a photo film container and blended in a laboratory designed small drum blender machine for about 30 minutes. The appropriate amounts of the mixture were accurately weighed in an electronic balance for the preparation of each tablet and finally compressed using Manesty D type 16 station compression machine with a 10.00 x 8.80 mm concave, plain faced punch and die set. The compression force was 1.5 ton. Before compression, the surfaces of the die and punch were lubricated with purified talc. All the preparations were stored in airtight containers at room temperature for further study.

**Table 1 Composition of All For mulation Trials**

| Ingredients (wt in mg) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | S1 | S2 | S3 |
|---|---|---|---|---|---|---|---|---|---|---|
| Drug | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 |
| MCC (Avicel PH102) | 76.5 | 35.5 | 35.5 | 35.5 | 35.5 | 35.5 | 35.5 | 35.5 | 35.5 | 35.5 |
| HPMC E-5 LV | 94.0 | 90.0 | 110 | 125 | --- | --- | --- | --- | --- | --- |
| HPMC E-50 LV | --- | --- | --- | --- | 100 | 105 | 110 | 110 | 110 | 110 |
| HPMC K4M | --- | 45.0 | 25.0 | 10.0 | 35.0 | 30.0 | 25.0 | 25.0 | 25.0 | 25.0 |
| Colloidal silicon dioxide | 5.7 | 5.7 | 5.7 | 5.7 | 5.7 | 5.7 | 5.7 | 5.7 | 5.7 | 5.7 |
| Magnesium stearate | 3.8 | 3.8 | 3.8 | 3.8 | 3.8 | 3.8 | 3.8 | 3.8 | 3.8 | 3.8 |
| Total (mg) | 380 | 380 | 380 | 380 | 380 | 380 | 380 | 380 | 380 | 380 |
| Opadry 85G | --- | --- | --- | --- | --- | --- | --- | 7.6 | 7.6 | 7.6 |
| Purified Water | --- | --- | --- | --- | --- | --- | --- | qs | qs | qs |
| Total (mg) | --- | --- | --- | --- | --- | --- | --- | 387.6 | 387.6 | 387.6 |

*S1, S2, S3 - Stability batch*

## Evaluation of matrix tablets:

Tables are evaluated for their chemical characteristics like potency, content uniformity and purity and physical characteristics like weight and weight variation, thickness, hardness, friability, disintegration and dissolution. Some of the important evalution parameters have been discussed below.

## Post-Compression Parameters

### Weight Variation [5]

The test ensures that all the tablets in a batch are of the same potency, wihin reasonable limits. Each tablet in a batch should be uniform in weight.

Firstly the average weight of 20 tablets was determined and then weighed the 20 tablet individually and the variation in the weight of each tablet was determined from the average weight.

**Table 2 Practical consideration of value weight variation**

| Average weight of a tablet (mg) | Percentage Difference |
|---|---|
| 130 mg or less | 10 |
| 130mg to 324mg | 7.5 |
| 324 mg or more | 5 |

### Thickness [6]

The thickness of twenty individual tablets was determined by Digital Vernier caliper (Mitutoyo corp, Japan). The measurements were recorded and the mean was calculated.

**Hardness testing** [8,9]

Hardness of tablet is expressed in terms of load/pressure required to crush it when placed on its edge. It indicates the tensile strength of a tablet. A hardness of 5 kg in taken as minimum of uncoated tablets for ensuring mechanical stability.

Tablet hardness was determined by using a tablet Monsento Hardness Tester (MHT – 20 Compbell Electronics, Mumbai). Mean hardness of 5 tablets from each formulation batch was determined.

**Friability testing** [9,10]

10 tablets were taken and carefully dedusted prior to testing. The tablets were weighed accurately, and placeed the tablets in the drum. The drum was rotated 100 times, and after that the tablets were removed. Removed loose dust from the tablets as before, and accurately weigh. The % loss was determined by using following formula:

$$\% \text{ Loss} = \frac{\text{Initial Weight - Final Weight}}{\text{Initial Weight}} \times 100$$

A maximum loss of mass not greater than 1.0 % is considered acceptable.

**Drug Content** [11]

Twenty tablets were crushed and powder containing equivalent to 200 mg of aceclofenac was dissolved in 100 ml of methanol. The solution was passed through a whatmann filter and analyzed spectrophotometrically at 274 nm after sufficient dilution with phosphate buffer (pH 6.8).

***In vitro* release Study**

The dissolution study for the prepared tablets was carried out using USP XXI Dissolution Test Apparatus-I (Basket method) in 900 ml Phosphate buffer pH 6.8 maintained at 37±0.5$^{o}$C, at 100 rpm. The 10 ml samples were withdrawn at predetermined time interval with the pipette. The volume withdrawn at each interval was replaced with fresh quantity of 10 ml of dissolution medium. The collected samples were suitably diluted and absorbance was measured spectrophotometrically at 274 nm. The percentage of Aceclofenac released at various time intervals was calculated and plotted against time. The results indicated for each dissolution studies are the average of three determinations.

**Swelling and erosion studies** [13]

Measurement of swelling and erosion rates of matrix tablets was carried out, after immersion of tablets in the distilled water, accurately Weighed tablets ($W_i$) were placed in Petridish containing about 50 ml of distilled water at room temperature. After 0.5,1, 2, 3, 4, 6,7,8 and 24 h, the tablet was withdrawn from the medium and blotted to remove excess water and then weighed ($W_w$) on an analytical balance (model AB304-S/FACT, Mettler–Toledo, Columbus). The wet samples were then dried in an oven at 80$^{o}$ C for 24-h time period, allowed cooling in a desiccator and finally weighed until constant weight was achieved (final dry weight,$W_d$). The experiment was

performed in triplicate for each time point and fresh samples were used for each individual time point.

The increase in wet weight represented the infiltration of medium into the interspaces of the tablet matrix. This was followed by swelling and erosion of the tablet matrix. The ratio of apparent medium content to matrix remaining in the tablet ($Q_W$ %) was calculated using following equation:

$$Q_W = \frac{(W_i - W_d)}{W_i} X 100 \qquad \text{---------- 8}$$

The percentage overall erosion of the tablet ($E_P$ %) was calculated using following equation:

$$E_P = \frac{(W_i - W_d)}{W_i} X 100$$

## RESULTS

The Wavelength of maximum absorbance (λmax) in Methanol was found to be 274. The FT-IR graphs of Aceclofenac and HPMC E 50LV, Aceclofenac and HPMC K4M, Aceclofenac, HPMC E 50LV and HPMC K4M and Tablet blend shows no interaction when compared with spectrum of pure drug. Drug loss on drying is shows in table 4. Pre-compression parameters like bulk density, tapped bulk density, compressibility index, hausner's ratio, angle of repose and loss on drying of all batches was shown in table 5. From the results of pre-compression parameter of blend, it was found that all the batches have good compressibility. Flow properties also found to be good for all batches (angle of repose between 31.74 - 35.83 indicates good flow). Hausner's ratio (between 1.25 - 1.351) for all batches indicate Fair to Passable flow properties. Loss on drying found in between 1.6 - 2.99. Post-compression parameter of tablet like weight variation, diameter, thickness, hardness, friability, and drug content was shown in table no. 6. Weight variation of tablet was found within limit. Friability of tablet was found less than 1%. Hardness was found to be in between 5.5 - 7.3 in all batches. Thickness was found to be in between 4.4 – 4.6. Diameter was found to be in between 10.34 – 10.36. Content uniformity of tablet was found to be between 97.8 – 101.2. The *invitro* release profile shows that F7 formulation shows better realease as compared to other formulations. It is shown in table 7. In figure 3 it is shown that F7 shows similar dissolution release as compared to marketed formulation.

**Table 4 Contains profile of loss of drug on drying**

| TEST | SPECIFICATION | OBSERVATION |
|---|---|---|
| LOSS ON DRYING | Not more than 0.5 %w/w | 0.1 % w/w |

**Table 5 Shows parameter of precompression tablet blend of all batches**

| Tests | F1 | F2 | F3 | F4 | F5 | F6 | F7 | S1 | S2 | S3 |
|---|---|---|---|---|---|---|---|---|---|---|
| *Bulk density (gm/ml) | 0.492 | 0.496 | 0.512 | 0.518 | 0.52 | 0.520 | 0.514 | 0.512 | 0.526 | 0.516 |
| *Tapped density (gm/ml) | 0.630 | 0.652 | 0.691 | 0.681 | 0.684 | 0.650 | 0.642 | 0.656 | 0.692 | 0.652 |
| *Hausner Ratio | 1.282 | 1.316 | 1.351 | 1.316 | 1.315 | 1.25 | 1.25 | 1.281 | 1.316 | 1.263 |
| *Comp. index (%) | 22.00 | 24.00 | 26.00 | 24.00 | 24.00 | 20.00 | 20.00 | 22.00 | 24.00 | 21.00 |
| *Angle of repose (θ) | 31.74 | 35.32 | 35.83 | 35.01 | 34.38 | 34.67 | 33.11 | 34.45 | 35.56 | 34.85 |
| *LOD (%) | 2.26 | 2.99 | 2.09 | 2.93 | 2.34 | 1.95 | 1.6 | 1.82 | 2.08 | 1.78 |

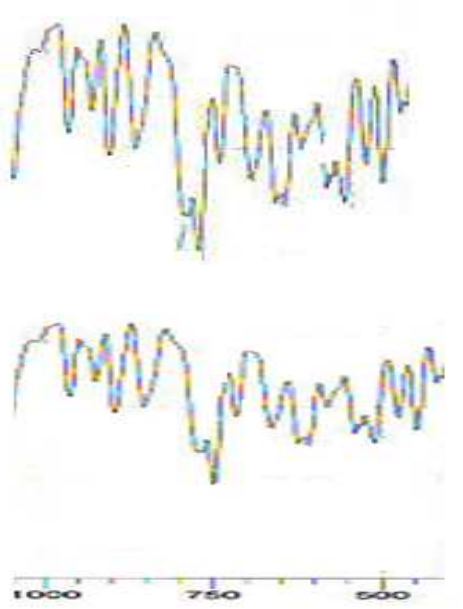



**Figure 1 FTIR of pure drug and FTIR Spectrum of Aceclofenac + HPMC K4M + HPMC E50 L**

The ratio of apparent medium content to matrix remaining in the tablet ($Q_W$ %) was plotted as a function of time. From Figure 5 shows the tablets had a higher apparent medium content, indicating a greater swelling capacity. Its shows 80% swelling in 24 hours

**Table 6 Shows post-compression parameters of all batches**

| Tests | Weight variation | *Hardness (kg/cm2) | *Thickness (mm) | *Diameter (mm) | *Friability (% loss) | *Drug content (%) |
|---|---|---|---|---|---|---|
| F1 | Pass | 7.30±0.15 | 4.40±0.12 | 10.34±0.01 | 0.19±0.05 | 98.20±0.23 |
| F2 | Pass | 6.00±0.12 | 4.57±0.11 | 10.36±0.01 | 0.17±0.02 | 97.80±0.34 |
| F3 | Pass | 5.50±0.18 | 4.56±0.15 | 10.35±0.03 | 0.21±0.04 | 101.2±0.22 |
| F4 | Pass | 6.00±0.15 | 4.57±0.17 | 10.35±0.02 | 0.09±0.01 | 99.50±0.37 |
| F5 | Pass | 6.50±0.14 | 4.56±0.21 | 10.35±0.04 | 0.071±0.01 | 98.60±0.25 |
| F6 | Pass | 6.00±0.21 | 4.56±0.18 | 10.35±0.03 | 0.08±0.02 | 99.20±0.17 |
| F7 | Pass | 5.50±0.134 | 4.58±0.13 | 10.36±0.02 | 0.079±0.01 | 99.60±0.18 |
| S1 | Pass | 7.00±0.11 | 4.59±0.11 | 10.34±0.01 | 0.073±0.01 | 100.5±0.21 |
| S2 | Pass | 6.50±0.15 | 4.60±0.12 | 10.34±0.01 | 0.26±0.02 | 98.90±0.25 |
| S3 | Pass | 6.80±0.09 | 4.57±0.16 | 10.35±0.02 | 0.012±0.01 | 99.10±0.26 |

**Table 7 Contains % Cumulative drug release of marketed, test and stability formulation**

| Time (hr) | M* | F1 | F2 | F3 | F4 | F5 | F6 | F7 | S1 | S2 | S3 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 11.9 | 32.8 | 5.1 | 15.2 | 20.9 | 10.0 | 11.1 | 10.4 | 9.4 | 9.8 | 10.7 |
| 2 | 18.1 | 55 | 8.4 | 26.9 | 45.1 | 16.2 | 17.6 | 18.4 | 17.8 | 17.0 | 18.8 |
| 3 | 24.3 | 74.5 | 11.7 | 40.5 | 54.3 | 20.8 | 22.2 | 24.3 | 25.9 | 22.6 | 23.2 |
| 4 | 32.3 | 91.2 | 15.0 | 54.8 | 71.9 | 25.5 | 27.4 | 29.9 | 30.0 | 30.9 | 31.4 |
| 6 | 44.0 | --- | 18.2 | 68.0 | 90.0 | 33.1 | 35.0 | 41.1 | 42.3 | 39.7 | 40.5 |
| 8 | 52.5 | --- | 20.6 | 81.3 | 101.1 | 39.3 | 44.1 | 49.8 | 50.6 | 48.1 | 52.1 |
| 10 | 59.8 | --- | --- | 92.4 | --- | 45.4 | 51.2 | 57.6 | 56.9 | 57.9 | 58.9 |
| 12 | 67.5 | --- | --- | --- | --- | 52.8 | 58.5 | 64.2 | 62.2 | 63.5 | 64.6 |
| 24 | 97.1 | --- | --- | --- | --- | 86.6 | 90 | 94.4 | 95.4 | 94.8 | 93.7 |

As illustrated in Figure 6 when the percentage overall erosion of the tablet (Ep) was plotted as a function of time, a faster apparent overall erosion rate was observed.

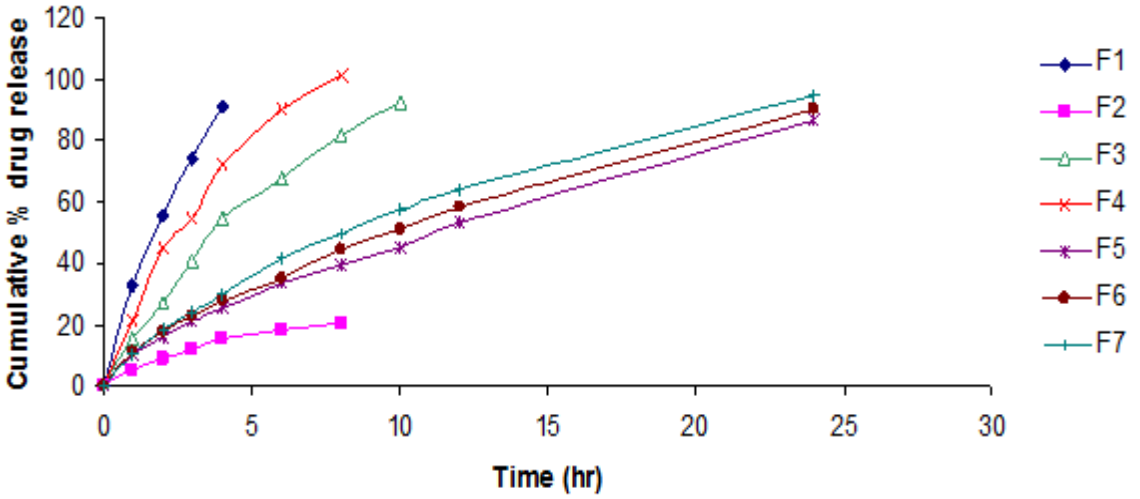



**Figure 2 Drug release profile of formulation F1 to F7**

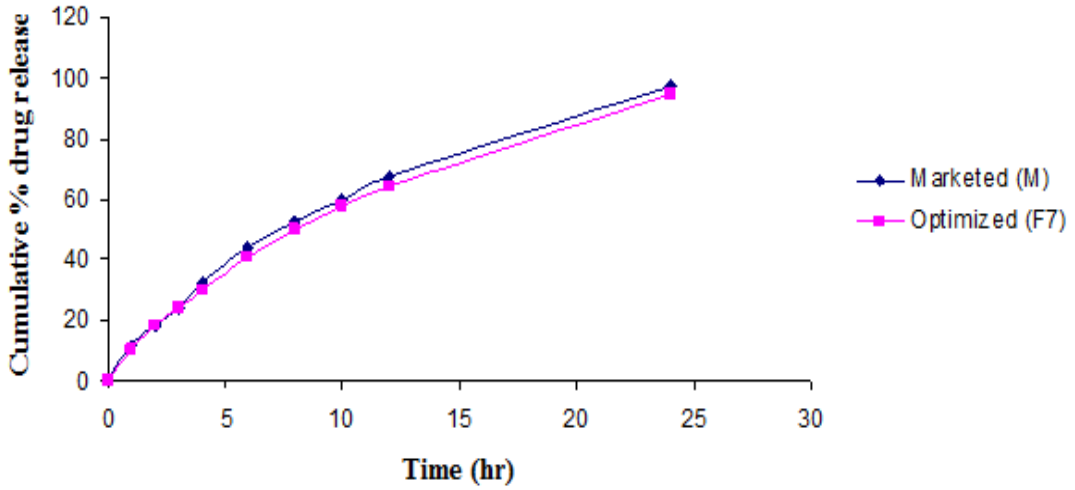



**Figure 3.Drug release profile of marketed and optimized Formulation (F7)**

The increase in wet weight represented the infiltration of medium into the interspaces of the tablet matrix. This was followed by swelling and erosion of the tablet matrix. It was shown that erosion of drug is 75% in 24 hours.

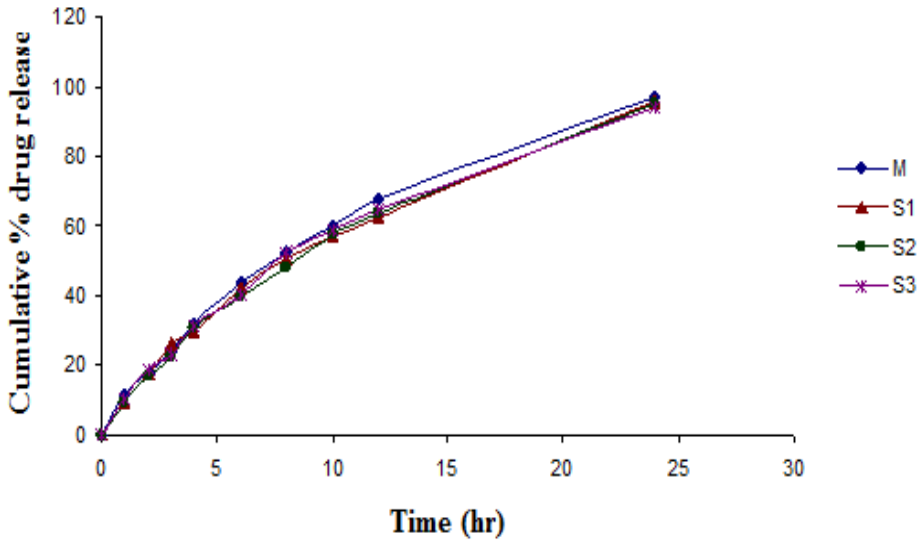



**Figure 4. Drug release profile of S1, S2 ,S3 formulation and marketed**

**Table 8 Swelling and Erosion Study of F7 Batch**

| Time (hr) | Initial wt. of tablet in mg ($W_i$) | Wt after swelling in mg ($W_w$) | Wt after drying in mg ($W_d$) |
|---|---|---|---|
| 0.5 | 381.9 | 579.8 | 374.4 |
| 1 | 381.2 | 618.4 | 365.1 |
| 2 | 382.8 | 684.3 | 356.7 |
| 3 | 381.3 | 725.9 | 338.4 |
| 4 | 380.3 | 733 | 327.8 |
| 5 | 381.9 | 751.2 | 319.5 |
| 6 | 381.7 | 775.4 | 279.9 |
| 7 | 379.0 | 770.1 | 263.3 |
| 8 | 380.4 | 764.3 | 259.5 |
| 24 | 384.3 | 276.6 | 55.7 |

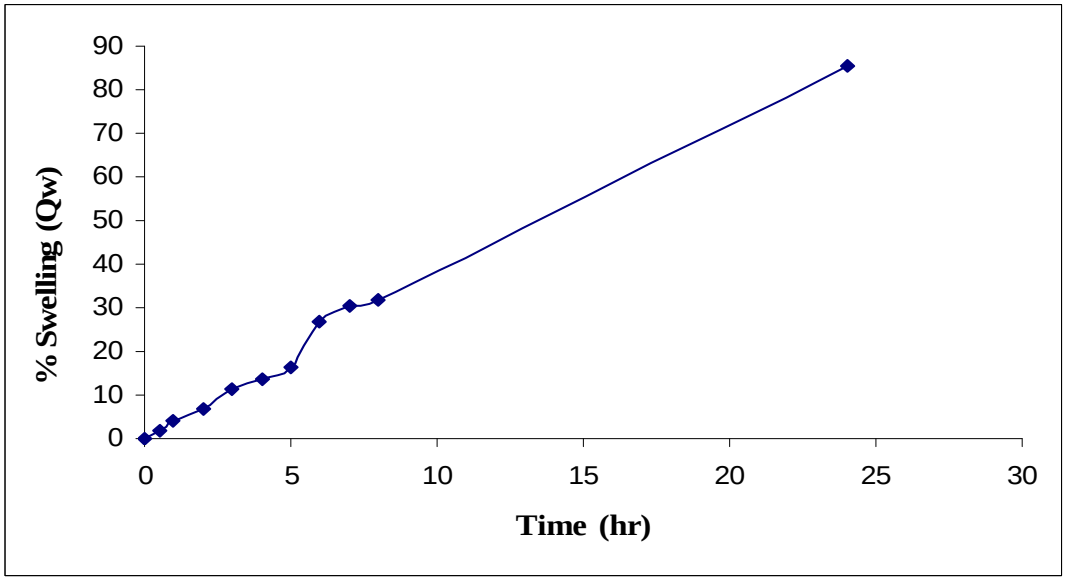
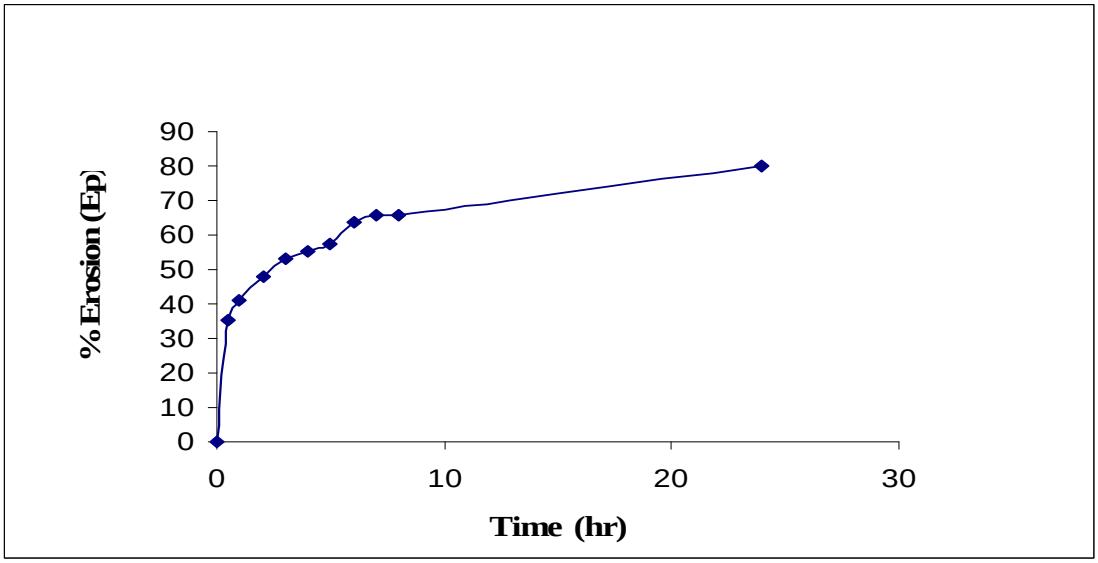



**Figure 5. Medium content ratio of tablets as a function of time**




**Figuer 6. Erosion of the tablets as a function of time**

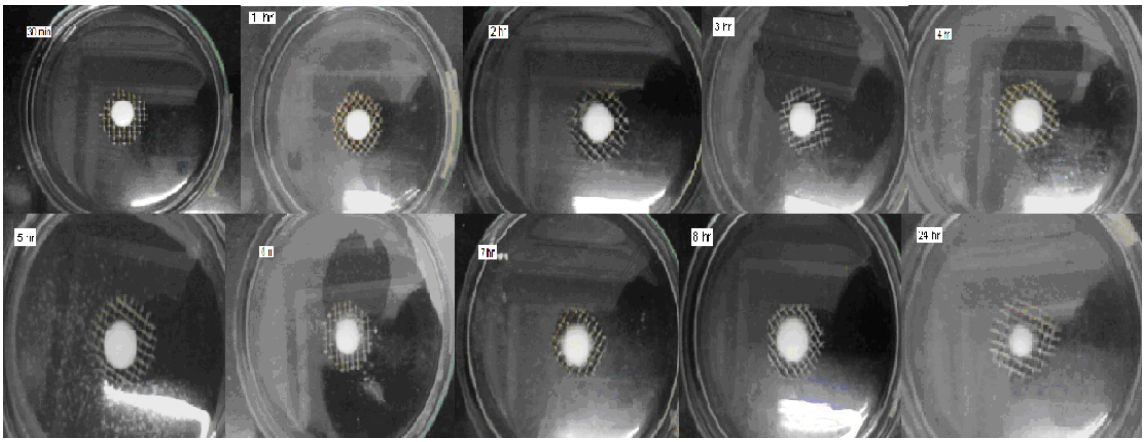


**Figure 7. Tablets after swelling at different time**

## CONCLUSION

In present work attempts have been made to formulate and evaluate sustained release matrix tablets of Aceclofenac by using hydrophilic polymer HPMC. Aceclosfenac shows potent analgesic and anti-inflammatory properties. Matrix tablets were prepared by direct compression technique. Aceclofenac meets all the ideal characteristics to formulate in the form of sustained release drug delivery system. Under preformulation study FT-IR study confirms identity of Aceclofenac drug powder. All the formulations were evaluated on the basis of standard specification. Shape of the tablets was round plain concave. Hardness was found to be in the range of 5.5 - 7.3. Thickness was found to be in between 4.4 – 4.6. Weight variation test for all the formulation were found to be in range.

Batch F7 was found to be optimized batch as it seems to be most promising formulation. Hardness, Thickness, Diameter, Weight variation, Friability test were found to be in limits and

satisfy the Pharmacopoeial standards. Dissolution study showed that batch F7 release drug up to 94.4 % at the end of 24 hr. Three batches of same formula of optimized batch F7 were prepared i.e. S1, S2, S3 and kept for stability study at 30°C, 65 % RH and 40°C, 75 % RH Condition for one month.

Assay of tablets were carried out for batch no.F7, S1, S2, S3 it was found to be 99.6%, 100.5%, 98.9%, and 99.1% respectively. After one month the product was removed from the stability chambers and evaluated for drug release and drug content. Stability studies of the selected formulated tablets at 30°C $\pm$ 2°C/ 65 $\pm$ 5 % RH and 40°C $\pm$ 2°C/ 75 $\pm$ 5 % RH (stability chamber) for 1 months. It showed slight acceptable difference in release pattern and drug content as compare to initial data. Thus it should be concluded that formulation F7 was stable.

Selected formulation for stability study, Batch No. S1, S2, S3 were also compared with the marketed product Zynac-SR (Zydus Alidac). The result of dissolution test was found almost similar to market sample.

The similarity (F2) and dissimilarity factor (F1) was calculated for optimized batch and stability batches which were found within acceptable range.
Kinetic study showed that the release rate of Aceclofenac from matrix tablets of batch F7 followed higuchi release kinetics. The 'n' value obtained from Korsmeymer-Peppas equation shows that formulations follow Super Case II transport where drug release mechanism was combination of swelling, diffusion and erosion. From the result it can be concluded that sustained release tablets of Aceclofenac containing HPMC E-50 (29 %) and HPMC K4M (6.5 %) i.e. F7 can be formulated successfully. Further detailed investigation is required to establish in vivo efficiency of matrix tablets of aceclofenac and long term stability studies were needed to confirm the stability of sustained release tablets.

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