**Formulation and evaluation of mucoadhesive microcapsules of aceclofenac**

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**ABSTRACT**

Aceclofenac loaded microcapsules with a coat consisting of sodium alginate and mucoadhesive polymer of different grades of hydroxy propyl methyl cellulose (HPMC) such as HPMC 50 CPS, HPMC K100M, HPMC E50LV were prepared by orifice-ionic gelation technique. The formulation was aimed to facilitate intimate contact of the drug with underlying absorption surface and to prolong the residence time of drug at the site of absorption. The formulations were evaluated for morphological characters, drug polymer interaction, drug content, microencapsulation efficiency, swelling ratio, mucoadhesive properties, and in vitro release. The prepared microcapsules were found to be discrete, spherical, and free-flowing, and microencapsulation efficiency was 37.8±0.49% to 59.8±0.64%. The swelling ratio of microcapsules was enhanced with increased alginate concentration. The microcapsules prepared with HPMC K100M in the ratio of 5:1 (F5) exhibited good mucoadhesive property in the in vitro wash off test and emerged as the overall best formulation based on drug release characteristics. Drug release from these mucoadhesive microcapsules was slow and extended over a period of 8 h and depends upon the concentration of the alginate. Hence prepared mucoadhesive microcapsule may be an effective strategy for the development of oral controlled release of Aceclofenac.

**INTRODUCTION**

Microencapsulation is a useful method for prolonging drug release from dosage forms and reducing adverse effects. Recently, dosage forms that can precisely control the release rates and target drugs to a specific body site have made an enormous impact in the formulation and development of novel drug delivery systems. Micro-encapsulation is a process in which tiny particles or droplets are surrounded by a coating to give small capsules of many useful properties. In a relatively simplistic form, a microcapsule is a small sphere with a uniform wall around it.

The objective of this study was to develop and evaluate mucoadhesive microcapsules of Aceclofenac prepared using mucoadhesive polymers. Aceclofenac is an orally administered non-steroidal anti-inflammatory drug (NSAID) used in the management of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. The conventional aceclofenac tablets administered 2 to 3 times a day due to its short biological half life (3-4 hours) produces side effects like gastric ulceration and bleeding. Thus to reduce the dosage frequency and gastrointestinal side effects it became essential to formulate aceclofenac in a new drug delivery system, which prolongs the residence time of the drug at the site of absorption and facilitate intimate contact of the drug with the underlying absorption surface to improve and enhance the bioavailability of drug. Six formulations were prepared by employing sodium alginate in combination with different grades of hydroxy propyl methyl cellulose such as HPMC 50 CPS, HPMC E50LV and HPMC K100M as mucoadhesive polymers by Orifice ionic gelation method in the drug polymer ratio 1:1 and varying the coating composition ratio (Sodium alginate : HPMC) 1:1 and 5:1. The novelty of this work is in combining the advantage of particulate system (microcapsule) and mucoadhesive drug delivery system by taking sodium alginate and mucoadhesive polymers.

**MATERIALS AND METHODS**

**Materials**

Aceclofenac was obtained from Micro Labs Pharmaceuticals, Hosur, India. Hydroxy propyl methylcellulose 50 CPS and HPMC E50LV were obtained from Loba Chem Pvt. Ltd, Mumbai, India. HPMC K100M and Calcium chloride (Dihydrate) were procured from Leo Chem, Bangalore, India. Sodium alginate was produced from Reachem Lab. Chemicals Pvt. Ltd, Chennai, India. All other reagents used were of analytical grade.

**Methods**

**Orifice-Ionic Gelation Method**

Microcapsules containing Aceclofenac were prepared by orifice ionic gelation method. The microcapsules were prepared by employing sodium alginate in combination with different grades of hydroxy propyl methyl cellulose such as HPMC 50 CPS, HPMC K100M and HPMC E50LV in the drug-polymer ratio 1:1 and coat composition ratio (sodium alginate; polymer) 1:1 and 5:1. The formulations of mucoadhesive microcapsules of Aceclofenac prepared are listed in Table 1.

**Table 1: Formulation of mucoadhesive Aceclofenac microcapsules**

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Sodium Alginate: HPMC Ratio</th>
<th>Drug (g)</th>
<th>Sodium alginate 50 CPS (mg)</th>
<th>Sodium alginate K 100M (mg)</th>
<th>Sodium alginate E50LV (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>1:1</td>
<td>1</td>
<td>500</td>
<td>500</td>
<td>-</td>
</tr>
<tr>
<td>F2</td>
<td>5:1</td>
<td>1</td>
<td>833</td>
<td>167</td>
<td>-</td>
</tr>
<tr>
<td>F3</td>
<td>1:1</td>
<td>1</td>
<td>500</td>
<td>-</td>
<td>500</td>
</tr>
<tr>
<td>F4</td>
<td>5:1</td>
<td>1</td>
<td>833</td>
<td>-</td>
<td>167</td>
</tr>
<tr>
<td>F5</td>
<td>1:1</td>
<td>1</td>
<td>500</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>F6</td>
<td>5:1</td>
<td>1</td>
<td>833</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Sodium alginate (500 mg) and the mucoadhesive polymer (500 mg) were dissolved in purified water (16 ml) to form a homogeneous polymer solution. The core material, aceclofenac (1.0 g) was added to the polymer solution and mixed thoroughly to form a smooth viscous dispersion. The
resulting dispersion was then added drop wise into calcium chloride (10% w/v) solution (20 ml) through a syringe with a needle of Size No.18. The added droplets were retained in the calcium chloride solution for 30 minutes to complete the curing reaction and to produce spherical rigid microcapsules. The microcapsules were collected by decantation and the product thus separated was washed repeatedly with water and dried at 45 °C for 12 hours.  

FT-IR Analysis

FT-IR analysis of pure drug, individual polymers and combination of drug and polymers in higher concentration were taken for the study. Samples were compressed with potassium chloride and transformed into disk. The disk was scanned between 4000-400 cm\(^{-1}\) in a SHIMADZU FT-IR (IR Affinity-1) spectrophotometer.

EVALUATION OF MICROCAPSULES

Micromeric Properties

The micromeric properties of microcapsules were studied by determining various parameters like the bulk density, tapped density, angle of repose and Carr’s index. The angle of repose was determined by the fixed-base cone method. Bulk and Tapped density was determined using digital bulk density apparatus. 

Percentage Yield (%)

The percentage yield of microcapsules of various batches were calculated using the weight of final product after drying with respect to the initial total quantity of the drug and polymer used for preparation of microcapsules.  

Percentage yield = \(\frac{\text{Theoretical yield}}{\text{Theoretical yield}}\) × 100

Surface Morphology (SEM Analysis)

Shape and surface morphology of microcapsules were studied using scanning electron microscopy (SEM). The microcapsules were mounted on metal stubs using double sided adhesive tape and the stub was then vacuum coated with gold film using sputter coater attached to the instrument. The photographs were taken using a Jeol scanning electron microscope (JEOL-JSM-6390LV, Japan).

Estimation of Drug content

Aceclofenac content in the microcapsules was estimated by UV Spectrophotometric method based on the measurement of absorbance\[^1\] of 10µg/ml solution at 275 nm in phosphate buffer solution pH 7.4.

Micro encapsulation Efficiency

Micro encapsulation efficiency was calculated using the formula:

\[
\text{Microencapsulation efficiency} = \left(\frac{\text{Estimated percent drug content}}{\text{Theoretical percent drug content}}\right) \times 100.
\]

Particle size Analysis

Microcapsules were separated into different size fractions by sieving for 20 minutes using mechanical sieve shutter containing standard sieves of different mesh numbers arranged in a nest with the coarsest at the top and finest at the bottom. The microcapsules retained on each sieve were weighed and the average diameter of microcapsules were determined.

Percentage moisture loss

The microcapsules weighed (W\(_1\)) initially were kept in desiccator containing calcium chloride at 37°C for 24 hours. The final weight (W\(_2\)) was noted when no further change in weight of sample was observed. Percentage Moisture loss was determined using the following formula:

\[
\text{Percentage Moisture loss} = \left(\frac{W_1 - W_2}{W_1}\right) \times 100.
\]

Where, W\(_1\) = Initial weight of microcapsules; 
W\(_2\) = Final weight of microcapsules.

Degree of Swelling

The swell ability of microcapsules in physiological media was determined by swelling them in phosphate buffer solution pH 7.4. Accurately weighed amount of microcapsules was immersed in little excess of phosphate buffer solution pH 7.4 for 24 hours and washed. The degree of swelling was calculated using following formula:

\[
a = \left(\frac{W_s - W_0}{W_0}\right)
\]

Where, a is the Degree of swelling.  
W\(_s\) = Weight of microcapsules before swelling,  
W\(_0\) = Weight of microcapsules after swelling.

Mucoadhesion by In vitro wash-off test

The Mucoadhesive property of the microcapsules was evaluated by an in vitro adhesion testing method known as wash off test. The test was performed in simulated gastric fluid (0.1 M HCl, pH 1.2) and in simulated intestinal fluid (phosphate buffer, pH 7.4). Pieces of intestinal mucosa (2 × 2 cm) were mounted onto glass slides of (3 × 1 inch) with cyanoacrylate glue. Two glass slides were connected with a suitable support. About 50 microcapsules were spread on to each wet rinsed tissue specimen and immediately thereafter the support was hung on to the arm of USP tablet disintegration test apparatus. The disintegration apparatus containing tissue specimen was given a slow regular up and down movement in a test fluid at 37°C taken in a 1L beaker of the disintegration test apparatus. At different time intervals up to 8 hours the apparatus was stopped and the number of microcapsules, still adhering to the tissue was counted.  

The adhesion number was determined by the following formula:

\[
N_n = \left(\frac{N}{No}\right) \times 100
\]

Where, \(N_n\) = Adhesion number.  
N = Number of microcapsules attached to the mucosa after washing.  
No = Initial number of microcapsules in the intestinal mucosa.

In vitro drug release studies

In vitro drug release of Aceclofenac from microcapsules was carried out by using USP Type-I dissolution test apparatus. 900 ml of simulated gastric fluid (0.1M Hydrochloric acid buffer, pH 1.2) was used as dissolution medium for first 2 hours and simulated intestinal fluid (phosphate buffer, pH 7.4) was used for next 8 hours. A quantity of microcapsules equivalent to 200 mg of Aceclofenac was filled in empty capsule shells and placed in the basket and rotated at 50 rpm. Bath temperature was maintained at 37±0.5°C throughout the study. Aliquots of samples (10 ml) were withdrawn at an interval of every 1 hour. Samples withdrawn were replaced with equal volumes of the dissolution medium. The absorbance of samples was measured using UV Double beam spectrophotometer at 275 nm after suitable dilution with the buffer.

RESULTS AND DISCUSSION

The FT-IR studies revealed that there was no shift in peaks of the combinations containing aceclofenac, sodium alginate and HPMC when compared to pure aceclofenac, indicating there was no interaction between aceclofenac and other polymers used.

The percentage yield varies with different concentration of alginate and mucoadhesive polymer. It was observed that percentage yield of formulations F\(_1\) and F\(_2\) (sodium alginate + HPMC 50CPS) were 91.7% and 92.3% respectively and formulations F\(_3\), F\(_4\), (sodium alginate + HPMC K100M) were 93.1% and 90.4% and formulations F\(_5\) and F\(_6\) (sodium alginate + HPMC E50LV) were 88.5% and 91.2% respectively. The formulation F\(_3\) showed maximum yield. Scanning electron micrographs of aceclofenac microcapsules revealed that the microcapsules were found to be discrete, uniform and spherical in shape. The difference in the shape of microcapsules was observed, representing that microcapsules containing higher amount of alginate are more spherical and regular as compared to that of microcapsules having lower percent of alginate. The surface of the microcapsules were
found to be smooth and the core was completely covered by the coating polymer as shown in Fig 1.

Fig 1: SEM showing surface morphology of Aceclofenac microcapsules

Micromeritic parameters were evaluated for the prepared microcapsules and the results are shown in Table 2. The angle of repose was found in the range of 21.54±2.5 to 24.03±1.1 which confirmed that the microcapsules were having excellent flow properties. The bulk density and tapped density of the microcapsules were found in the range of 0.352±0.03 to 0.360±0.06 g/ml and 0.387±0.02 to 0.400±0.03 g/ml respectively. The compressibility index of microcapsules was found in the range of 8.93 to 10.12% and Hausner’s ratio lies in the range 1.09 to 1.11. All the formulations showed excellent flowability as expressed in term of micromeritic parameters (Table 2).

Table 2: Micromeritic properties of Aceclofenac microcapsules

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Angle of repose (°)</th>
<th>Bulk density (g/ml)</th>
<th>Tapped density (g/ml)</th>
<th>Carr’s index (%)</th>
<th>Hausner’s ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>22.09±1.6</td>
<td>0.359±0.03</td>
<td>0.399±0.04</td>
<td>9.82</td>
<td>1.10</td>
</tr>
<tr>
<td>F2</td>
<td>23.95±1.1</td>
<td>0.353±0.04</td>
<td>0.385±0.02</td>
<td>9.06</td>
<td>1.09</td>
</tr>
<tr>
<td>F3</td>
<td>21.54±2.5</td>
<td>0.360±0.06</td>
<td>0.400±0.03</td>
<td>10.12</td>
<td>1.11</td>
</tr>
<tr>
<td>F4</td>
<td>23.11±1.8</td>
<td>0.354±0.02</td>
<td>0.394±0.01</td>
<td>9.09</td>
<td>1.10</td>
</tr>
<tr>
<td>F5</td>
<td>22.77±1.2</td>
<td>0.358±0.02</td>
<td>0.396±0.03</td>
<td>9.54</td>
<td>1.10</td>
</tr>
<tr>
<td>F6</td>
<td>24.03±1.1</td>
<td>0.352±0.06</td>
<td>0.387±0.02</td>
<td>8.93</td>
<td>1.09</td>
</tr>
</tbody>
</table>

*All the values are expressed as mean ± standard deviation; n=3

Three samples were tested from each batch and the drug content was determined by UV spectrophotometric method. The results are given in Table 3. The standard deviations among the three values were found to be less. This indicates that the drug was distributed almost uniformly throughout the batch of microcapsules. The microencapsulation efficiency was in the range of 37.8±0.49% to 59.8±0.64%. The results revealed that the encapsulation efficiency of microcapsules increased as alginate concentration increased in the coat composition. The average particle size of all microcapsules were found to be in the range of 873.9±3.33µm to 922.8±2.96µm. The percentage moisture loss was found in the range of 3.23±0.02% to 4.16±0.26 %. The results ensure the presence of diminutive water content which can be due to the involvement of water in process method and hydrophilic property of mucoadhesive polymer. But lesser proportion of water obtained may be due to the reason that increase in the amount of alginate increases the number of COOH groups which are cross linked by calcium ions resulting in formation of more intact matrix which makes the drug release more difficult. Microcapsules of alginate – HPMC may be due to ionization of carboxyl and other functional groups in the polymer at this pH, which increases their solubility and reduces adhesive strength. The results are shown in Table 4.

The drug release study revealed that Aceclofenac release from the microcapsules was slow and spread over extended period of time. Drug release from microcapsules varied with varying the coat composition (alginate-HPMC). It was observed that with the increase in the concentration of sodium alginate the release of Aceclofenac from the polymer matrix was retarded. This may be due to the reason that increase in the amount of alginate increases the number of COOH groups which are cross linked by calcium ions resulting in formation of more intact matrix which makes the drug release more difficult. Microcapsules of alginate – HPMC E50LV gave relatively faster release compared to alginate – HPMC 50CPS and alginate- HPMC K100M.

Table 3: Evaluation of Aceclofenac microcapsules

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Drug content (mg)</th>
<th>Encapsulation efficiency (%)</th>
<th>Particle size (µm)</th>
<th>Percentage moisture loss (%)</th>
<th>Degree of swelling (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>50</td>
<td>21.7±0.55</td>
<td>43.4±0.55</td>
<td>920.9±2.63</td>
<td>3.86±0.21</td>
</tr>
<tr>
<td>F2</td>
<td>50</td>
<td>28.4±0.70</td>
<td>56.8±0.70</td>
<td>885.8±2.91</td>
<td>3.23±0.02</td>
</tr>
<tr>
<td>F3</td>
<td>50</td>
<td>28.2±0.68</td>
<td>56.4±0.68</td>
<td>922.8±2.96</td>
<td>4.16±0.26</td>
</tr>
<tr>
<td>F4</td>
<td>50</td>
<td>29.9±0.64</td>
<td>59.8±0.64</td>
<td>887.2±4.62</td>
<td>3.02±0.16</td>
</tr>
<tr>
<td>F5</td>
<td>50</td>
<td>18.9±0.49</td>
<td>37.8±0.49</td>
<td>905.6±3.24</td>
<td>3.92±0.42</td>
</tr>
<tr>
<td>F6</td>
<td>50</td>
<td>26.8±0.76</td>
<td>53.6±0.76</td>
<td>873.9±3.33</td>
<td>3.25±0.08</td>
</tr>
</tbody>
</table>

*All the values are expressed as mean ± standard deviation; n=3

Fig 2: In vitro release profiles of Aceclofenac formulations
The drug release was found to be rapid in F₅ microcapsules and slow in F₄ microcapsules. The in vitro release profiles of aceclofenac formulations were shown in Fig 2.

CONCLUSION
The spherical microcapsules with a coat consisting of alginate and a mucoadhesive polymer (HPMC) could be prepared by orifice-ionic gelation process. The microcapsules exhibited good mucoadhesive properties in the wash off test. Aceclofenac release from these mucoadhesive microcapsules was slow and extended over longer period of time and depended on compositions of the coat. From all the parameters studied, it can be concluded that formulation F₄ containing sodium alginate-HPMC K100M (5:1) ratio was found to be best formulation for the development of oral controlled release of Aceclofenac.

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