Chapter 5

Formulation

of

Aceclofenac Matrix Tablet

containing

Synthetic and Natural

Polymers
5. Formulation of Aceclofenac Matrix Tablet containing Synthetic and Natural Polymers.

5.1. Introduction:
Several matrixes based sustained release products of Aceclofenac have been reported based on their use as either a hydrophilic or hydrophobic polymers [1-7]. The reported sustained release formulations of Aceclofenac did not involve any attempt to prevent drug release in the upper GI tract. The matrix system of a polymer intended with drugs provides long duration of treatment and reduced adverse effects in patients. An attempt has been made here to achieve a better therapeutic profile through tablets with various viscosity of HPMC, Guar gum and ethyl cellulose. The \textit{in vitro} release of the experimental formulation, which showed a release profile similar to that of the innovator's product, was compared with that of a commercially sustained release formulation. Furthermore, the purpose of the study was also to establish an \textit{in vitro} release rate profile for various prepared Aceclofenac matrix sustained release tablet and a commercial formulation.

In India natural gums and mucilage have been well known for their medicinal use. In the modern era they are widely used in the pharmaceutical industry as thickeners, water retention agents, emulsifier, gelling agent, suspending agents, binders, film formers and sustained release agents. Apart from their use in the medicinal products, other uses have been found in cosmetics, textiles, paints and paper-making. Demand for these substances is increasing and new sources are being developed. India, due to its geographical and environmental position, has traditionally been a good source for such products among the...
Asian countries. Natural gums and mucilage are preferred to semi-synthetic and synthetic excipient due to their lack of toxicity, low cost, ready availability, soothing action and non-irritant nature [8 – 11].

Though a variety of polymeric substances are available to serve as release retarding matrix material, there is a continued need to develop new, safe and effective release retarding material. Oral drug delivery systems continue to dominate the market despite the advancements made in newer drug delivery systems such as transdermal, liposome, microspheres, etc.

5.1.1. Disadvantages of synthetic polymers

The synthetic polymers have certain disadvantages such as high cost, toxicity, environmental pollution during synthesis, non-renewable sources, side effects, less patient compliance.

1 Acute and chronic adverse effects (skin and eye irritation) have been observed in workers handling the related substances methyl methacrylate and poly-(methyl methacrylate) (PMMA) [12].

2 Reports on adverse reactions to povidone primarily concern the formation of subcutaneous granulomas at the injection site formulated with povidone. Evidence also exist that povidone may accumulate in organs following intramuscular injections [13].

3 Acute oral toxicity studies in animals indicated that carbomer-934P had a low oral toxicity at a dose up to 8 g/kg when administered without fatalities occurring. Carbomer dust is irritating to the eyes, mucous membranes and respiratory tract. So, gloves, eye protection and dust respirator are recommended during handling [14].
Studies in rats have shown that 5% polyvinyl alcohol aqueous solution injected subcutaneously can cause anemia and can infiltrate into various organs and tissues [15].

Some disadvantages of biodegradable polymers in tissue engineering application are their poor biocompatibility, release of acidic degradation products, poor process ability and loss of mechanical property very early during degradation. It was studied that poly glycolides, polylactides and their co-polymers have an acceptable biocompatibility but shown systemic or local reactions due to acidic degradation products. An initial mild inflammatory response has been reported by using poly-(propylene fumarate) on rat implant studies [16].

5.1.2. Advantages of natural gums & mucilages [17 - 19]

The advantages of natural plant based materials includes-

1. Biodegradable
2. Biocompatible and non toxic
3. Low cost
4. Renewable source
5. Environmental-friendly processing
6. Local availability (especially in developing countries)
7. Better patient tolerance as well as public acceptance
8. From edible sources
5.1.3. Disadvantages of natural gums & mucilages [20]

1. Microbial contamination
2. Batch to batch variation
3. Uncontrolled rate of hydration
4. Thickening nature
5. Drop in viscosity on storage
5.2. Introduction to Methocel K4M [21].

5.2.1. Synonyms: HPMC, Pharmacoat, Metolose, Methocel.

5.2.2. Chemical name & CAS registry no.: Cellulose, 2- Hydroxypropylmethyl ether (9004-65-3)

5.2.3. Empirical formula:

The Ph. Eur. describes Hydroxypropylmethylcellulose (HPMC) as partly -O-methylated & -O- (2-hydroxypropylated) cellulose. It is available in a several grades, which vary in viscosity & extent of substitution. Grades may be distinguished by appending a number of indicative of apparent viscosity, in milipascal seconds of 2 % w/v solution measured at 20°C.

5.2.4. Molecular weight: Approx.10000-1500000 daltons.

5.2.5. Description: Tasteless, odorless, white or creamy- white coloured fibrous or granular powder.

5.2.6. Functional category: Film former, rate-controlling polymer for sustained release, stabilizing agent, suspending agent, fixative, tablet binder & filler and viscosity increasing agent.

5.2.7. Solubility: Soluble in cold water, forming a viscous colloidal solution, practically insoluble in chloroform, ethanol (95%) and ether, but soluble in mixture of ethanol and dichloromethane, mixture of methanol and dichloromethane. Typical viscosity value of 2%w/v aqueous solution of methocel, viscosity at 20°C.
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**Methocel grades**  Viscosity (mPas)
- K4M  3000-5600.
- K15M  12000-21000.
- K100M  80000-120000.

5.2.8. **Storage:** At temperature not exceeding 32°C in dry area from all sources.

5.2.9. **Safety:** Non-toxic and Non-irritant.
- LD 50(Mouse IP) : 5g/kg
- LD 50(Rat IP) : 5.2g/kg.

5.2.10. **Incompatibilities:** With some Oxidizing agents.

5.2.11. **Stability:** Heat stable and Impact strength.

5.2.12. **Pharmaceutical uses:**
HPMC is widely used in oral and topical pharmaceutical formulations. In oral products, Hydroxy propyl methyl cellulose is primarily used as tablet binder in the film coating and as an extended release tablet matrix concentration of between 2-5% may be used as a binder in either wet or dry granulation processes. High viscosity grades may be used to retard the release of drug from the matrix at level of 10-80% w/w in tablet and capsules. Hydroxy propyl methylcellulose is also used as suspending agent and thickening agent in topical preparation, particularly ophthalmic preparation. It is also widely used in cosmetics and food products.
5.3 Introduction to Guar gum [22].

5.3.1. Non proprietary name: Guar galactomannan.

5.3.2. European Pharmacopoeia: Guar galactomannan

5.3.3. United state Pharmacopoeia: Guar Gum

5.3.4. Synonyms: Galactosol, Guar Flour, Jaguar gum.

5.3.5. Chemical name: Galactomannan polysaccharide.

5.3.6. Empirical formula: \((\text{C}_6\text{H}_{12}\text{O}_0)_n\)

5.3.7. Molecular weight: Approx. 220000

5.3.8. Functional category:

Suspending agent, tablet binder, tablet disintegrant, viscosity increasing agent.

5.3.9. Pharmacopoeia:

BP, Eur. Pharmacopoeia, and USPNF.

5.3.10. Description:

Odorless or a nearly odorless, white to yellowish-white powder with a bland taste.

5.3.11. Aqueous viscosity: 4860 cps.

5.3.12. Solubility:

Practically insoluble in organic solvents. In cold or hot water, guar gum disperses and swells almost immediately to form a highly viscous, thixotropic sol.
5.3.14. Stability and storage condition:

Aqueous guar gum dispersion have a buffering action and are stable between pH 4.0 and 10.5 however, prolonged heating reduces the viscosity of dispersion. Guar gum powder should be stored in a well-closed container in a cool, dry place.

5.3.15. Incompatibilities:

It is compatible with most other plant hydrocolloids such as tragacanth. Guar gum is compatible with acetone, tannins, strong acids and alkalis acetone, tannins, strong acids and alkalis.

5.3.16. Safety:

It is generally regarded as a nontoxic and non-irritant material although excessive oral consumption may cause gastrointestinal disturbance such as flatulence, diarrhea, or nausea.

5.3.17. Application:

Guar gum is widely used in oral and topical pharmaceutical formulation. It has also been investigated in the preparation of sustain release matrix tablets in the place of cellulose derivatives such as methyl cellulose.

In pharmaceutical, guar gum is used in solid-dosage forms as binder and disintegrant. In oral or topical products as a suspending, thickening and stabilizing agent.
5.4. Introduction to Ethyl Cellulose [23 - 51].


Ethyl Cellulose is a non-ionic ethyl ether of cellulose, soluble in a wide range of organic solvents. Typically, ethylcellulose is used as a non-swellable, insoluble component in matrix or coating systems. When water soluble binders cannot be used in dosage processing because of water sensitivity of the active ingredient, ethylcellulose is often chosen.

Ethylcellulose can be used to coat one or more active ingredients of a tablet to prevent them from reacting with other materials or with one another. It can prevent discoloration of easily oxidizable substances such as ascorbic acid, allowing granulations for easily compressed tablets and other dosage forms. Ethylcellulose can be used on its own or in combination with water-soluble polymers to prepare sustained release film coatings that are frequently used for the coating of micro-particles, pellets and tablets.

**DEFINITION:** Ethyl ether of cellulose, prepared from wood pulp or cotton by treatment with alkali and ethylation of the alkali cellulose with ethyl chloride. The article of commerce can be specified further by viscosity.

5.4.1. Nonproprietary Names:

BP: Ethylcellulose

PhEur: Ethylcellulose

USP-NF: Ethylcellulose
5.4.2. Synonyms:
Aquacoat ECD; Aqualon; Ashacel; E462; Ethocel; ethylcellulosum; Surelease.

5.4.3. Chemical names: Cellulose ethyl ether, ethyl ether of cellulose

5.4.4. C.A.S. number: 9004-57-3

5.4.5. Empirical Formula and Molecular Weight
Ethylcellulose is partially ethoxylated. Ethylcellulose with complete ethoxyl substitution (DS = 3) is \( \text{C}_{12}\text{H}_{22}\text{O}_{6} \) \((\text{C}_{12}\text{H}_{22}\text{O}_{6})_n\text{C}_{12}\text{H}_{23}\text{O}_{5} \) where \( n \) can vary to provide a wide variety of molecular weights. Ethylcellulose, an ethyl ether of cellulose, is a long-chain polymer of \( \beta \)-anhydroglucose units joined together by acetal linkages.

5.4.6. Assay: Not less than 44% and not more than 50% of ethoxyl groups (-OC\(_2\)H\(_5\)) on the dried basis (equivalent to not more than 2.6 ethoxyl groups per anhydroglucose unit).

5.4.7. DESCRIPTION: Free-flowing, white to light tan powder

5.4.8. IDENTIFICATION:

5.4.8.1. Solubility: Practically insoluble in water, in glycerol, and in propane-1,2-diol, but soluble in varying proportions in certain organic solvents, depending upon the ethoxyl content. Ethyl cellulose containing less than 46-48% of ethoxyl groups is freely soluble in tetrahydrofuran, in methyl acetate, in chloroform, and in aromatic hydrocarbon ethanol mixtures. Ethylcellulose containing 46-48% or more of ethoxyl groups is freely soluble in ethanol, in methanol, in toluene, in chloroform, and in ethyl acetate.

5.4.8.2. Film forming test: Dissolve 5 g of the sample in 95 g of an 80:20 (w/w) mixture of toluene-ethanol. A clear, stable, slightly yellow solution is formed. Pour a few ml of the solution onto a glass plate, and allow the solvent to evaporate. A thick, tough continuous, clear film remains. The film is flammable.
5.4.8.3. **pH**: Neutral to litmus (1 in 20 suspension)

5.4.8.4. **Loss on drying**: Not more than 3% (105°C, 2 h)

5.4.8.5. **Sulfated ash**: Not more than 0.4%, Test 1 g of the sample (Method I)

5.4.8.6. **Lead**: Not more than 2 mg/kg

5.4.9. **Functional Category**

Coating agent, flavoring agent, tablet binder, tablet filler, and viscosity increasing agent.
## Table 5.1. Various grades of Ethyl cellulose with their applications.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Viscosity (mPas) % w/w</th>
<th>Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC N 7 Pharm</td>
<td>6 - 8</td>
<td>Microencapsulation, Tablet Coating – Film coating for sustained release.</td>
</tr>
<tr>
<td>EC N 10 Pharm</td>
<td>8 – 11</td>
<td>Tablet Binder – Plastic flow, suitable for direct compression, injection molding and melt extrusion.</td>
</tr>
<tr>
<td>EC N 14 Pharm</td>
<td>12 – 16</td>
<td>Taste Masking</td>
</tr>
<tr>
<td>EC N 22 Pharm</td>
<td>18 – 24</td>
<td></td>
</tr>
<tr>
<td>EC N 50 Pharm</td>
<td>18 – 24</td>
<td></td>
</tr>
<tr>
<td>EC N 100 Pharm</td>
<td>80 – 105</td>
<td>Directly compressible, micronized grade with high ethoxy content and low viscosity for optimum compactibility and good powder flow. Eliminates the need for solvents in direct compression controlled release matrices.</td>
</tr>
<tr>
<td>EC T 10 Pharm</td>
<td>8 - 11</td>
<td></td>
</tr>
</tbody>
</table>
5.4.10. Applications in Pharmaceutical Formulation or Technology

The main use of ethyl cellulose in oral formulations is as a hydrophobic coating agent for tablets and granules. Ethyl cellulose coatings are used to modify the release of a drug, to mask an unpleasant taste, or to improve the stability of a formulation; for example, where granules are coated with ethyl cellulose to inhibit oxidation. Modified-release tablet formulations may also be produced using ethyl cellulose as a matrix former.

Ethyl cellulose, dissolved in an organic solvent or solvent mixture, can be used on its own to produce water-insoluble films. Higher-viscosity ethyl cellulose grades tend to produce stronger and more durable films. Ethyl cellulose films may be modified to alter their solubility, by the addition of hypromellose or a plasticizer.

Drug release through ethyl cellulose-coated dosage forms can be controlled by diffusion through the film coating. This can be a slow process unless a large surface area (e.g. pellets or granules compared with tablets) is utilized. In those instances, aqueous ethyl cellulose dispersions are generally used to coat granules or pellets. Ethyl cellulose-coated beads and granules have also demonstrated the ability to absorb pressure and hence protect the coating from fracture during compression.

High-viscosity grades of ethylcellulose are used in drug microencapsulation. Release of a drug from an ethylcellulose microcapsule is a function of the microcapsule wall thickness and surface area. In tablet formulations, ethylcellulose may additionally be employed as a binder, the ethylcellulose being blended dry or wet granulated with a solvent such as ethanol (95%). Ethylcellulose produces hard tablets with low friability, although they may demonstrate poor dissolution. Ethylcellulose has also been used as an agent for delivering therapeutic agents from oral (e.g. dental) appliances. In topical formulations,
ethylcellulose is used as a thickening agent in creams, lotions, or gels, provided an appropriate solvent is used. Ethylcellulose has been studied as a stabilizer for emulsions. Ethylcellulose is additionally used in cosmetics and food products.

5.4.11. Stability and Storage Conditions

Ethylcellulose is a stable, slightly hygroscopic material. It is chemically resistant to alkalis, both dilute and concentrated, and to salt solutions, although it is more sensitive to acidic materials than are cellulose esters.

Ethylcellulose is subject to oxidative degradation in the presence of sunlight or UV light at elevated temperatures. This may be prevented by the use of antioxidant and chemical additives that absorb light in the 230–340nm range.

5.4.12. Incompatibilities

Incompatible with paraffin wax and microcrystalline wax.

5.4.13. Method of Manufacture

Ethylcellulose is prepared by treating purified cellulose (sourced from chemical-grade cotton linters and wood pulp) with an alkaline solution, followed by ethylation of the alkali cellulose with chloroethane as shown below, where R represents the cellulose radical:

5.4.14. Safety

Ethylcellulose is widely used in oral and topical pharmaceutical formulations. It is also used in food products. Ethylcellulose is not metabolized following oral consumption and is therefore a noncalorific substance. Because ethylcellulose is not metabolized it is not recommended for parenteral products; parenteral use may be harmful to the kidneys.
Ethylcellulose is generally regarded as a nontoxic, non-allergenic, and nonirritating material. As ethylcellulose is not considered to be a health hazard, the WHO has not specified an acceptable daily intake. The highest reported level used in an oral product is 308.8 mg in an oral sustained release tablet.
5.5. **Aim of present work**

The present work was undertaken using various 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 various polymer like HPMC (different grades), Guar Gum and Ethyl cellulose using at various concentrations.
3. Stability study
5.6. Methods:

5.6.1. Preparation of Matrix tablets

The tablets were prepared by wet granulation technique. The compositions of the tablet formulations are given in Table 5.2. Weighed amounts of Aceclofenac, retardant (HPMC, Guar gum, ethylcellulose and diluents (lactose), were taken into a bowl by passing through a 40 mesh screen and mixed manually for 5 min. Then the blend was granulated with PVPK-30 using water as the granulating agent. The mass was dried in a hot air oven at 50°C and sieved through a 30 mesh screen. Magnesium stearate was then added to the dried, sieved granules and mixed for about 5 min in a poly-bag. The produced mixture was compressed into tablets using a 12 station tablet compression machine, (Rotary Tablet Machine, Rimek – II, Karnavati Engg., Ahmedabad, India) equipped with an 11 mm biconcave-faced punches. The selected batch (Batch G) was coated using the coating formula as given in Table 5.3 and using a laboratory coater under controlled condition. The efficiency of mixing was verified by the determination of drug content.

5.6.2. Coating

Batch G was coated using a laboratory coater (Model GAC-250, Gansons Ltd, Mumbai, India) under controlled condition.
Table 5.2. Composition of sustained release tablet formulation.

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
<th>H</th>
<th>I</th>
<th>J</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aceclofenac</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
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<tr>
<td>Methocel K4M</td>
<td>25</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>40</td>
<td>--</td>
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</tr>
<tr>
<td>Methocel K15M</td>
<td>--</td>
<td>25</td>
<td>--</td>
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<td>--</td>
<td>--</td>
<td>--</td>
<td>15</td>
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<td>--</td>
</tr>
<tr>
<td>Methocel K100M</td>
<td>--</td>
<td>--</td>
<td>20</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>10</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Guar gum</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>30</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>60</td>
</tr>
<tr>
<td>Ethyl cellulose</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>20</td>
<td>--</td>
<td>--</td>
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<td>--</td>
</tr>
<tr>
<td>HPMC</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>50</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Lactose</td>
<td>62.5</td>
<td>62.5</td>
<td>67.5</td>
<td>57.5</td>
<td>67.5</td>
<td>37.5</td>
<td>47.5</td>
<td>72.5</td>
<td>77.5</td>
<td>27.5</td>
</tr>
<tr>
<td>Povidone</td>
<td>7.5</td>
<td>7.5</td>
<td>7.5</td>
<td>7.5</td>
<td>7.5</td>
<td>7.5</td>
<td>7.5</td>
<td>7.5</td>
<td>7.5</td>
<td>7.5</td>
</tr>
<tr>
<td>Purified water</td>
<td>q.s.</td>
<td>q.s.</td>
<td>q.s.</td>
<td>q.s.</td>
<td>q.s.</td>
<td>q.s.</td>
<td>q.s.</td>
<td>q.s.</td>
<td>q.s.</td>
<td>q.s.</td>
</tr>
<tr>
<td>Mg-stearate</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>300</td>
<td>300</td>
<td>300</td>
<td>300</td>
<td>300</td>
<td>300</td>
<td>300</td>
<td>300</td>
<td>300</td>
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</tr>
</tbody>
</table>
Table 5.3. Composition of Coating containing Sustained Release Tablet.

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Quantity Per Tablet (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H.P.M.C (6CPS)</td>
<td>7.5</td>
</tr>
<tr>
<td>Isopropyl alcohol</td>
<td>0.13</td>
</tr>
<tr>
<td>Methylene chloride</td>
<td>0.32</td>
</tr>
<tr>
<td>Titanium dioxide</td>
<td>1.65</td>
</tr>
<tr>
<td>PEG 6000</td>
<td>0.85</td>
</tr>
<tr>
<td>Castor oil</td>
<td>2.50</td>
</tr>
<tr>
<td>Ponceaur 4 R supra color</td>
<td>0.9</td>
</tr>
</tbody>
</table>

5.6.3. Physiochemical characterization of tablets

The weight variation was evaluated on 10 tablets using an electronic balance (Digital Balance- AUX -220 Uniblock Technology, Shimadzu, Japan). Tablet hardness was determined for 10 tablets using a Monsanto (Standard type) tablet hardness tester and Friability Test Apparatus USP XXIII, Model EF2, Friabilator, Electrolab India, Mumbai, India, for 4 min at 25 rpm.

5.6.4. In-vitro release rate studies

The in vitro dissolution study was carried out using USP Type II dissolution apparatus. The study was carried out in 900 ml of phosphate buffer pH 7.5 from 2 to 12 h. The dissolution medium was kept in a thermostatically controlled water bath, maintained at 37 ± 0.5°C. The paddle was lowered so that the lower end of the stirrer was 25 mm above the base of the beaker. The pre-weighed tablet was then introduced into the dissolution
jar and the paddle was rotated at 100 rpm. At different time intervals, 5 ml sample was withdrawn and analyzed spectrophotometrically at 275 nm for drug release. At each time of withdrawal, 5 ml of fresh corresponding medium was replaced into the dissolution flask.

5.6.5. Stability studies

Stability studies were conducted on Aceclofenac matrix tablet containing 11.4% of HPMCK4M (G) to assess their stability with respect to their physical appearance, drug content and drug release characteristics after storing them at 40°C/75% RH for 6 months. Samples were withdrawn at 0, 90 and 180 days for evaluation of appearance, drug content and in vitro drug release.
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5.7. RESULTS AND DISCUSSION

5.7.1. Results of Physical Properties:

The physical properties of the finished good are shown in Table 5.4. The following parameters; weight uniformity, drug content, thickness, hardness and friability were calculated. Tablets prepared by wet granulation were uniform in weight and thickness and complied with the USP 32 requirements. From the obtained data in Table, the percentage of drug contents in prepared tablets was found to be within the range of 99.08 to 104.5%. The values of the disintegration time of the prepared tablets were within the allowable range of the USP 32 for uncoated tablets. The friability of the tablets was higher than marketed products. Generally, the values for friability ranged from 0.12 to 0.45%, which was an acceptable value according to the USP 32 requirements. The prepared tablets showed hardness levels in the range of 3.0 to 7.0 kg/sq.cm.
Table 5.4. Physical properties of the prepared Aceclofenac sustained release tablets.

<table>
<thead>
<tr>
<th>Batch Code</th>
<th>Weight variation (%)</th>
<th>Thickness (mm)</th>
<th>Hardness (kg/cm²)</th>
<th>Friability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>300 ± 2.0</td>
<td>3.9 ± 0.2</td>
<td>5-6</td>
<td>0.24</td>
</tr>
<tr>
<td>B</td>
<td>302 ± 2.5</td>
<td>3.8 ± 0.2</td>
<td>5-7</td>
<td>0.26</td>
</tr>
<tr>
<td>C</td>
<td>304 ± 1.5</td>
<td>3.6 ± 0.2</td>
<td>4-7</td>
<td>0.12</td>
</tr>
<tr>
<td>D</td>
<td>299 ± 2.0</td>
<td>3.6 ± 0.2</td>
<td>5-6</td>
<td>0.15</td>
</tr>
<tr>
<td>E</td>
<td>302 ± 2.5</td>
<td>3.7 ± 0.2</td>
<td>3-5</td>
<td>0.45</td>
</tr>
<tr>
<td>F</td>
<td>300 ± 2.5</td>
<td>3.7 ± 0.2</td>
<td>5-7</td>
<td>0.20</td>
</tr>
<tr>
<td>G</td>
<td>300 ± 1.5</td>
<td>3.6 ± 0.2</td>
<td>5-6</td>
<td>0.20</td>
</tr>
<tr>
<td>H</td>
<td>301 ± 2.5</td>
<td>3.7 ± 0.2</td>
<td>5-6</td>
<td>0.35</td>
</tr>
<tr>
<td>I</td>
<td>300 ± 2.0</td>
<td>3.7 ± 0.2</td>
<td>4-6</td>
<td>0.15</td>
</tr>
<tr>
<td>J</td>
<td>303 ± 1.5</td>
<td>3.8 ± 0.2</td>
<td>5-6</td>
<td>0.25</td>
</tr>
</tbody>
</table>
5.7.2. Results of Assay & In vitro Drug Release:

Aceclofenac is highly soluble (199mg/ 250 ml) in an alkaline medium (pH 6.5–7.5) and is reported. Therefore, dissolution studies were carried out in a phosphate buffer pH (7.5) for 0 -12 h. This medium was considered as most suitable as the drug was freely soluble at this pH and it also mimics the alkaline environment of the small intestine. The selection of wet granulation technique for matrix tablet preparation was based on a previously reported study which suggested wet granulation in time and energy consumption when compared to direct compression. In our study, the use of water as a granulating vehicle was based on the partial solubility of PVPK-30 in this granulating vehicle which resulted in providing the necessary adhesion between the various matrix components and precluded the use of a separate binder.
Table 5.5. Assay and *in vitro* release profile of the prepared Aceclofenac sustained release tablets.

<table>
<thead>
<tr>
<th>Batch Code</th>
<th>Assay (%)</th>
<th>% Drug Release (At time zero)</th>
<th>% Drug Released (After 2 h)</th>
<th>% Drug Released (After 4 h)</th>
<th>% Drug Released (After 6 h)</th>
<th>% Drug Released (After 8 h)</th>
<th>% Drug Released (After 12 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>104.5 ± 0.35</td>
<td>0</td>
<td>32 ± 1.5</td>
<td>49 ± 1.7</td>
<td>71 ± 2.0</td>
<td>86 ± 2.2</td>
<td>99 ± 2.5</td>
</tr>
<tr>
<td>B</td>
<td>99.08 ± 0.39</td>
<td>0</td>
<td>16 ± 0.5</td>
<td>27 ± 0.8</td>
<td>31 ± 1.0</td>
<td>44 ± 1.3</td>
<td>54 ± 1.5</td>
</tr>
<tr>
<td>C</td>
<td>99.75 ± 0.42</td>
<td>0</td>
<td>9 ± 0.1</td>
<td>19 ± 0.5</td>
<td>27 ± 0.7</td>
<td>40 ± 1.0</td>
<td>45 ± 1.3</td>
</tr>
<tr>
<td>D</td>
<td>99.33 ± 0.50</td>
<td>0</td>
<td>13 ± 0.5</td>
<td>23 ± 0.7</td>
<td>33 ± 0.8</td>
<td>48 ± 1.5</td>
<td>60 ± 1.7</td>
</tr>
<tr>
<td>E</td>
<td>99.46 ± 0.49</td>
<td>0</td>
<td>22 ± 0.8</td>
<td>41 ± 1.0</td>
<td>73 ± 1.5</td>
<td>85 ± 1.8</td>
<td>98 ± 2.0</td>
</tr>
<tr>
<td>F</td>
<td>100.05 ± 0.34</td>
<td>0</td>
<td>51 ± 2.0</td>
<td>75 ± 2.5</td>
<td>87 ± 2.5</td>
<td>96 ± 2.8</td>
<td>99 ± 3.0</td>
</tr>
<tr>
<td>G</td>
<td>100.75 ± 0.28</td>
<td>0</td>
<td>22 ± 0.8</td>
<td>40 ± 1.0</td>
<td>60 ± 1.5</td>
<td>71 ± 1.8</td>
<td>93 ± 2.0</td>
</tr>
<tr>
<td>H</td>
<td>99.89 ± 0.44</td>
<td>0</td>
<td>21 ± 0.8</td>
<td>35 ± 1.5</td>
<td>51 ± 1.8</td>
<td>61 ± 2.0</td>
<td>68 ± 2.2</td>
</tr>
<tr>
<td>I</td>
<td>101.11 ± 0.25</td>
<td>0</td>
<td>13 ± 0.5</td>
<td>25 ± 0.7</td>
<td>33 ± 1.0</td>
<td>47 ± 1.4</td>
<td>60 ± 1.6</td>
</tr>
<tr>
<td>J</td>
<td>102.33 ± 0.35</td>
<td>0</td>
<td>20 ± 0.8</td>
<td>32 ± 1.0</td>
<td>69 ± 1.5</td>
<td>90 ± 2.3</td>
<td>96 ± 2.3</td>
</tr>
</tbody>
</table>

Results are the mean ± S.E.M. of three independent experiments.
Figure 5.1. *In vitro* Drug Release of Batches of Aceclofenac.

Figure 5.2. *In vitro* Drug Release of Batches of Aceclofenac.
Figure 5.3. *In vitro* Drug Release of Batches of Aceclofenac.

Results of *in vitro* data are shown in Table 5.5. and Figure 5.1., 5.2., and 5.3. The *in vitro* drug release studies of these tablets showed that the cumulative drug release was in the following order F>E>A>J>G>H>I>D>B>C. This might be due to the nature, viscosity and concentration of the various polymers used, that is different viscosity containing HPMC, Guar gum and ethyl cellulose and has a powerful retardant property resulting in matrix formation which is required for sustained release formulation. The similarity in the release profiles of marketed tablet and formulation G was compared by making use of the "Model independent approach". A simple model independent approach uses a difference factor (f1) and a similarity factor (f2) to compare dissolution profiles. For G formulation, when compared with marketed tablet, f1 and f2 values were found to be 2.44 and 82.89 respectively, indicating a good equivalence between these two formulations. The release profiles of the matrix tablets of aceclofenac containing varying proportions of HPMC K4M that is, A and G, respectively.

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The same result has been seen in matrix formulation C and I containing HPMCK100M. Higher concentration with low viscosity HPMC 15cps containing formulation F does not sustain the release rate of aceclofenac tablet. That indicated that HPMC6cps has no longer sustaining the tablet due to its low viscosity. The release pattern of aceclofenac from the matrices made with 7.5% w/w of hydrophobic polymer Guar gum indicates that the hard matrix had been formed and decreased the release rate. However, on subsequent increase from 7.5 to 20% w/w of drug, there was no appreciable decrease in the release rate and extension in duration of release. This indicated that a tight non-porous matrix had been formed in the former case and addition of more polymers could not modify the matrix character any further.

Film coating was applied over the tablet to mask the bitter taste of aceclofenac. No significant difference was observed in the release profile of coated and uncoated tablets at pH 7.5 phosphate buffer medium. Also, since 90% drug release was attained in about 11-12 h, it can be expected that drug release would be complete within the residence time of the dosage form in the GI tract. The reason was attributed to the preferential solubility of the drug above pH 6.0 and HPMC 6cps is likely to be soluble from pH 1.2 to 6.8. This is due to the formation of a porous and eroded matrix upon dissolution of HPMC 6cps at a higher pH. No significant difference was observed in the release profile of different batches of each matrix formulation, indicating that the manufacturing process employed was reliable and reproducible. Also, the release kinetics remained unaltered for up to one year of storage and there were no changes in the tablet’s characteristics, suggesting that Aceclofenac was stable in HPMC K4M matrices [52 – 55].
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The data for stability studies carried out for G formulation at 40°C with 75% RH for 180 days revealed no considerable differences in drug content and dissolution rate. In conclusion, matrix embedding technique using HPMCK4M as the retardant has successfully extended the release of aceclofenac from its tablet formulations. In the present case, we found that the incorporation of HPMC K4M in the matrix not only helped to provide good initial retardation in the release but also helps to enhance the overall release rate of the drug after a suitable lag time. The manufacturing method employed is simple and easily adaptable in the conventional tablet.
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5.8. Conclusions

In the present study, the formulation and production technology of Aceclofenac 200 mg hydrophilic matrix tablets have been developed, which produced SR formulation with good physical characteristics, predictable and reproducible drug release profiles. This study demonstrated that Methocel K4 MCR provides a reliable sustained release matrix formulation recommendation for high dose and BCS II class drugs such as Aceclofenac.
5.9. REFERENCES


Chapter 5  Aceclofenac Matrix Tablet Containing Synthetic & Natural Polymers


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