Formulation and evaluation of biphasic Delivery system of aceclofenac mini-tablets in Hard gelatin capsules

D. Karthikeyan*, A. Vijayalaxmi, C. Santhosh Kumar.

Department of Pharmaceutics, Srikrupa Institute of Pharmaceutical Sciences, (Affiliated to Osmania University), Vill: Velikatta, Mdl: Kondapak, RD: Siddipet, Dist: Medak-502277, A.P, India.

INTRODUCTION
Aceclofenac, 2-[2-(2, 6-dichloro phenyl aminophenyl] acetyl] oxyacectic acid, is a nonselective cox-2 inhibitor. Aceclofenac (AFC) is Non-steroidal anti-inflammatory drug (NSAID) for the relief of a wide variety of pain and inflammatory conditions, but it is better tolerated than other NSAID's. After oral administration the drug is rapidly and extensively absorbed. It is rapidly distributed, extensively bound to albumin and eliminated with a terminal half-life of about 3- 4 hr. Excretion of the unchanged drug in urine and faeces is negligible [1]. These characteristics make AFC a candidate for incorporation in a sustained-release dosage form. Many oral sustained-release formulations have been developed, including polymer-coated preparations, matrix systems, osmotically driven systems, floating systems, and bioadhesive systems. Multiple-unit dosage forms offer several advantages over conventional single-unit dosage forms, including a higher degree of dispersion in the gastrointestinal tract, a reduced risk of systemic toxicity due to dose dumping, and a reduced risk of high local concentrations [2].

Mini Tablets are used as multiple unit dosage forms and are equal or smaller than 3.0 mm in diameter. MT exhibit several advantages like reduce risk of dose dumping and independence of the rhythm of food transport compared to single unit dosage forms. For application, the compacts can be filled into hard gelatin capsules or can be administered with a dose dispenser for individual dosing (Figure 1). With respect to a subsequent coating step, mini-tablets reveal several advantages compared to irregularly shaped units like granules. MT can be coated reproducibly and require less coating material compared to granules, due to their constant specific surface area, smooth outer surface and robust mechanical properties. So the development of MT for controlling drug release is an important focus of research into oral controlled-release solid dosage forms [3]. The rationale of this study was to optimize a sustained-release AFC dosage form using an

Keywords
Aceclofenac, mini-tablets, Immediate release, Sustained release.

Abstract
Investigated the feasibility of formulating a biphasic delivery system using mini-tablets in hard gelatin capsules delivering drug with a variety of release profiles. Aceclofenac (NSAID analgesic) were chosen as model drug. Immediate release mini-tablets (IRMT) were manufactured by direct compression using microcrystalline cellulose and cross carmellose as a superdisintegrant, each mini-tablet containing approximately 25 mg Aceclofenac (AFC). Sustained release mini-tablets (SRMT) were formulated using various ratios of HPMC K4M and HPMC K100M. Capsules were filled with individual mini-tablets to deliver 100 mg of AFC. The IR and SRMT were combined in the capsule designed to provide a pulsatile or multi-phase delivery of drug as immediate and sustained dissolution release profiles. Capsules containing AFC immediate release mini-tabs were shown to release nearly 100% of the drug within 60 minutes. Capsules containing SRMT released 98 % of AFC over 12 hours. The feasibility of delivering a drug in biphasic immediate sustained release manner was reputeable by combining mini-tablets in a hard gelatin capsule.
encapsulated mini-tablet (EMT) system. We aimed to reduce the size of the AFC tablet such that it could be enclosed in a capsule, and then deploy tablets with different release properties within the one EMT. The EMT system comprises immediate-release mini-tablets (IRMT) and sustained release mini-tablets (SRMT) in a hard gelatin capsule.

MATERIALS AND METHODS

Materials

Aceclofenac (Natco Laboratories Hyderabad), Hydroxypropyl methylcellulose (HPMC) K4M K100M, Polyvinylpyrrolidine K30 (S.D fine chemicals, Mumbai) and other pharmaceutical excipients were of Indian pharmaceutical excipients grade. All other chemicals were of analytical grade and were used without further purification.

Methods

Drug polymer compatibility studies

Compatibility of drug with excipients was determined by carrying out FTIR studies. Infrared spectrum of Aceclofenac, Sodium starch glycolate, Cross carmellose, PVPK 30, HPMC K4M, HPMC K100M, Microcrystalline cellulose and physical mixture of drug and polymer was determined on Fourier Transform Infrared spectrophotometer using KBr dispersion method.

Preparation of IRMT

The IRMT containing AFC 50% (wt/wt) were prepared by direct compression method. First, AFC was mixed with 42.25% (wt/wt) of microcrystalline cellulose (MCC), 7.75% (wt/wt) excipients in proportions varying according to the experimental design (Table 1). Compression of mini tablets was done in rotary compression tablet machine Rimek Mini Press-I using 3mm concave punch [4].

Preparation of SRMT

The SRMT containing AFC 50% (wt/wt) were prepared by direct compression method. First, AFC was mixed with 39.25% (wt/wt) of microcrystalline cellulose (MCC), 10.75% (wt/wt) excipients in proportions varying according to the experimental design (Table 2). Compression of mini tablets was done in rotary compression tablet machine, Rinek Mini Press-I using 3mm concave punch [5].

Evaluation of physical properties of mini tablets

The tablets were examined the shape of the tablet and colour by keeping the tablets in light. All prepared matrix tablets were evaluated for uniformity of weight and drug content, as per I.P. Friability was determined using Electrolab friabilator. Hardness was measured by using Pfizer hardness tester. Diameter and thickness was measured by Vernier caliper [6].

In-vitro dissolution studies

In vitro release studies were carried out using a modified USP XXIII dissolution test apparatus. The dissolution study was conducted for all the formulation using basket method. The dissolution test was performed using 900 ml of buffer (pH 1.2) for first 2 hrs and then phosphate buffer pH 6.8 at a speed of 100 rpm and the temperature of 37°C was used in each test. Samples of dissolution medium (5ml) were withdrawn and absorbance was measured at 273nm using analysis by UV spectroscopy [7].

Kinetic treatment of dissolution data

In order to describe the kinetics of drug release, zero- order (Qt= Q0 + K0t), first- order (ln Qt = In Q0 + K1t). Higuchi (Qt =Kht1/2) and Korsmeyer-Peppas (Qt/Q∞= Ktn) models were fitted to the dissolution data of selected formulation (F8), using linear regression analysis. A value of n = 0.5 indicates case I (Fickian) diffusion 0.5<n<1 anomalous (Non-Fickian) diffusion, n=1 Case –II transport and n>1 Super Case II transport [8].

Stability studies

Accelerated stability study was carried out to observe the effect of temperature and relative humidity on selected formulation, by keeping at 40 ± 2°C, in air tight high density polyethylene bottles for three months, at RH 75±5 %. Physical evaluation, drug content and in-vitro drug release were carried out in each month [9].

RESULTS AND DISCUSSION

Drug polymer compatibility studies

Compatibility between drug and excipients was studied by FTIR (Figure 2) spectroscopy, the characteristic peak of aceclofenac O-H stretching around 3460.00 cm⁻¹, NH stretching at 3319.20 cm⁻¹ and C=C stretch at 1589.49 cm⁻¹ clearly observed in optimized formulation. This result suggested there was no incompatibility between drug and excipients.

Evaluation of physical properties of mini tablets

All the tablets have common concave, round shape. The white colour of the MT was indicating that no physical reaction occurred. These results showed
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in Figure 3. Thickness for the IR and SR mini tablets was found to be between 2.28-2.62mm. The crushing strength of the tablets of each batch ranged between 3.0 to 5.0 kg/cm². This ensures good handling characteristics of all batches. The percent friability of all the formulation was 0.3 to 0.9% ensuring that the tablets were mechanically stable. The maximum weight variation from all the formulations was 51.24 ± 0.1 and minimum variation was 49.1 ± 0.9. The results are within the limit of IP. Thus, the weights of all the tablets were found to be uniform with low standard deviation. The percentage of drug content for all formulation was found to 96-99.3% which lies in the IP limit. All the formulations showed the disintegration time less than 10 min.

**In-vitro dissolution studies**

IRMT containing AFC were containing Sodium starch glycolate cellulose and cross carmelllose. The microcrystalline cellulose is commonly used as a superdisintegrant in tablets, and the degree to which it swells and takes up water is reportedly dependent on the degree of hydroxyl substitution and the particle size of the polymer. This suggests that these two properties may exert a strong influence on the disintegration time of the tablets. As shown in Figure 4, the dissolution profiles were very similar for IRMT containing different amounts Sodium starch glycolate cellulose and cross carmelllose. The percentage drug released in the first 30 min was similar in the all formulations. However, in IRMT F6, 98% of the AFC was released within the first 60 min, and the content of disintegrant in the tablet significantly inclined AFC release.

**Release kinetics**

Various mathematical models were selected to evaluate the kinetics and mechanism of drug release from immediate and sustained release mini-tablet formulation. Best model was selected for release data which showed high correlation coefficient (r) value. The mechanism of release for the optimized mini tablet formulation was based on regression coefficient (r²) value. From the above table it can be concluded that the drug release follow peppas, zero order model (Figure 5, 6,).

**Accelerated stability studies**

The optimized formulation was found to be stable after exposure to accelerated temperature and humidity conditions for a period of 3 months. No significant changes were seen in physical evaluation parameters and in vitro drug release data was given in the above table 5.

**Figure 1: Encapsulated mini-tablet**
Table 1: Formulations of IRMT

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
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<tbody>
<tr>
<td>Aceclofenac 25mg</td>
<td>25mg</td>
<td>25mg</td>
<td>25mg</td>
<td>25mg</td>
<td>25mg</td>
<td>25mg</td>
</tr>
<tr>
<td>Sodium starch glycolate</td>
<td>1mg</td>
<td>1.5mg</td>
<td>2mg</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cross carmelllose</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1mg</td>
<td>1.5mg</td>
<td>2mg</td>
</tr>
<tr>
<td>PVPK 30</td>
<td>2.5mg</td>
<td>2.5mg</td>
<td>2.5mg</td>
<td>2.5mg</td>
<td>2.5mg</td>
<td>2.5mg</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>0.25mg</td>
<td>0.25mg</td>
<td>0.25mg</td>
<td>0.25mg</td>
<td>0.25mg</td>
<td>0.25mg</td>
</tr>
<tr>
<td>Talc</td>
<td>0.125mg</td>
<td>0.125mg</td>
<td>0.125mg</td>
<td>0.125mg</td>
<td>0.125mg</td>
<td>0.125mg</td>
</tr>
</tbody>
</table>

Table 2: Formulations of SRMT

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
<th>F10</th>
<th>F11</th>
<th>F12</th>
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<tbody>
<tr>
<td>Aceclofenac 25mg</td>
<td>25mg</td>
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<td>25mg</td>
<td>25mg</td>
<td>25mg</td>
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<tr>
<td>HPMC K4M</td>
<td>2.5mg</td>
<td>5mg</td>
<td>7.5mg</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>HPMC K100M</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2.5mg</td>
<td>5mg</td>
<td>7.5mg</td>
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<tr>
<td>PVP K30</td>
<td>2.5mg</td>
<td>2.5mg</td>
<td>2.5mg</td>
<td>2.5mg</td>
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<td>2.5mg</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>0.25mg</td>
<td>0.25mg</td>
<td>0.25mg</td>
<td>0.25mg</td>
<td>0.25mg</td>
<td>0.25mg</td>
</tr>
<tr>
<td>Talc</td>
<td>0.125mg</td>
<td>0.125mg</td>
<td>0.125mg</td>
<td>0.125mg</td>
<td>0.125</td>
<td>0.125</td>
</tr>
<tr>
<td>MCC</td>
<td>19.625mg</td>
<td>17.125mg</td>
<td>14.625mg</td>
<td>19.625mg</td>
<td>17.125mg</td>
<td>14.625mg</td>
</tr>
</tbody>
</table>

Figure 2: FTIR Spectra of drug and excipients
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**Figure 3: Physical properties of AFC mini tablets**

![Physical properties of AFC mini tablets](image1)

**Figure 4: In-vitro dissolution profile of IRMT and SMRT**

![In-vitro dissolution profile of IRMT and SMRT](image2)
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Figure 5: Release kinetics of IRMT

![First order plot of optimized formulation](image1)

\[ y = 0.8942x + 2.2119 \]
\[ R^2 = 0.9207 \]

![Zero order plot of optimized formulation](image2)

\[ y = 0.5293x - 0.8037 \]
\[ R^2 = 0.9084 \]

Figure 6: Release kinetics of SRMT

![Higuchi plot of optimized formulation](image3)

\[ y = 38.84x - 45.32 \]
\[ R^2 = 0.9616 \]

![Peppas plot of optimized formulation](image4)

\[ y = 1.1918x + 0.7073 \]
\[ R^2 = 0.9916 \]

Table 3: Accelerated stability studies of optimized formulation

<table>
<thead>
<tr>
<th>Stability period</th>
<th>%drug content</th>
<th>%in vitro release</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>93 ±0.30</td>
<td>99.57 ±0.36</td>
</tr>
<tr>
<td>First month</td>
<td>92.93±0.16</td>
<td>99.18 ±0.21</td>
</tr>
<tr>
<td>Second month</td>
<td>92.74±0.14</td>
<td>98.89 ±0.18</td>
</tr>
<tr>
<td>Third month</td>
<td>92.41±0.12</td>
<td>98.56 ±0.14</td>
</tr>
</tbody>
</table>

CONCLUSION

In the present study, an attempt was made to develop a biphasic MT in-capsule system device containing IR and SRMT. In IRMT (F1-F6) containing 2,3 and 4% of sodium starch glycolate and Cross carmelleose, microcrystalline cellulose were used as good compaction released the aceclofenac drug within 60 mins. whereas as in SRMT (F7-F12) the release rate of aceclofenac increased with HPMC K4M and HPMC K100M increase with increasing of its concentration it results in decreased release of AFC.

Among the entire MT in capsule system formulations F6, F8 were considered as the best formulations releasing AFC both as immediate and as a sustained manner and also shown better release at the end of 12 hrs. The kinetics study revealed that all the formulations followed zero order, peppas as their \( r^2 \) values ranged 0.9916 and the mechanism of the drug release was found to be super case II transport predominated with all formulations. The developed formulation was found to be stable even after subjecting to accelerated stability conditions.
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REFERENCES


