Intestinal Controlled Delivery of Diclofenac Sodium through pH-Sensitive Hydrogel Beads

Tapan Kumar Giri

Abstract—pH-sensitive hydrogel beads of hydrolyzed polyacrylamide (PAAm) grafted locust bean gum (LBG) and carboxymethyl cellulose (CMC) were prepared by ionotropic gelation and covalent cross-linking method for the controlled delivery of diclofenac sodium. The developed hydrogel beads are to survive the harsh acidity of stomach and preferably release drugs in intestine. The results showed that hydrogel beads are pH responsive. The release of diclofenac sodium (DS) from hydrogel beads was slower for the pH 1.2 solution than that of the pH 6.8 buffer solution. It has been observed that an increase in aluminium chloride (AlCl3) concentration causes a decrease in the drug release from the hydrogel beads. Moreover, hydrogel beads developed showed a consistent swelling pattern, high entrapment efficiency and promoting sustained release profiles of the drug.

Keywords— pH sensitive, locust bean gum, hydrogel, graft copolymer, in-vitro release, controlled delivery.

I. INTRODUCTION

DICLOFENAC sodium is a non-steroidal drug having a effective anti-inflammatory, analgesic, and antipyretic effect. It is used for the relief of pain and inflammation in circumstances such as osteoarthritis, rheumatoid arthritis, acute gout, ankylosing spondylitis, and subsequent surgical procedures [1]. It has a short biological half-life of 1-2 h and the most common side effects are gastritis and peptic ulceration [2]. Controlled release drug delivery systems have the prospective of solving these tribulations. Controlled release systems are the methods that can attain therapeutically useful concentration of drug in the systemic circulation over an extensive period of time with improved patient conformity [3]-[5]. Therefore, it is advantageous to develop diclofenac sodium controlled release dosage forms to decrease the unpleasant effects on upper gastrointestinal tract. Controlled release systems are the methods that can attain therapeutically useful concentration of drug in the systemic circulation over an extensive period of time with improved patient conformity. Controlled release systems are the methods that can attain therapeutically useful concentration of drug in the systemic circulation over an extensive period of time with improved patient conformity.

One method of formulating controlled release dosage forms and releasing the drug in the lower gastrointestinal tract is by the inclusion of the drug in a matrix containing pH-receptive hydrogel. pH-receptive hydrogels are three dimensional cross-linked hydrophilic polymers which swell exclusive of dissolving with water or other biological fluids [6]-[7]. Both synthetic and natural polymers have been used in the preparation of pH-responsive hydrogel [8]-[9]. However, hydrogels based on natural polymers have been extensively used for controlled release of drug.

In the present work, pH-sensitive hydrogel beads of hydrolyzed PAAm grafted LBG and carboxymethyl cellulose was prepared. The main purpose of grafting and hydrolysis of graft copolymer was to increase the number of carboxylic groups in the backbone matrix that is required for the development of Al3+cross-linked hydrogel beads. These carboxylic groups are likely to take part in minimizing the swelling at upper gastrointestinal tract (pH 1.2) and maximizing the swelling at lower gastrointestinal tract (pH 6.8).

II. MATERIALS AND METHODS

A. Materials

Diclofenac sodium was obtained as gift sample from Arti Pharmaceutical Company, Orissa, India. LBG was purchased from Victory Essence Mart, Bangalore, India. AAm and methanol were purchased from Loba Chemie, Mumbai, India. CAN was purchased from Universal Fine Chem, India. Glutaraldehyde (GA) was purchased from SD Fine-Chem. Ltd., Mumbai, India as 25% v/v aqueous solution. All other reagents were of analytical grades and used as received.

B. Methods

1. Synthesis of Graft Copolymer

Requisite quantity (175 mg) of LBG was dissolved in 25 ml of distilled water. 700 mg of acrylamide was dissolved in 5 ml of distilled water and mixed with LBG solution. The reaction temperature was kept constant 70°C. At this stage 5 ml ceric ammonium nitrate solution (10x10^{-3} mol/L) was added and the reaction was continued to 60 min. The polymer was precipitated by addition of excess of methanol at the end of the reaction. It was then dried at 40°C to a constant weight.

2. Alkaline Hydrolysis of Graft Copolymer

500 mg of graft copolymer was dissolved in 25 ml of sodium hydroxide solution (0.9M) and stirred at 70°C for 60 minutes. The solution was then cooled and poured in excess methanol. The hydrolyzed product was separated by filtration and washed repeatedly with methanol. Then the resultant product was dried overnight at 40°C.

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3. Preparation of Hydrogel Beads

Weighed quantity of DS corresponding to 20% of dry mass of the polymer was dispersed in an aqueous solution of hydrolyzed LBG-grafted-AAm and CMC. Then dispersion was added drop wise through 22-gauze needle into slightly agitated 100 ml of AlCl$_3$ solution. The beads were removed after 30 min and washed with distilled water and dried at 40°C till constant weight.

Further the beads incubated in AlCl$_3$ solution for 30 minutes, were transferred into 50 ml of pH 2 HCl containing GA for 10 min at 50°C to introduce covalent cross-links. The cross-linked beads were removed and washed with distilled water repeatedly to remove nonreacted gluteraldehyde. Fig.1 shows the images of dry beads.

4. Fourier Transforms Infrared Spectroscopic Study

FT-IR spectra of pure drug and drug loaded beads were recorded in a FT-IR spectrophotometer (Prestige-21 Shimatzu, Japan) using KBr pellets. The spectra were recorded within 4000-400 cm$^{-1}$ wave number.

5. Differential Scanning Colorimetry Study

The thermal analysis of drug and drug loaded beads were carried out with thermal analyzer (Pyris diamond, PerkinElmer, Singapore). Differential scanning calorimetry of all the samples was performed up to a temperature of 400°C at 12°C/min.

6. Scanning Electron Microscopic Study

The shape and surface morphology of hydrogel beads were investigated using scanning electron microscopy (JEOL, JSM-6360, UK).

7. Determination of Drug Content

20 mg of beads were crushed with a mortar-pestle and transferred into 200 ml of pH 6.8 phosphate buffer solution. After 3 hours, the suspension was filtered and samples were analyzed with a spectrophotometer (Shimadzu Model: 1800) at 273nm. Entrapment efficiency (%) = (actual drug content/theoretical drug content) × 100[10]

8. Swelling Study

The swelling of the beads was studied in 25ml of pH 1.2 buffer solutions and pH 6.8 USP phosphate buffer solution. The beads were removed at different times by filtration and blotted carefully to remove excess surface water. The swollen beads were weighed. Swelling ratio = (Final weight-Initial weight)/Initial weight [11]

9. In-vitro Drug Release Study

In-vitro drug release study was carried out in pH 1.2 buffer solution and pH 6.8 phosphate buffer solution using USP II dissolution rate test apparatus (Electro lab- TDT-08L). 20 mg dried beads was placed in 500 ml acidic solution for 2 hr then alkaline solution for remaining time maintained at 37±0.5°C. The paddle was rotated at 50 rpm. Aliquot was withdrawn at different times and were analyzed spectrophotometrically at 273nm for acidic solution and 276 nm for alkaline solution.

III. RESULTS AND DISCUSSION

When a dispersion of drug and hydrolyzed PAAm-g-LBG graft copolymer was extruded through the needle into the solution containing Al$^{3+}$ cations, the beads were formed instantaneously. However, the bead exhibits very poor mechanical strength. In order to improve the mechanical strength, we prepare the beads of hydrolyzed PAAm-g-LBG and CMC by ionotropic gelation process using AlCl$_3$ as a common cross-linking agent for both polymers. As soon as the Al$^{3+}$ ions are brought in contact with the polymer solution, they form ionic cross-links between two polymer molecules and different parts of the same polymer chain. The exchange of Na$^+$ ions of both polymers occurs with Al$^{3+}$. These Al$^{3+}$ are ionically substituted at the carboxylated site and a second strand of CMC or hydrolyzed PAAm or LBG strands together to form hydrogel beads. The prepared hydrogel beads were spherical in shape having surface folding as evidenced by SEM (Fig.2).

The IR spectra of DS (Fig.2) exhibited distinctive peaks at 3387 cm$^{-1}$ (NH stretching of the secondary amine), 1573.91 cm$^{-1}$ (C=O stretching of the carboxyl functional group), 1719 cm$^{-1}$ (C=O stretching of the amide functional group) and 2903 cm$^{-1}$ (C-H stretching of the methylene group).
1305.80 (C-N stretching) and at 746.45 cm\(^{-1}\) (C-Cl stretching) [12]. All the principal peaks of DS were present in drug loaded hydrogel beads (Fig.3) with minor differences in frequencies which confirms that there was no interaction between drug and polymers and reflects the stability of DS in hydrogel beads.

The DSC thermogram of pure diclofenac sodium (Fig.4) showed two endothermic peaks. The first small endothermic peak at 60.99\(^\circ\)C was due to water loss. The second sharp endothermic peak at 288.76\(^\circ\)C was due to its melting point. Melting point of the drug was not appeared in drug loaded hydrogel beads (Fig.4). This indicates that most of the drug was uniformly dispersed at the molecular level in the beads.

Fig. 4 Differential scanning colorimetry of diclofenac sodium and diclofenac sodium loaded hydrogel bead (F5)

X-ray diffraction pattern of DS showed the important crystallographic reflection at different scattering angle ranges which was due to the crystalline nature of DS (Fig.5). However, these drug peaks were disappeared in the X-ray diffraction pattern of DS loaded hydrogel beads (Fig.5). It was thought that the DS showed its specific crystal peaks when existed in a crystalline form but after drug entrapped into the beads, the drug can be existed as a molecular dispersion in the beads.

Fig.5 X-ray diffraction patterns of diclofenac sodium and diclofenac sodium loaded hydrogel bead (F5)

Particles were generally spherical in shape with sizes ranging from 803.33-849.33 µm(Table 1). As the concentration of AlCl\(_3\) was increased, smaller beads were produced (849.33, 836.67, 823.67 and 803.33 µm for 1, 2, 3 and 4% w/v of AlCl\(_3\) respectively). This suggests that during cross-linking, the hydrogel might have undergone rapid shrinkage leading to the formation of smaller and rigid matrix at high cross-linking density [13]. The drug entrapment efficiency of the beads decreased with increasing concentration of AlCl\(_3\). The drug entrapment efficiency of the beads decreased from 96.78 to 90.90 with the increase in AlCl\(_3\) concentration from 1 to 4% w/v (Table 1). It is assumed that as gelation proceeds water is expelled due to cross-linking. There, the higher the degree cross-linking, the higher is the water loss. The expulsion of water will cause loss of drug from beads. The release of a drug from a polymeric matrix is controlled by the swelling behavior of the polymer. The swelling ratio of the hydrogel beads was very low in acidic solution (pH 1.2), the same property increased considerably in phosphate buffer solution (pH 6.8). The main functional group present in both the polymers that undergoes cross-linking with Al\(^{3+}\) ions is –COOH group. In acidic solution, –COOH group remains protonated and exerts insignificant electrostatic repulsive force. As a result, the beads swell to very less extent. At higher pH value, -COOH group undergoes ionization which exerts electrostatic repulsion between the ionized groups, and the results in higher swelling. It was observed that the swelling tendencies of the beads decreased in either of the swelling medium with the increase in AlCl\(_3\) concentration. It was estimated that gradual increase in AlCl\(_3\) concentration to 4% reduced the swelling ratio by 19.40%. Similarly, in alkaline medium gradual increase in AlCl\(_3\) concentration to 4% reduced the swelling
Hydrogel beads of CMC and hydrolyzed PAAm-g-LBG were prepared successfully by ionotropic gelation and covalent cross-linking method. DSC and XRD studies confirmed the presence of drug mostly in amorphous state and homogeneity of drug dispersion in hydrogel beads. The hydrogel beads showed extended release profile. The results of the study indicate that drug loaded hydrogel beads could be used to minimize the release of diclofenac sodium in stomach and to modulate the drug release in intestine, which would help to minimize the gastric side-effects of diclofenac sodium.

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### Table I: Composition of Hydrogel Beads

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Particle Size (µm) ± SD</th>
<th>Drug Content (%) ± SD</th>
<th>Swelling Ratio in pH 1.2 After 1.5 hr ± SD</th>
<th>Swelling Ratio in pH 6.8 After 1.5 hr ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>849.33±11</td>
<td>96.78±0.4</td>
<td>0.67±0.020</td>
<td>2.65±0.032</td>
</tr>
<tr>
<td>F2</td>
<td>83667±2.52</td>
<td>94.6±0.4</td>
<td>0.647±0.021</td>
<td>2.665±0.01</td>
</tr>
<tr>
<td>F3</td>
<td>823.67±2.21</td>
<td>92.57±0.27</td>
<td>0.563±0.025</td>
<td>2.460±0.02</td>
</tr>
<tr>
<td>F4</td>
<td>803.33±2.08</td>
<td>90.90±0.67</td>
<td>0.540±0.010</td>
<td>2.423±0.02</td>
</tr>
<tr>
<td>F5</td>
<td>785.33±2.08</td>
<td>89.16±0.06</td>
<td>0.190±0.010</td>
<td>0.427±0.03</td>
</tr>
</tbody>
</table>

In vitro drug release profile of the beads has been illustrated in Fig. 6. The release of drug in pH 1.2 solutions was slower compared with that in pH 6.8 buffer solution. This was due to a higher swelling of beads in alkaline pH condition. It was observed that release rate depend upon the amount of AlCl3 used as a cross-linking agent during the preparation. Release was slower for the beads in which higher amount of AlCl3 was used as compared with those beads in which lower amount of AlCl3 was present. In order to compare the drug release rate, a time point approach was adopted. The values of t50% were 12.93, 13.48, 13.65 and 13.93 min, respectively in the order of their increasing AlCl3 concentration. This could be due to the fact that at higher cross-linking free volume of the matrix will decrease, thereby hindering the transport of drug molecules through the matrix. This could also reduce the swelling as well as release rate from the matrix. This is in agreement with the previous results [14].

The GA treatment of the beads suppressed the drug release in acidic as well as weakly basic dissolution medium. In addition to ionic cross-links, GA brought about covalent linkages and showed the retarded drug release in both dissolution media than those having ionic linkages only. At higher cross-linking free volume of the matrix will decrease, thereby hindering the transport of drug molecules through the matrix [15].

Fig. 6: The release profile of diclofenac sodium from hydrogel beads.


