Research Article

Development and Evaluation of Gellan Gum Based Hydrogel Microbeads for Controlled Release of Ketoprofen

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Abstract

Compared to single unit-dosage forms, multi-unit controlled release dosage forms like microbeads and microparticles are advantageous as they prevent the exposure of absorbing site to high drug concentration on chronic dosing. Gellan gum based hydrogel microbeads loaded with ketoprofen were prepared by ionotropic gelation method and evaluated for size analysis, surface morphology, dynamic swelling and drug release behavior. The scanning electron microscopy (SEM) revealed that the prepared beads were spherical in nature. The effects of crosslinking agent and polymer concentrations on the release of drug were studied. With increase in concentrations of crosslinking agent and polymers, a decreased drug release was observed. The release data were fitted to an empirical equation to calculate the release mechanism. Drug release followed non-Fickian mechanism. Thus the prepared microbeads are useful carriers for controlled release of ketoprofen.

Keywords:
Ketoprofen
Hydrogel beads
Gellan gum
Controlled release

INTRODUCTION

Ketoprofen is a widely used non-steroidal anti-inflammatory drug (NSAID) in the treatment of musculoskeletal and joint disorders. It is readily absorbed from the gastro-intestinal tract and exhibits a short biological half life of 2 h. When administered orally, it causes certain gastric side effects like gastric irritation, ulceration, hemorrhage etc. The shorter biological half life and associated side effects make the ketoprofen a suitable candidate for controlled release formulations \[1\]. However, when compared to single unit-dosage forms, multi-unit controlled release dosage forms like microbeads and microparticles pass through the gut as if a solution avoiding the vagaries of gastric emptying and different transit rates, release drugs more uniformly in a predictable manner and spread over a large surface area preventing exposure of the absorbing site to high drug concentration on chronic dosing \[2-5\]. Multiple units can be filled into hard gelatin capsules or they can be compressed into tablets \[6\].

Polymeric hydrogels are three-dimensional cross-linked networks that have the ability to absorb water and swell without losing their shape \[7\]. Their most remarkable macroscopic property is their high swelling ability, which depends largely on the external conditions (i.e. pH, temperature) and the parameters of the gel (i.e. mesh size) \[8, 9\]. Hydrogels have been widely used in medicine and pharmacy as controlled delivery devices of various active materials \[10-12\].

Recently, much research has been focused on the development of multi-unit controlled release systems using natural hydrophilic polymers as they are easily available. However, there is no report on the gellan gum (GG) based hydrogel microbeads for prolonged release of ketoprofen.

The present work is aimed at the development and evaluation of gellan gum based hydrogel microbeads for the prolonged release of ketoprofen by ionotropic gelation method.

MATERIALS AND METHODS

Ketoprofen (KP) was obtained as gift sample from Rhone-Poulenc, (Mumbai, India) Gellan gum (GG), calcium chloride dihydrate and sodium hydroxide (NaOH) were purchased from SD fine Chemicals, (Mumbai, India). Double distilled water was used throughout the study. All other chemicals were extra pure reagent grade and were used as received.

Preparation of microbeads

An accurately weighed quantity of ketoprofen was dispersed in an aqueous solution of GG and mixed homogeneously using magnetic stirrer. Twenty milliliters of dispersion was extruded in the form of droplets into 100 ml aqueous solution of CaCl\(_2\) solution using 25 ml hypodermic syringe through a needle (number 23). The beads were removed after the gelation period of 30 min and washed with distilled water repeatedly to make free from un-reacted ions and dried at room temperature for 24 h and then at 40°C for 10 h \[13\]. The composition of beads is given in Table 1.
Scanning electron microscopic studies (SEM)
The microbeads were mounted onto stubs using double sided adhesive tape and sputter coated with platinum to make them conducting using sputter coater (Edward S 150, UK). The coated beads were observed under scanning electron microscope (JEOL, JSM-6360, Japan) at X70 and X200 magnifications at room temperature.

Measurement of bead size
The microbead size was measured using a digimatic micrometer (MDC-2S5 Mitutoyo, Japan) having an accuracy of 0.001 mm. The average diameter of the 100 beads per batch was measured [13].

Estimation of drug entrapment efficiency (DEE)
Known amount of microbeads were incubated with 100 ml of phosphate buffer pH 7.4 for complete swelling. Then the beads were crushed in a glass mortar with pestle, the solution was heated gently for 3 h to extract the drug completely and centrifuged to remove the polymeric debris. The clear supernant solution was analyzed for the drug content using UV-visible spectrophotometer (Model Pharmaspec UV-1700, Shimadzu, Japan) at 260 nm. The entrapment efficiency was calculated using the following equation [14];

\[ \text{DEE} = \frac{\text{Experimental drug content}}{\text{Theoretical drug content}} \times 100 \]

Dynamic swelling study
The dynamic swelling behavior of the microbeads was studied by mass measurement. The beads were incubated with 25 ml phosphate buffer pH 7.4 in a petridish at 37°C. The beads were taken out at different time intervals using stainless steel grid and blotted carefully without pressing hard to remove the excess surface liquid. The swollen beads were weighed using the electronic microbalance. The studies were performed in triplicate and average values were taken in data analysis [15].

RESULTS AND DISCUSSION
The obtained microbeads were spherical in shape having rough and dense surface with microscopic cracks on the surface as evidenced by SEM (Fig.1) and they fell in the size range of 812 to 1452 \( \mu \)m (Table 2). As the concentration of CaCl\(_2\) was increased, smaller beads were produced and on the other hand, by increasing the concentrations of GG and drug in the microbeads, an increase in size of the beads was observed. Table 2 shows that drug entrapment efficiency (DEE) of the beads prepared with lower concentration of CaCl\(_2\) was lowest as compared to those prepared with higher concentration of CaCl\(_2\).

Table 1: Composition of microbeads

<table>
<thead>
<tr>
<th>Code</th>
<th>GG (% w/v)</th>
<th>Ketoprofen (% w/w of dry polymer)</th>
<th>CaCl(_2) (% w/v)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>1.0</td>
<td>20</td>
<td>3</td>
</tr>
<tr>
<td>G2</td>
<td>1.5</td>
<td>20</td>
<td>3</td>
</tr>
<tr>
<td>G3</td>
<td>2.0</td>
<td>20</td>
<td>3</td>
</tr>
<tr>
<td>G4</td>
<td>2.0</td>
<td>20</td>
<td>6</td>
</tr>
<tr>
<td>G5</td>
<td>2.0</td>
<td>20</td>
<td>9</td>
</tr>
<tr>
<td>G6</td>
<td>2.0</td>
<td>40</td>
<td>9</td>
</tr>
</tbody>
</table>

**In vitro drug release**
In-vitro drug release study was carried out in triplicate using a USP-23 rotating paddle dissolution tester (Electrolab TDT-06P, Mumbai, India). The dissolution rates were measured at 37.0 ± 0.5 °C and 50 rpm paddle speed. Drug release from the microbeads was studied in 900 ml phosphate buffer medium (pH 7.4). At predetermined time intervals, 5 ml aliquots were withdrawn and replaced with the same volume of fresh solution. The samples were analyzed using UV-visible spectrophotometer at a \( \lambda_{\text{max}} \) of 260 nm with suitable dilutions [13].

Table 2: Average bead size, drug entrapment efficiency (DEE), diffusion coefficients (D) and release parameters (n) of the microbeads

<table>
<thead>
<tr>
<th>Beads</th>
<th>Average size (( \mu )m)</th>
<th>DEE (%)</th>
<th>( D ) (cm(^2)/s)</th>
<th>( n )</th>
<th>( r^2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>812 ± 2.15</td>
<td>52.71 ± 0.46</td>
<td>5.12 X 10(^{-4})</td>
<td>0.56</td>
<td>0.981</td>
</tr>
<tr>
<td>G2</td>
<td>1276 ± 2.87</td>
<td>54.85 ± 0.85</td>
<td>4.98 X 10(^{-4})</td>
<td>0.59</td>
<td>0.987</td>
</tr>
<tr>
<td>G3</td>
<td>1452 ± 4.46</td>
<td>56.45 ± 0.62</td>
<td>4.01 X 10(^{-4})</td>
<td>0.62</td>
<td>0.994</td>
</tr>
<tr>
<td>G4</td>
<td>1342 ± 6.70</td>
<td>62.89 ± 0.75</td>
<td>3.15 X 10(^{-4})</td>
<td>0.66</td>
<td>0.989</td>
</tr>
<tr>
<td>G5</td>
<td>1198 ± 5.52</td>
<td>70.46 ± 0.35</td>
<td>2.42 X 10(^{-4})</td>
<td>0.73</td>
<td>0.986</td>
</tr>
<tr>
<td>G6</td>
<td>1264 ± 1.78</td>
<td>75.56 ± 0.95</td>
<td>2.95 X 10(^{-4})</td>
<td>0.64</td>
<td>0.991</td>
</tr>
</tbody>
</table>

\( r^2 \) values indicate correlation coefficients.
An increase in initial drug loading also increased the drug release. To understand the drug release mechanism in the hydrogel network, release data was fitted to an empirical equation:

\[ \frac{M_t}{M_\infty} = K t^n \]  

In which \( M_t \) is the amount of drug released at time \( t \), and \( M_\infty \) is the total amount of drug loaded, \( n \) values are the indication of the type of release mechanism. The calculated \( n \) values along with the correlation coefficients have been shown in Table 2. The values of \( n \) depend upon the cross-link density and GG concentration; the \( n \) values increase with increase in cross-link density and GG concentration. Calculated \( n \) values suggested that the mechanism of drug release followed non-Fickian transport.

**CONCLUSION**

The gellan gum based hydrogels microbeads were prepared by ionotropic gelation method for the controlled release of ketoprofen. The swelling of beads and drug release depends upon the polymer concentration and extent of crosslinking in the hydrogel matrix. Drug release followed non-Fickian mechanism. This work demonstrates the feasibility of preparing multiparticulate drug delivery system for controlled release of ketoprofen.

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**REFERENCES**


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