Formulation and Characterization of Microparticulate Carriers for Diclofenac Sodium

Yogyata S. Pathare1*, Seema Hiray2, Fayeza A. H.2

1. Shree Chanky Education society’s Indira College of Pharmacy, Tathawade, Pune Pin- 411033. Maharashtra. India.
[Email- yogyataspthare@gmail.com; Tel: +91 9823091755]
2. K.B.H.S.S.T’s Institute of Pharmacy, Malegaon, Dist, Nasik, Maharashtra, India.

The present study deals with formulation of a sustained-release calcium alginate microbeads containing Diclofenac sodium by the ionotropic gelation technique at various concentrations of sodium alginate and calcium chloride. Prepared microbeads were evaluated for drug entrapment efficiency, drug content, density, flow properties, particle size and in vitro drug release. The prepared beads were free-flowing, white in color and showed an acceptable range of bulk density, tapped density and angle of repose. Mean diameter of the particles was found to be in the range of 350-450µ. The drug loaded beads showed 83.5 – 95.57 % drug entrapment, which was found to increase with increase in sodium alginate. In vitro drug release study of these microbeads indicated controlled release for Diclofenac sodium 84.54 – 95.23 % release at the end of 10 h. From this study it is concluded that the calcium alginate microbeads can provide a better carrier system for delivery of drugs.

Keyword: Sodium Alginate, Ionotropic Gelation Technique, Micobeads.

1. Introduction

Microbeads are uniform polymer particles, typically 0.5 to 1000 micrometres in diameter. Bio-reactive molecules can be adsorbed or coupled to their surface, and used to separate biological materials such as cells, proteins, or nucleic acids. Sodium alginate has been used as a matrix material to achieve controlled-release drug delivery due to its hydrogel-forming properties. Alginate salts are known to form a reticulated structure when in contact with calcium ions and their characteristic has been used to produce sustained release particulate systems for a variety of drugs. The ability of alginate sodium salt, to rapidly form viscous solutions and gels on contact with aqueous media has been exploited by the pharmaceutical industry in sodium alginate’s wide application as a carrier in hydrophilic matrix controlled release oral dosage forms[1,2].

Ionotropic gelation is based on the ability of polyelectrolytes to cross link in the presence of counter ions to form hydrogels. Microencapsulation by ionotropic gelation is one of the widely used method for preparation of calcium-alginate microspheres/beads which has ability to form gels reaction with calcium salts. Recently the use of calcium-alginate gel beads as a vehicle for controlled drug delivery system has attracted considerable attention because of their property of reswelling which is susceptible to environment pH. Consequently, acid sensitive drugs

incorporated into beads would be protected from gastric juice. However, major disadvantages of alginate beads are their fast disintegration in simulated intestinal fluid and high porosity, which result in rapid drug release\cite{3}.

Diclofenac sodium is a non-steroidal anti-inflammatory agent, which is widely used in long-term therapy for rheumatoid arthritis. The biological half-life of Diclofenac sodium is about 1-2 hours, therefore it requires multiple dosing to maintain therapeutic drug blood level. The most frequent adverse side effects of Diclofenac sodium on long-term administration are gastrointestinal disturbances, peptic ulceration, and perforation. In order to eliminate these adverse effects, enteric coated and/or SR forms have been developed and commercialized.

Here in this study Sodium alginate is used as the polymer and micro beads are formed basing on the ionotropic gelation technique. The gelation is caused by forming an egg box junction to associate divalent metal ions of alginate polymer chain.

2. Objectives
An attempt was made to formulate a SR dosage form containing beads of Diclofenac sodium for controlled release, which eliminates the need for multiple dosing thereby, increasing patient compliance and decreasing the occurrence of adverse effects. Here in this study Sodium alginate is used as the polymer and micro beads Diclofenac sodium are formed based on the ionotropig gelation technique with following objectives

1. To formulate microbeads of sodium alginate by ionic gelation technique.
2. To study the effect of concentration of Sodium alginate & Calcium chloride on the different characteristic of microbeads
3. To evaluate microbeads for the following parameters like Bulk density, Tapped density, Flow properties, Particle size, Drug content, drug loading and entrapment efficiency, In vitro drug release study.

3. Materials and Methods
Diclofenac sodium was obtained as a gift sample from Glenmark Laboratories Ltd., Aurangabad. Sodium alginate and calcium chloride (SD Fine chemicals) were purchased. All other chemicals and solvents were of analytical grade.

3.1 Experimental Methods:
3.1.1 Construction of calibration curve
Calibration curve for Diclofenac Sodium was constructed in phosphate buffer pH 7.4 using UV-visible spectrophotometer.

3.1.2 Preparation of Alginate Beads
The calcium alginate microbeads were prepared by ionotropic gelation technique. In the present work six sets of microbeads were formulated by using sodium alginate and calcium chloride in different proportions. The detailed composition of the various formulation batches (D1-D6) were mentioned in Table 1. In the first set three batches of drug loaded microbeads were prepared (D1, D2 & D3). In 50ml of sodium alginate solution, weighed quantity (100mg) of Diclofenac sodium was dispersed uniformly using mechanical stirrer at 500 RPM. Bubble free dispersion was dropped through a syringe with a needle of 18 guage into 100ml aqueous calcium chloride solution (1\%w/v) and stirred at 100 RPM. After stirred for 15 min the formed beads were separated by filtration, washed with distilled water, dried at 60\(^\circ\)C for 2 hr in an oven.

In the second set three batches of drug loaded microbeads were prepared (D4, D6) using sodium alginate. The procedure was similar to the described above method, only the drug sodium alginate dispersion was dropped into 100 ml of 2\%w/v aqueous calcium chloride solution\cite{4}.
Table 1: Formulation of Diclofenac Sodium Microbeads

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Drug in mg</th>
<th>Sodium alginate (%w/v)</th>
<th>Calcium chloride(%w/v)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1</td>
<td>250</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>D2</td>
<td>250</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>D3</td>
<td>250</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>D4</td>
<td>250</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>D5</td>
<td>250</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>D6</td>
<td>250</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

3.2 Evaluation of Calcium Alginate Microbeads

A: Determination of Bulk and Tapped Density
The bulk density and tapped density of prepared microbeads was determined using bulk density apparatus.

B: Flow Properties
The flow properties of drug-loaded microbeads were investigated by measuring the angle of repose using funnel method. Depend upon these values we can assume the flow properties of the microbeads.

C: Granulometric Studies
Size distribution of the microbeads was determined using standard test sieves (Filterwel, Mumbai, India). Particles that passed through one sieve but were retained on the other were collected and weighed. Distribution of particles was analyzed based on weight fraction on each sieve.

D: Determination of Drug Content
About 50 mg of microbeads were weighed and added to 50 ml of phosphate buffer (pH 7.4). The resulting mixture was agitated on mechanical shaker for 24 hrs, then solution was filtered and the drug content was estimated at 264 nm spectrophotometrically after suitable dilution.

E: Determination of Drug Loading and Entrapment Efficiency
Accurately weighed 50 mg of drug-loaded microbeads were suspended in 100 ml of phosphate buffer pH 7.4±0.4. The resulting solution was kept for 24 h. Next day it was stirred for 5 min and filtered. After suitable dilution, Diclofenac sodium content in the filtrate was analyzed spectrophotometrically at 264 nm. The drug loading and entrapment efficiency of prepared microbeads was determined using the following formula:

\[
\text{% of Drug Loading} = \left( \frac{\text{Amount of drug in bead}}{\text{Amount of bead taken}} \right) \times 100
\]

\[
\text{% Entrapment Efficiency} = \left( \frac{\text{Practical drug}}{\text{Theoretical drug}} \right) \times 100
\]

F: In vitro Drug Release Study:
In vitro Drug release studies were carried out in a USP XIII rotating basket apparatus containing 900 ml of phosphate buffer pH 7.4 at 37 ±0.5°C. Hard gelatin capsule filled with microbeads equivalent to 100 mg of Diclofenac sodium were placed in basket rotated at a constant speed of 75 RPM. Aliquots of sample were withdrawn after predetermined periods and replenished immediately with the same volume of fresh medium. Aliquots, following suitable dilution and with suitable dilution, were analyzed spectrophotometrically at 264 nm.

4. Results and Discussion
Microbeads of Diclofenac sodium were prepared (six formulations) by ionotropic gelation technique and different evaluation parameters were assessed, with a view to obtain oral sustained release of Diclofenac sodium. Compatibility of drug with the various polymers was determined by IR spectrometer using a (Shimadzu FTIR-8000 model). I.R. spectrometer, suggest that the drug and polymer are compatible and free from chemical interactions. Calibration curve for Diclofenac Sodium was constructed in
phosphate buffer pH 7.4 using UV-visible spectrophotometer. Graph 1 shows the standard calibration curve of Diclofenac Sodium with regression value 1. The calculation for estimation of drug content, \textit{in vitro} drug release studies are based on standard calibration curve.

The prepared beads were free flowing and white in color. All the formulations showed an acceptable range of bulk density and tapped density. In the granulometric study, it was observed that mean diameter of the particles was found to in the range of 350-450µ. The mean diameter of the particles was found to decrease by increasing in the concentration of calcium chloride solution. It has been stated as Ca$^{2+}$ ions penetrates into interior sodium alginate droplets, water is squeezed out, resulting in contraction of the beads. The flow property of the microbeads was checked by using the angle of repose method. Acceptable range of angle of repose was found to be 20 – 30°. All the formulations angle of repose values were showed on the table no. 2. The drug loaded beads showed 83.5 – 95.57% drug entrapment efficiency. Drug entrapment efficiency of microbeads increases with increasing in the concentration of sodium alginate. \textit{In vitro} drug release study of these microbeads indicated controlled release for Diclofenac sodium 84.54 – 95.23% release at the end of 10 hrs. The results obtained are shown in Table 2. The formulation D6 shows the highest amount of drug release i.e. 95.23% at the end of 10 hrs. Graph 2 and 3 shows the cumulative percentage of drug release of prepared formulations.

**Table 2:** Characterization of Diclofenac sodium microbeads

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Bulk density (g/ml)</th>
<th>Tapped density (g/ml)</th>
<th>Angle of repose (°)</th>
<th>Particle Size (μm)</th>
<th>Drug in mg /50 mg of microbeads</th>
<th>% Drug Entrapment Efficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1</td>
<td>1.13</td>
<td>1.56</td>
<td>25</td>
<td>350.5</td>
<td>0.005</td>
<td>83.5</td>
</tr>
<tr>
<td>D2</td>
<td>0.62</td>
<td>0.76</td>
<td>27</td>
<td>385.67</td>
<td>0.008</td>
<td>86.9</td>
</tr>
<tr>
<td>D3</td>
<td>0.67</td>
<td>0.68</td>
<td>28</td>
<td>395.93</td>
<td>0.01</td>
<td>89.1</td>
</tr>
<tr>
<td>D4</td>
<td>0.73</td>
<td>0.76</td>
<td>24</td>
<td>381.11</td>
<td>0.013</td>
<td>85.7</td>
</tr>
<tr>
<td>D5</td>
<td>0.70</td>
<td>0.71</td>
<td>29</td>
<td>441.40</td>
<td>0.015</td>
<td>90.8</td>
</tr>
<tr>
<td>D6</td>
<td>0.61</td>
<td>0.63</td>
<td>30</td>
<td>404.93</td>
<td>0.019</td>
<td>95.57</td>
</tr>
</tbody>
</table>
5. Conclusion
The spherical and free flowing microbeads of Diclofenac sodium could be successfully prepared by ionotropic gelation technique with high entrapment efficiency and prolonged release characteristics. From this study it is concluded that the calcium alginate microbeads can provide a better carrier system for delivery of drugs.

6. References