Chapter 4

Formulation of Sustained Release Tablet of Aceclofenac containing Synthetic Polymer
4. Formulation of Sustained Release Tablet of Aceclofenac containing Synthetic Polymer

4.1. Introduction:
Hydrophilic matrices are widely used to develop oral sustained release formulations. They can be used for controlled release of both water soluble and insoluble drugs. The release of drugs varies with the nature of the matrix and also with the complex interaction of swelling, diffusion and erosion process [1]. Oral controlled release dosage forms have been developed to restrict this system to specific regions of the gastrointestinal tract, to improve the pharmacological activity and to reduce toxicity [2]. The most important method of fabricating controlled release formulations is incorporation of the drug in a matrix containing a hydrophilic, rate controlling polymer like HPMC [3]. Hydrophilic polymer matrix systems are widely used because of their flexibility to provide a desirable drug release profile, cost effectiveness and broad regulatory acceptance [4]. Aceclofenac (AC) [2-(2',6'-dichlorophenyl)amino]phenylacetoxyacetic acid is a phenylacetic acid derivative with potent analgesic and anti-inflammatory properties. The high concentration with rapid drug absorption causes adverse effects to GIT. To improve the therapeutic efficacy of Aceclofenac and reduce the severity of upper GI tract side-effects a dosage form with modified release properties should be prepared.
Thus, the objective of the present study was to develop a controlled release formulation of AC as matrix tablets, prepared by using different concentrations of HPMC (K15M).
4.2. Introduction to HPMC (Hydroxy propyl methyl cellulose) [5]:

4.2.1. Synonyms: Methocel; hydroxyl propyl methyl ether; metolose; pharmacoat

4.2.2. Chemical name: Cellulose, 2-hydroxypropyl methyl ether

4.2.3. Functional category:
Coating agent, film former, rate controlling polymer for sustained release, stabilizing agent; suspending agent, tablet binder, viscosity increasing agent.

4.2.4. Description: It is white or creamy white colored fibrous or granular powder.

4.2.5. Typical properties:

Acidity/alkalinity: pH=5.5-8.0 for 1% solution

Ash: 1.5-3% depending upon the grade.

Melting point: 190-200°C

Solubility: soluble in cold water, forming a viscous colloidal solution. Insoluble in chloroform, ethanol and ether. Certain grade of HPMC is soluble in aqueous acetone solutions.

4.2.6. Stability and storage condition:
HPMC powder is a stable material although, it is hygroscopic after drying. Solutions are stable at pH 3-11. Increasing temperature reduced viscosity of solution. HPMC undergoes a reversible sol to gel transformation upon heating and cooling respectively. The gel point is 50-90°C depending upon the grade and concentration. Aqueous solution is enzyme-resistance, providing good viscosity stability during long term storage. Aqueous solutions are liable to microbial spoilage and should be preserved with antimicrobial preservatives. When used as a viscosity increasing agents in ophthalmic solution; benzalkonium...
chloride is commonly used for this purpose. HPMC should be stored in a well closed container.

4.2.7. Method of manufacturing:
A purified form of cellulose, obtained from cotton linters or wood pulp, is reacting with sodium hydroxide solution to produce swollen alkali cellulose which is chemically more reactive than unreacted cellulose. The alkali cellulose is then treated with chloromethane and propylene oxide to produced methyl hydroxyl propyl ether of cellulose. The fibrous reaction product is then purified and ground to a fine, uniform powder or granules.

4.2.8. Safety:
The WHO has not specified an acceptable daily intake for HPMC the level consumed is not considered to represent a hazard to health. LD$_{50}$ (mouse, IP): 5g/Kg LD$_{50}$ (rat, IP): 5.2 g/Kg

4.2.9. Handling precautions:
HPMC dust may be irritant to the eyes and eye protection is recommended. Excessive dust generation should be avoided to minimize the risk of explosion. HPMC is combustible.

4.2.10. Regulatory status:
Accepted as a food additive in Europe. Included in the FDA. Included in non parenteral medicines licensed in the UK.

4.2.11. Related substances:
Hydroxy propyl cellulose, hydroxy propyl methyl cellulose methyl cellulose.
4.2.12. Application:

It is used in oral and topical pharmaceutical formulation. In oral, as a binder, in film coating, as a extended release tablet matrix. In topical, as a suspending and thickening agent, as a emulsifying agent and stabilizing agent in topical gels.

It is also used in cosmetics and food product.
4.3. Introduction to Micro crystalline cellulose (MCC) [6]:

4.3.1. Synonym: Avicel, Cellulose gel, crystalline cellulose, E460, Emocel, Fibrocel, Vivace!

4.3.2. Chemical Name: cellulose

4.3.3. Empirical formula: \((C_6H_{10}O_5)_n\), where \(n = 220\).

4.3.4. Molecular weight: 36000.

4.3.5. Functional Category:

Tablet and capsule diluents, suspending agent, adsorbent and tablet disintegrant.

4.3.6. Application:

Primarily used as diluents in tablets and capsule formulation where it is used in the both wet granulation and direct compression in tablet and capsule formulation. It also has some lubricant and disintegrant property.

4.3.7. Description:

It occurs as a white color, tasteless, crystalline powder composed of porous particles.

4.3.8. Solubility:

Slightly soluble in 5% sodium hydroxide solution, practically insoluble in water.

4.3.9. Stability and Storage condition:

It is stable, though hygroscopic material. The bulk material should be stored in well closed container in a cool and dry place.

4.3.10. Incompatibility:

Incompatible with strong oxidizing agent.
4.3.11. Safety:

It is generally regarded as a nontoxic and non irritant material.

4.3.12. Pharmaceutical uses:

Pharmaceutically, primarily as a binder/diluent in oral tablet formulations, where it is used in both direct compression and wet granulation methods. In addition to its use as binder/diluent, MCC also has some lubricant and disintegrant properties that makes it useful in tableting.
4.4. Aim of present work

Synthetic polymers are approved by US FDA and various agencies as compared to natural polymers. The present work was undertaken to explore the use of synthetic pharmaceutical excipient in the formulation of Aceclofenac tablet for pharmaceutical dosage form. So, plan of work was carried out as follows;

1. Formulation of Aceclofenac tablet containing synthetic polymer like HPMC and MCC using it’s at various concentration.


3. *In vitro* Dissolution data were fitted to various models.

4. Stability study
4.5. Methods:

4.5.1. Preparation of tablets

All formulations were prepared by the direct compression method. AC, polymer and other Excipients were mixed in a double cone blender for 15 min [7]. The amounts of polymer and other ingredients are given in Table 4.1. The quantities of ingredients required for preparing sustained release formulations were compressed using a single punch-tableting machine (Cadmach® Machinery Co. Pvt. Ltd., India) equipped with 6.5 mm circular, flat and plain punches. The batch size of each formulation for each drug was 100 tablets.

Table 4.1. Composition of sustained release matrix tablets of Aceclofenac

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Aceclofenac (mg)</th>
<th>HPMC K15M (mg)</th>
<th>MCC (mg)</th>
<th>Talc (mg)</th>
<th>Mg-stearate (mg)</th>
<th>Total (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>200</td>
<td>10</td>
<td>80</td>
<td>5</td>
<td>5</td>
<td>300</td>
</tr>
<tr>
<td>F2</td>
<td>200</td>
<td>20</td>
<td>70</td>
<td>5</td>
<td>5</td>
<td>300</td>
</tr>
<tr>
<td>F3</td>
<td>200</td>
<td>30</td>
<td>60</td>
<td>5</td>
<td>5</td>
<td>300</td>
</tr>
<tr>
<td>F4</td>
<td>200</td>
<td>40</td>
<td>50</td>
<td>5</td>
<td>5</td>
<td>300</td>
</tr>
</tbody>
</table>

4.5.2. Evaluation of matrix tablets

Quality control tests for the matrix tablets, such as hardness, friability and drug content were determined using the reported procedure.

Drug content of 20 tablets were determined after finely powdered and an amount equivalent to 200 mg of Aceclofenac tablet powder was accurately weighed and
transferred to a 100 mL volumetric flask and extracted with phosphate buffer (pH 7.2). The mixture was then filtered and 1 mL of the filtrate was suitably diluted and analyzed at 275 nm for Aceclofenac using a UV/Visible double beam spectrophotometer (UV-1700, Shimadzu, Japan). The method was validated for linearity, precision and accuracy. Hardness was determined by taking 6 tablets from each formulation using a digital tablet hardness tester (Electro lab Ltd, India). Friability was determined using 20 tablets in a Roche® friabilator (Electrolab Pvt. Ltd., India), which was rotated for 4 min at 25 rpm.

4.5.3. In vitro drug release

Release of AC was determined using a six stage dissolution rate test apparatus [8] (Type II, TDL - 08, Electrolab India, Mumbai) at 50 rpm. The dissolution rate was studied using 900 mL of phosphate buffer (pH 7.2). The temperature was maintained at 37 ± 0.2 °C. Samples of 5 mL each were withdrawn at different time intervals, filtered through Whatman filter paper No. 1 (Auroco Pvt Ltd, Thailand) and replaced with an equal amount of fresh dissolution medium. Samples were suitably diluted and analyzed for AC content spectrophotometrically. Release studies were conducted in triplicate. The rate and mechanism of release of both drugs from the prepared matrix tablets were analyzed by fitting the dissolution data into the various models:

4.5.4. Swelling and Erosion

Swelling and erosion studies were performed on twelve tablets using the method described by Reynold et al. [9] in phosphate buffer (pH 7.2) at 37 °C. The experiment was repeated three times for each individual time interval. Swelling and erosion studies were carried out at a stirring speed of 100 rpm (paddle type).
4.5.5. Stability study:
The tablets were charged for the accelerated stability studies as per ICH guidelines (40±2°C and 75±5% RH) for a period of 6 months in stability chambers. They were placed in flint vials and hermetically sealed with rubber plugs and aluminum caps. The samples were taken out at 15, 30, 60, 90 and 180 days and evaluated for the drug content and physical parameters like color change, hardness, friability and cumulative drug release (n=3).
4.6. Result and Discussion:

4.6.1. Physical characterization of tablets

All formulations were prepared according to the formula given in Table 4.1. The prepared matrix tablets were evaluated for various physical properties, as indicated in Table 4.2. All the batches were produced under similar conditions to avoid processing variables. The hardness of the tablets was found in between $5.3 \pm 0.2$ to $6.2 \pm 0.4$ kg/cm$^2$. The percentage friability of all formulations was between 0.1 and 1.0 %. The results of the hardness and friability tests indicate good handling properties of prepared tablets. The mean drug content in the tablets was $99.9 \pm 2.3$ %.

Table 4.2. Tablets Properties of Compressed Tablets.

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Hardness (kg cm$^{-2}$)</th>
<th>Friability (%)</th>
<th>Drug Content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>$5.8 \pm 0.3$</td>
<td>$0.5 \pm 0.1$</td>
<td>$98.9 \pm 3.8$</td>
</tr>
<tr>
<td>F2</td>
<td>$5.3 \pm 0.2$</td>
<td>$0.7 \pm 0.1$</td>
<td>$99.7 \pm 2.5$</td>
</tr>
<tr>
<td>F3</td>
<td>$6.2 \pm 0.4$</td>
<td>$0.2 \pm 0.1$</td>
<td>$100.7 \pm 1.3$</td>
</tr>
<tr>
<td>F4</td>
<td>$5.9 \pm 0.3$</td>
<td>$0.4 \pm 0.1$</td>
<td>$100.2 \pm 1.1$</td>
</tr>
</tbody>
</table>

4.6.2. In vitro drug release

Formulations containing Aceclofenac (200 mg) were developed by the simple direct compression method using HPMC K15M. The effect of polymer level on the release of water insoluble AC was studied for tablets containing 5, 10, 15 and 20 % HPMC K15M (formulations F1-F4, respectively). Data are shown in Table 4.3 and Fig. 4.1. The release rate was found to be decreasing as the concentration of polymer increased from 5 to 20 %. Water insoluble Aceclofenac formulations F1, F2 and F3 containing 5,
Aceclofenac Containing Synthetic Polymer

10 and 15 % HPMC, respectively, were able to sustain the drug release for 8, 10 and 12 hours, respectively. For F1 96.1 % of the drug was released within 8 hours, for F2 94.4 % within 10 hours and for F3 94.2 % within 12 hours. Formulations F1 and F2 underwent swelling; then gradually erosion could take place, resulting in slower release due to the hydrophobic nature of the drug. In the case of formulation F3, 15 % of HPMC was sufficient to sustain the drug release for 12 hours. On increasing the quantity of HPMC up to 20 %, the release of the drug was too slow and only 78.2 % of the drug was released within 12 hours.

It was observed that when the polymer concentration was increased, the drug release rate decreased. This is due to the higher degree of the swelling because of higher concentration of polymers. However, further increase in polymer concentration did not significantly affect the drug release rate. Water insoluble drug required a smaller amount of polymer to sustain the release as compared to the water soluble drug because the hydrophobic nature of the drug restricts the penetration of the solvent inside the matrix, which retarded drug release from the matrix [10-13].

From formulations F1, F2, F3 and F4, where hydrophobic drug was combined with hydrophilic polymer, no burst release was observed. It has been reported that if more than 20 % of the drug is released in the first hour of dissolution, this may indicate a chance of dose dumping. So, there is a probability of dose dumping for formulations containing hydrophilic drug with hydrophilic polymer HPMC.

Formulation F1 to F4 showed high linearity with the zero-order equation \( R^2 = 0.959-0.990 \). The value of release exponent \( n \) ranged from 0.910 to 1.000 in case of formulations F1 to F4 containing Aceclofenac [14-19].
### Table 4.3. *In vitro* Drug Release from Formulations.

<table>
<thead>
<tr>
<th>Time (hr)/Formulation</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>25 ± 1.0</td>
<td>22 ± 1.0</td>
<td>20 ± 0.9</td>
<td>12 ± 0.5</td>
</tr>
<tr>
<td>2</td>
<td>35 ± 1.5</td>
<td>32 ± 1.4</td>
<td>28 ± 1.2</td>
<td>19 ± 0.7</td>
</tr>
<tr>
<td>3</td>
<td>47 ± 1.8</td>
<td>42 ± 1.7</td>
<td>36 ± 1.6</td>
<td>27 ± 1.0</td>
</tr>
<tr>
<td>4</td>
<td>57 ± 2.0</td>
<td>53 ± 1.9</td>
<td>44 ± 1.8</td>
<td>33 ± 1.2</td>
</tr>
<tr>
<td>5</td>
<td>67 ± 2.2</td>
<td>62 ± 2.3</td>
<td>54 ± 2.1</td>
<td>40 ± 1.3</td>
</tr>
<tr>
<td>6</td>
<td>77 ± 2.8</td>
<td>70 ± 2.6</td>
<td>62 ± 2.5</td>
<td>47 ± 1.4</td>
</tr>
<tr>
<td>7</td>
<td>89 ± 3.0</td>
<td>78 ± 3.1</td>
<td>69 ± 3.2</td>
<td>55 ± 1.5</td>
</tr>
<tr>
<td>8</td>
<td>96.1 ± 3.2</td>
<td>86 ± 3.3</td>
<td>76 ± 2.9</td>
<td>62 ± 1.5</td>
</tr>
<tr>
<td>9</td>
<td>90 ± 3.5</td>
<td>82 ± 3.1</td>
<td>69 ± 1.6</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>94.4 ± 3.5</td>
<td>88 ± 3.2</td>
<td>75 ± 1.7</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>94.2 ± 3.2</td>
<td>80 ± 1.8</td>
<td></td>
</tr>
</tbody>
</table>
The linear regression analysis is given in Table 4.4. The kinetic data of formulations F1 to F4 showed good fit with the zero-order equation ($R^2 = 0.959-0.990$) [20]. The value of release exponent $n$ ranged from 0.910 to 1.000 in case of formulations F1 to F4 with Aceclofenac.

From the release exponent in the Korsmeyer-Peppas model, it can be suggested that the mechanism that led to the release of Aceclofenac was an anomalous Non-Fickian diffusion transport [21], which indicates that the drug release occurred through diffusion in the hydrated matrix and polymer relaxation. In case of Aceclofenac, the mechanism of drug release shifted from anomalous Non-Fickian diffusion to swelling controlled drug delivery systems with zero-order kinetics [22-30].
Table 4.4. Kinetics of Drug Release from Aceclofenac Matrix Tablets.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Drug release kinetics ($R^2$)</th>
<th>Release exponent ($n$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Zero-order</td>
<td>First-order</td>
</tr>
<tr>
<td>F1</td>
<td>0.959</td>
<td>0.945</td>
</tr>
<tr>
<td>F2</td>
<td>0.985</td>
<td>0.916</td>
</tr>
<tr>
<td>F3</td>
<td>0.990</td>
<td>0.908</td>
</tr>
<tr>
<td>F4</td>
<td>0.987</td>
<td>0.968</td>
</tr>
</tbody>
</table>

4.6.3. Swelling and Erosion

Swelling and erosion studies indicate that swelling and erosion mechanisms might be operative during the drug release from matrix formulation F3. It was observed that all the formulations were initially intact and when they were placed in dissolution media they gradually formed pores. It was also observed that swelling and erosion increased with time. Data are shown in Table 4.5 and Figure 4.2. It was observed for all formulations that swelling and erosion occurred simultaneously in the matrix helping to constant release of the drug from the matrices [31]. Constant release in such situations occurs because the increase in the diffusion path length due to swelling is compensated by continuous erosion of the matrix [32]. It was also observed that the formulations containing the water soluble drug showed higher water uptake and erosion capacity than the water in soluble drug, because, the former allows the solvent to penetrate the matrix.
and form a viscous gel around it, whereas the insoluble drug restricts solvent penetration inside the matrix and retards matrix swelling and erosion [33-35].

Table 4.5. Swelling and erosion behavior of Formulation F3 containing Aceclofenac Tablets.

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>Swelling ± S.D. (n=3) (%)</th>
<th>Erosion ± S.D. (n=3) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>33 ± 1.5</td>
<td>9 ± 0.5</td>
</tr>
<tr>
<td>2</td>
<td>80 ± 2.5</td>
<td>15 ± 0.5</td>
</tr>
<tr>
<td>3</td>
<td>90 ± 2.7</td>
<td>18 ± 0.7</td>
</tr>
<tr>
<td>4</td>
<td>100 ± 2.9</td>
<td>22 ± 0.7</td>
</tr>
<tr>
<td>5</td>
<td>120 ± 3.0</td>
<td>25 ± 1.0</td>
</tr>
<tr>
<td>6</td>
<td>130 ± 3.0</td>
<td>29 ± 1.0</td>
</tr>
</tbody>
</table>

Fig. 4.2. % Swelling and Erosion of Optimized Batch.
3.6.5. STABILITY STUDY:

At the end of the testing period, the matrix tablets were observed for changes in physical appearance, analyzed for drug content, and subjected to *in vitro* drug release studies. No visible changes in the appearance of the matrix tablets were observed at the end of the storage period. The drug content was found to be 98.4 ± 0.053%. At the end of 24 hours of dissolution testing, the amount of Aceclofenac released from F3 matrix tablets before storage was 99.83 ± 0.035% whereas that released from the F3 formulation after storage was 99.27 ± 0.026%. There was no significant difference in the mean amount of aceclofenac released from F3 matrix tablets after storing for 6 months at 40°C/75% RH. (t test, p<0.05)
4.7. CONCLUSIONS

Aceclofenac sustained release matrix tablets were prepared successfully using HPMC as polymer to retard the release and achieve the required dissolution profiles. Results of the present study demonstrate that drug solubility has a significant effect on the release kinetics and mechanism of drug release. Water soluble drug required a larger amount of polymer to sustain the drug release compared to the insoluble drug the mechanism of drug release followed anomalous non-Fickian diffusion transport and zero-order for water soluble and insoluble drugs, respectively.
4.8. REFERENCES


Chapter 4

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