Characterization and Screening of a Novel Multiparticulate Pulsatile Delivery of Aceclofenac

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Received June 1, 2016; accepted July 20, 2016

ABSTRACT

In the present investigation, sodium alginate based multiparticulate system overcoated with time and pH dependent polymer was studied in the form of oral pulsatile system to achieve pulsatile with sustained release of aceclofenac for chronotherapy of rheumatoid arthritis. Seven batches of microbeads with varying concentration of sodium alginate (2-5%) were prepared by ionotropic-gelation method using CaCl₂ as cross-linking agent. The prepared Ca-alginate beads were coated with 5% Eudragit L100 and filled into pulsatile capsule with varying proportion of plugging materials. Drug loaded microbeads were investigated for physicochemical properties and drug release characteristics. The mean particle sizes of drug-loaded microbeads were found to be in the range 596±1.1 to 860±1.2 micron and %DEE in the range of 65-85%. FT-IR and DSC studies revealed the absence of drug polymer interactions. The release of aceclofenac from formulations F1 to F7 in buffer media (pH 6.8) at the end of 5h was 65.6, 60.7, 55.7, 41.2, 39.2, 27% and 25% respectively. Pulsatile system filled with eudragit coated Ca-alginate microbeads (F2) showed better drug content, particle size, surface topography, in-vitro drug release in a controlled manner. Different plugging materials like Sterculia gum, HPMC K4M and Carbopol were used in the design of pulsatile capsule. The pulsatile system remained intact in buffer pH 1.2 for 2 hours due to enteric coat of the system with HPMCP. The enteric coat dissolved when the pH of medium was changed to 7.4. The pulsatile system developed with Sterculia gum as plugging material showed satisfactory lag period when compared to HPMC and Carbopol.

KEYWORDS: Aceclofenac; Chronotherapy; Microbeads; Plugging; Pulsatile; Screening; Sterculia.

intestinal zone from a novel multiparticulate pulsatile system filled with mixed blend polymer microcapsules and selected swellable hydrophilic plugging materials to achieve the chronotherapy of rheumatoid arthritis.

**Materials and Methods**

Aceclofenac sample was purchased from CDH, Kolkata, India. The natural polymers such as sodium alginate, guar gum, carbopol, HPMC K4M were purchased from Krystall Colloids, Gujrat, India. Eudragit L100 (Rohm Pharma, GmbH, Darmstadt, Germany). Supplied by CDH Kolkata. Hydrated Calcium Chloride is obtained from CDH, Kolkata, India. All other chemicals used were of analytical grade.

**Solubility of Aceclofenac Sodium in Calcium Chloride Solution**

The solubility of drug in calcium chloride (1%w/v) was determined by adding excess of drug into the medium containing vials and shaking at constant temperature 37°C in a water bath for 12h. The sample was filtered diluted with distilled water and assayed spectrophotometrically at 274 nm (Roy and Shaiwala, 2008; Pawer et al., 2007).

**Saturation Solubility Determination**

Excess quantity of aceclofenac sodium was added to each 25ml volumetric flask containing measured amount of distilled water, phosphate buffer pH 6.8, and phosphate buffer pH 7.4, water to get a saturated solution and agitated continuously at room temperature at 8 hour on a shaker (Dandagi et al., 2004; Rana and Pal et al., 2010; Najmuddin et al., 2010). An aliquot was filtered and the filtrate was suitably diluted and analysed for drug content on a UV Spectrophotometer (Schimadzu, Japan, UV 1800 240V).

**FT-IR study**

Drug polymer interactions were studied by FT-IR spectroscopy. One to two mg of aceclofenac sodium alone, mixture of drug and polymer were weighed and mixed properly with potassium bromide uniformly. A small quantity of the powder was compressed into a thin semitransparent pellet by applying pressure of 10 kg/cm². The IR-spectrum of the pellet from 450-4000 cm⁻¹ was recorded taking air as the reference and compared to achieve the chronotherapy of rheumatoid arthritis.

**Preparation of sodium alginate microbeads of aceclofenac**

Sodium alginate microbeads were prepared by ionotropic-gelation method. Briefly, sodium alginate (2 to 4% w/v) was dissolved in deionized water and aceclofenac was homogeneously dispersed in it (Table 1). Air bubbles were removed from the dispersion by sonication on a bath sonicator. The alginate-drug mixture was then added drop wise (1 ml min⁻¹ from 5 cm distance) to a gently agitated cross-linking solution (5% calcium chloride aqueous solution (pH 5.5) through a blunt end needle (25 G) at room temperature (RT). The beads formed were allowed to stand in the solution for specified time interval with gentle agitation. The beads were then separated, washed with distilled water, and subsequently dried at room temperature for 24 hr and stored in desiccators. The prepared seven batches of microbeads with varying concentration of sodium alginate (2-4 %w/v) were coated with 5% w/v Eudragit L100 solution by simple dip coating procedure before incorporated in to the final designed pulsatile capsule (Dandagi, 2004; Shivakumar et al., 2006).

**Physical Evaluation of the Prepared Microsphere**

**Size analysis of microspheres**

Different sizes in a batch are separated by sieving using a range of standard sieves 20/40, 40/60 and 60/80 and the amount retained on different sieves were weighed. Studies were carried out in triplicate. The average sizes of the microspheres were calculated by using the equation (Dandagi 2004; Najmuddin et al., 2010).

\[ D_{\text{ave}} = \frac{\sum X_i f_i}{f_i} \]

Where,

- \( X_i \) is the mean size of the range
- \( f_i \) is the percent material retained on the smaller sieve in the size range of sieve no. 20
- \( f_i \) is the percent material retained on the larger sieve in the size range of sieve no. 40

**% yield determination**

The percentage yield of the microbeads was calculated by using the following formula (Rana et. al 2010; Najmuddin et al., 2010).

\[ \% \text{ yield} = \frac{\text{Microbeads practically found}}{\text{Theoretical weight of drug and excipients}} \times 100 \]

**Drug entrapment efficiency**

Crushed microbeads (100 mg) were taken in a 100 ml volumetric flask and volume was made up to mark with phosphate buffer of pH 6.8. The flask was shaken for 4 hrs using water bath shaker. Then the solution was filtered and from the filtrate appropriate dilutions were made and absorbance was measured at 274 nm by using UV-Visible spectrophotometer. The encapsulation efficiency
was calculated using the formula (Rana et al., 2010; Najmuddin, 2010).

D. E. E = Actual drug content / Theoretical wt. of drug and excipient × 100.

**In-vitro Drug Release Studies of Aceclofenac Loaded Microbeads**

In vitro dissolution profile of each formulation was determined by employing USP type-I rotating basket method (900 ml of pH 6.8-phosphate buffer, 100 rpm, 37 ± 0.5 °C). Eudragit coated alginate microspheres equivalent to 100 mg of drug was loaded into the basket of the dissolution apparatus and continued the dissolution process. 5 ml of the sample was withdrawn from the dissolution media at suitable time intervals and the same amount was replaced with fresh buffer. The amount of drug present in the filtrate was determined at wavelength of 274 nm by using UV-visible spectrophotometer (Rana et al., 2010; Najmuddin, 2010).

**Preparation of Cross-Linked Gelatin Capsules**

Initially hard gelatin capsule bodies were treated with formaldehyde solution to render them insoluble in gastro intestinal fluids while the caps remained untreated. 25 ml of 15% (v/v) formaldehyde was taken into desiccator and a pinch of potassium permanganate was added to it to generate formalin vapors. About 100 numbers of empty bodies of hard gelatin capsule (# 00) were placed over wire mesh and then exposed to formaldehyde vapors. The desiccator was tightly closed, exposed for 12 hrs and dried at 50°C for 30 min to ensure complete reaction between gelatin and formaldehyde vapors. The bodies were then dried at room temperature to facilitate removal of residual formaldehyde. These bodies were joined with untreated caps and stored in a polythene bag (Mastimalimoth et al., 2007; Vyas et al., 1997).

**Fabrication of Capsular Type Pulsatile System Containing Aceclofenac Loaded Coated Alginate Microbeads**

Eudragit coated alginate beads (F2) equivalent to 100 mg of drug were accurately weighed and filled into the treated bodies by hand filling. The capsules containing the microcapsules were then plugged with different amounts (20, 30 and 40 mg) of various swellable polymers, i.e., Sterculia gum, HPMC, K4M, carboxpol etc. The joint of the capsule body and cap was sealed with a small amount of the 5% ethyl cellulose ethanolic solution. The sealed capsules were completely coated with 5% w/v HPMCP solution to prevent variable gastric emptying. Coating was repeated until to obtain an increase in weight gain of 5% w/w. The % weight gain of capsules before and after coating was determined (Mastimalimoth et al., 2007; Jose et al., 2009). The detail of formulation composition is presented in Table 2.

**Evaluation of Designed Multiparticulate Pulsatile System**

**Determination of thickness of coating**

The thickness was measured by using screw gauge and expressed in mm.

**Release behaviour of multiparticulate pulsatile system**

Dissolution studies were carried out by using USP type-II dissolution test apparatus (paddle method). Capsules were tied to paddle with a cotton thread so that the capsule should be immersed completely in dissolution media but not float. In order to simulate the pH changes along the GI tract, three dissolution media with pH 1.2 (2 h), 7.4 (3 h) and 6.8 till the end of the study were sequentially used. Nine hundred milliliters of the dissolution medium was used at each time. Rotation speed was 100 rpm and temperature was maintained at 37 ± 0.5 °C. 5 millilitres of dissolution media was withdrawn at predetermined time intervals and fresh dissolution media was replaced. The withdrawn samples were analyzed at 274 nm, by UV absorption spectroscopy and the cumulative percentage release was calculated over the sampling times (Mastimalimoth et al., 2007; Morta et al., 1998).

**Results and Discussion**

Aceclofenac sodium is a weak acid; the solubility of aceclofenac sodium in HCl was very less compared with distilled water. However, the addition of surfactant is a reasonable approach for solubilizing such drugs, because various surfactants are present in the GI-fluid. Saturation solubility of aceclofenac sodium in different media increased with an increase in buffer pH as well as with an increase in surfactant concentration. The significant increase is attributed to the micellar solubilisation by SLS. Aceclofenac sodium showed sufficient solubility in 0.1N HCl with 2% w/v of SLS which was adequate to maintain sink condition and was selected as the dissolution medium for in-vitro drug release studies. The solubility of aceclofenac sodium in calcium chloride was found to be 0.96±1.54 mg/ml.

**Drug Excipient Compatibility Testing**

The compatibility of aceclofenac sodium with polymer was investigated by IR spectroscopy study as shown in Figure 1 (a,b). The IR spectra of the drug and polymer blends were compared with the spectra of the pure drug and individual polymer spectra. The characteristic absorption peaks of pure aceclofenac sodium were obtained 3276.5, 2915.5, 1716.5, 1589.3 cm⁻¹ corresponding to NH- stretching, C=O stretching of –COO and –COOH group respectively. The characteristic absorption peaks of SA powder showed peaks around 3077.15, 2914.98, 1615.34, 1359.60 and 754.05 cm⁻¹ reflective of O–H, C=H, COO⁻ (asymmetric), COO⁻ (symmetric), and C–O–C stretching respectively. The cross-linking process of sodium alginate with calcium caused an obvious shift to higher wave numbers and a decrease in the intensity of COO⁻ stretching peaks. Additionally, a change to lower wave numbers and a decrease in the intensity of the C–O–C stretching peak of alginate was observed. This indicated the presence of an ionic bond between the calcium ion and the carboxyl groups of sodium alginate and partial covalent bonding between the calcium and oxygen atoms of the ether groups. The physical mixture alginate powder and aceclofenac sodium characteristic peaks were obtained at 2820.28, 1591.72, 1384.91 cm⁻¹.
caused a shift in the O–H, COO− (asymmetric), and COO− (symmetric) stretching peaks to lower wave numbers, suggesting that a slight molecular interaction between alginate and aceclofenac was formed due to hydrogen bonding and electrostatic force. From the FT-IR study it was clearly evident that the identical FT-IR bands were well retained with no considerable changes in the peaks of drug-polymer physical mixture confirming the absence of potential drug-excipient interactions.

**Differential Scanning Calorimetry (DSC) Studies**

The thermal behavior of the pure aceclofenac sodium, drug loaded alginate beads were characterized using DSC, as shown in Figure 2 (a,b). The thermogram of pure aceclofenac showed a sharp endothermic peak at 156.64 °C followed by corresponding melting point. The obvious peak of the drug (156.64 °C) was observed in the physical mixture but not observed in any type of the prepared microbeads indicating uniform molecular solubility of the drug in polymeric beads. The presence of sharp endothermic melting peak were found in the physical mixture, indicating that there are no changes in thermal behaviour of drug with the excipients used for beads preparation.

![FT-IR spectra](image)

**Fig. 1.** (a) Comparative FT-IR spectrum of aceclofenac, sodium alginate, Eudragit L100 and drug-polymer physical mixture.
Characterizations and Evaluation of Microbeads

Drug-loaded microbeads using natural polymer sodium alginate was successfully prepared and the results were presented in Table 1. The mean particle sizes of drug loaded microbeads were performed by optical microscopy and BIS sieves. The mean particle sizes of the alginate formulations (F1-F7) of microbeads were obtained in the range between 596.45 ± 1.04 to 880 ± 1.23 micron. It was found that the particle size distribution was within a narrow size but the mean particle size was different among the formulations. The results indicated that the proportional increase in the mean particle size of microbeads increased with the amount of sodium alginate in the formulations. The total percentage yields of drug-loaded microbeads obtained were in the range between 78.4 to 86.2 %w/w. It was observed that increasing the concentration of sodium alginate in the formulation significantly lower the product yield, due to the formation of high viscous polymer dispersion which may be lost during manufacturing process. The drug entrapment efficiency of the loaded microbeads was found to be in the range 65.43±0.42 to 84.5±1.05. The % weight gain of coated beads F2 was found to be 2.2 %w/w.
Fig. 2. (a) DSC thermogram of pure drug, sodium alginate, Eudragit L100, drug-polymer physical mixture and eudragit coated drug-loaded alginate beads.

Fig. 2. (b) Comparative DSC thermogram of Eudragit L100 coated alginate beads with plugging materials (Sterculia gum, HPMC, Carbopol).
In-vitro Dissolution Studies of Drug Loaded Alginate Beads

The drug release from uncoated alginate beads was pH independent, showing immediate release in acidic pH 1.2 without any lag time followed by slow sustained release as shown in Figure 3. This may be due to the presence of small portion of drug on the surface of the beads which are immediately accessible to the media giving rapid solubility. The reason of slower release may be attributed to stability of polymers at lower pH and conversion of Ca-alginate to the insoluble alginic acid to form tightening of the gel mesh work. On the other hand, the Eudragit L100 coated beads eroded as the pH increases towards alkaline side like 6.8, 7.4 and the contents are released in a sustained manner by both diffusion and slow erosion of polymer matrix. Release study revealed that formulations F1 to F7 showed the percentage of drug release in pH 6.8 buffer media at the end of 5h was 65.6, 60.7, 55.7, 41.2, 39.2, 27.17and 25.4 respectively. Release data revealed that as the drug-polymer ratio increased, the release rate of aceclofenac sodium from the microbeads decreased. The DEE values for formulations F1 to F7 were 86.2, 82.1, 84.5, 81.5, 81.2, 80.5 and 82.4 respectively. With these formulations 96.56, 86.30% and 77.80% of drug was released at the end of 16th hr. This respectively and at the end of 20th hour FH1 formulation had released 94.47% of drug. Whereas FH2 formulation released 90.42% of drug up to 24 h in controlled manner. In case of FH3 (40 mg), hydrogel plug ejected out in 6.8 buffers, releasing the entire drug in large intestine, in a controlled manner.

Effect of Different Plugging Materials on In-vitro Release

The in vitro release profile for formulations (a) Sterculia gum (FS1–FS3), (b) HPMC (FH1–FH3) and (c) Carbopol (FC1–FC3) respectively as hydrogel plugging materials at different proportions are shown in Figure 4. With formulations FS1 (20 mg), FS2 (30 mg), at the end of 5th hour there was 6.38% and 2.15% cumulative drug release was found. In case of FS1 and FS2 it was observed that polymer concentration was sufficient to retard the drug release in small intestinal fluid and the plug ejected out in 6.8 buffers, releasing the entire drug in large intestine, in a controlled manner. At the end of 24 h, 92.22%, 94.14%, 87.18% of drug release was found in FS1, FS2 and FS3 respectively. With formulation FH1 (20 mg), FH2 (30 mg), at the end of 5th hour 5.33% and 4.26% of drug was released respectively and at the end of 20th hour FH1 formulation had released 94.47% of drug. Whereas FH2 formulation released 90.42% of drug up to 24 h in controlled manner. In case of FH3 (40 mg), hydrogel plug ejected out in between 6th and 8th hour, indicating decrease in expelling power of plug. At the end of 24th hour 86.43% of drug was released. For the formulations FC1, FC2 and FC3 Carbopol was employed as plugging material in three different concentrations like 20, 30 and 40 mg respectively. With these formulations 96.56, 86.30% and 77.80% of drug was released at the end of 16th hr. This virtually indicated the failure of these formulations in maintaining the desired lag phase and also failed to maintain the drug release for a period of 24 hrs.

**Table 1**

<table>
<thead>
<tr>
<th>Batch Code</th>
<th>Drug /Polymer ratio</th>
<th>Sodium alginate ( %w/v)</th>
<th>Conc.of CaCl₂ (%w/v)</th>
<th>Curing Time (mins)</th>
<th>Mean Particle Size (micron)</th>
<th>%Yield</th>
<th>%DEE</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>1:1</td>
<td>2</td>
<td>5.0</td>
<td>30</td>
<td>596 ± 1.04</td>
<td>86.2</td>
<td>65.43 ± 0.42</td>
</tr>
<tr>
<td>F2</td>
<td>1:2</td>
<td>2.5</td>
<td>5.0</td>
<td>30</td>
<td>631 ± 1.12</td>
<td>82.1</td>
<td>76.5 ± 0.12</td>
</tr>
<tr>
<td>F3</td>
<td>1:2.5</td>
<td>3.0</td>
<td>5.0</td>
<td>30</td>
<td>667 ± 1.54</td>
<td>84.5</td>
<td>76.8 ± 0.21</td>
</tr>
<tr>
<td>F4</td>
<td>1:2.75</td>
<td>3.5</td>
<td>5.0</td>
<td>30</td>
<td>710 ± 1.21</td>
<td>81.5</td>
<td>78.5 ± 0.47</td>
</tr>
<tr>
<td>F5</td>
<td>1:3</td>
<td>4.0</td>
<td>5.0</td>
<td>30</td>
<td>764 ± 0.44</td>
<td>81.2</td>
<td>81.2 ± 1.02</td>
</tr>
<tr>
<td>F6</td>
<td>1:3.5</td>
<td>4.5</td>
<td>5.0</td>
<td>30</td>
<td>810 ± 0.24</td>
<td>80.5</td>
<td>82.4 ± 1.12</td>
</tr>
<tr>
<td>F7</td>
<td>1:4</td>
<td>5.0</td>
<td>5.0</td>
<td>30</td>
<td>860 ± 1.14</td>
<td>78.4</td>
<td>84.5 ± 1.03</td>
</tr>
</tbody>
</table>

**Figure 3.** Comparative in-vitro drug release profile of coated alginate microbeads (F1-F7) in phosphate buffer media pH 6.8.

**Figure 4.** Cumulative drug release for different formulations of coated alginate microbeads (FS1–FS3, FH1–FH3 and FC1–FC3) at different pH conditions.

**Characterization and In-vitro Evaluation of Designed Pulsatile System Containing Coated Alginate Microbeads**

Results show that coated alginate microbeads were successfully incorporated in to the pulsatile delivery capsule using different quantities of hydrophilic swellable plugging materials as depicted in Table 2. During dissolution studies, it was observed that, the enteric coat of the HPMC remain intact for 2 h in pH 1.2, but dissolved in intestinal pH, above pH 7.4 leaving the soluble cap of capsule, which also is dissolved in pH 7.4, then the exposed polymer plug absorbed the surrounding fluid, swelled and released the drug through the swollen matrix. After complete wetting of the plug, it formed a soft mass, which was then easily ejected out of the capsule body; releasing the eudragit coated micro-capsules into pH 6.8 phosphate media buffer. With all the formulations, there was absolutely no drug release in pH 1.2, thus indicating the efficiency of 5% HPMCP for enteric coating. Different concentrations of the swellable polymers such as guar gum, HPMC and carbopol were used and their effect on drug release from the designed pulsatile capsule was investigated using the dissolution media mimicking the pH conditions in the GI tract.
TABLE 2
Composition of proposed pulsatile system based on design summary.

<table>
<thead>
<tr>
<th>Batch Code</th>
<th>Wt. of empty Cap. body (mg)</th>
<th>Wt of eudragit coated alginate microbeads (mg)</th>
<th>Wt. of gelatin Cap. (Non-formal dehydrated)</th>
<th>Swellable plugging materials</th>
<th>Wt. of plugging material (mg)</th>
<th>Total wt.of capsule (mg)</th>
<th>Wt. after HPMC Coating (mg)</th>
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</thead>
<tbody>
<tr>
<td>FS1</td>
<td>78</td>
<td>362</td>
<td>47</td>
<td>Sterculia Gum</td>
<td>20</td>
<td>503</td>
<td>538</td>
</tr>
<tr>
<td>FS2</td>
<td>79</td>
<td>362</td>
<td>45</td>
<td>Sterculia Gum</td>
<td>30</td>
<td>519</td>
<td>558</td>
</tr>
<tr>
<td>FS3</td>
<td>78</td>
<td>362</td>
<td>46</td>
<td>Sterculia Gum</td>
<td>40</td>
<td>533</td>
<td>570</td>
</tr>
<tr>
<td>FH1</td>
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<td>362</td>
<td>46</td>
<td>HPMC</td>
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<td>FH3</td>
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<td>HPMC</td>
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<td>FC1</td>
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<td>Carbopol</td>
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<td>559</td>
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<tr>
<td>FC3</td>
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<td>47</td>
<td>Carbopol</td>
<td>40</td>
<td>536</td>
<td>574</td>
</tr>
</tbody>
</table>

Fig. 4. Comparative in-vitro drug release profile of aceclofenac from multiparticulate pulsatile system containing varying quantity of hydrophilic plugging materials (FS1-FS3, FH1-FH3, FC1-FC3) in pH 1.2, 7.4 and 6.8.

Conclusions

The calcium alginate-eudragit coated multiparticulate beads was successfully prepared ionic-gelation and the developed pulsatile system containing Sterculia gum as hydrophilic plugging materials shows the best release as compared to other polymers. With all the above observations, it was found that Sterculia gum and HPMC as plugging materials were found better in maintaining the desired lag period and eudragit coated alginate microbeads provides sustained release of aceclofenac after ejection of the plugs. It was also observed that the plug was ejected only at the end of 6 hours of dissolution and released variable amount of drug depending on the type and proportion of the swellable plugging materials. The lag period and the drug release could be efficiently modulated by altering the concentration of plugging material to a certain extent. Thus, the study reveals the efficacy and suitability of these natural polymers as plugging materials in the design of chronotherapeutic delivery of aceclofenac and appears to be effective delivery system for the treatment of rheumatoid arthritis.

Acknowledgements

The authors greatly acknowledge Girijananda Chowdhury Institute of Pharmaceutical Science, (GIPS), Guwahati, Assam to carry out DSC, FT-IR and other laboratory studies. The authors are also thankful to CDH, Kolkata India for sending aceclofenac as gift sample.

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