CHAPTER X

PREPARATION OF THE CROSSLINKED SODIUM ALGINATE MICROPARTICLES USING GLUTARALDEHYDE IN METHANOL

X.1. Abstract

Polymeric sodium alginate microparticles have been prepared by precipitating sodium alginate in methanol followed by crosslinking with glutaraldehyde. The extent of crosslinking was controlled by the time of exposure to glutaraldehyde. Topology of the microparticles as studied by SEM indicated the smooth surfaces. The equilibrium swelling experiments were carried out in water to observe the effect of crosslinking and also on drug loading for better utilization of the microparticles produced. It was found that swelling decreased, but drug loading increased with an increase in crosslinking of the matrix.

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X.2. Introduction

Alginate belongs to a family of polysaccharides composed of α-L-glucoronic acid (G) and β-D-mannuric acid (M) residues arranged in homopolymeric blocks of each type (MM, GG) and in heteropolymeric blocks (MG). These are known to be haemocompatible and do not accumulate in any organs of the human body. In the literature, several formulations of calcium alginates in various combinations have been prepared and used as CR devices [1,2]. Comparatively, not much attention has been focused on the preparation of sodium alginate (Na-Alg) microparticles [3,4]. Earlier, it was shown [5] that release of the drug-loaded Na-Alg microparticles are affected by the type of crosslinker and the method of crosslinking. The Na-Alg microspheres prepared by emulsifying the Na-Alg aqueous solution into an oil followed by crosslinking with calcium will produce spherical particles initially, but after complete drying, the particles will collapse to yield irregular shapes with a wide range of particle size distribution.

Several methods are available in the literature for the preparation of drug-loaded Na-Alg microspheres and these methods are preferred for the hydrophilic drugs. In our earlier studies on the CR of pesticides [6,7] and pharmaceuticals [8], Na-Alg was successfully crosslinked with glutaraldehyde (GA). In this chapter, a new method was adopted for preparing the Na-Alg microparticles. The water-soluble ‘nimesulide’ is a non-steroidal anti-inflammatory drug (NSAID) [9-11], which has a high solubility in most common solvents like water, methanol and liquid paraffin. This drug was loaded in the form of microparticles. Because nimesulide is highly soluble in methanol and water, it leads to a low % of drug loading. However, this problem can be circumvented by first preparing the microparticles and then loading them with the drug. The extent of crosslinking and % of loading can be monitored to produce the stable microparticles for CR applications.
X.3. Experimental

The materials used and the detailed experimental procedures have already been explained in Chapter II under section II.11.

X.4. Results and Discussion

Because of the difficulty in crosslinking the Na-Alg microspheres without precipitating it in alcohol, the Na-Alg microdroplets produced in oil/liquid paraffin phase could not be crosslinked by GA. But, the Na-Alg precipitated in methanol could be easily crosslinked with GA in an acidic media [12]. Following these observations, we have first precipitated the Na-Alg particles in methanol and these were subsequently hardened by crosslinking with GA. The GA concentrated in toluene was used to crosslink the Na-Alg so as to reduce the entry of GA molecules inside the microparticles. This favored the crosslinking only on the outer periphery of the particles. However, theoretically it is not possible to crosslink Na-Alg microparticles in the outer surface because GA will diffuse into the particles due to its smaller diameter even though it is highly soluble in toluene.

The encapsulation efficiency represents the % of encapsulated drug with respect to the total drug introduced into the polymer solution. The % content in nimesulide reflects the composition and rigidity of the microparticles produced because % nimesulide content mainly depends upon the space available within the microparticles. The extent of crosslinking of Na-Alg microparticles produced in methanol was monitored by controlling the time of exposure to GA. The particles thus produced were characterized by conducting swelling experiments in water and also by loading the particles with nimesulide. However, no previous studies are available for nimesulide encapsulation in Na-Alg microparticles, probably due to its leaching during formulation step and thereby, leading to low % loading.
The morphology of microspheres as examined by SEM (see Fig. X.1) indicated the smooth surfaces of the particles. However, the formation of dips was attributed to the rapid and massive solubilization of the drug at the beginning of preparation as well as during the drying stage.

The results of % loading of the drug and swelling of the Na-Alg matrix are presented in Table X.1.

<table>
<thead>
<tr>
<th>Time of exposure to GA (min)</th>
<th>% Loading of nimesulide (w/w) in microparticles produced by washing</th>
<th>Average diameter of particles (μm)</th>
<th>% Increase in diameter</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>without washing</td>
<td>dry swollen</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1.74</td>
<td>215</td>
<td>380</td>
</tr>
<tr>
<td>15</td>
<td>13.24</td>
<td>231</td>
<td>301</td>
</tr>
<tr>
<td>30</td>
<td>17.13</td>
<td>183</td>
<td>235</td>
</tr>
</tbody>
</table>

The % entrapment efficiency varied significantly depending upon the method adopted to load the drug. For instance, the highest efficiency was observed for microparticles loaded with nimesulide without washing (Method I) than when compared to the microparticles produced by washing (Method II). The % entrapment efficiency decreased with increasing the crosslinking in case of the drug-loaded microparticles prepared by Method I. This may due to the fact that the microparticles produced at higher crosslinking will swell to a lesser extent thereby, resulting in lower entrapment efficiencies.

In case of drug-loaded microparticles prepared by Method II, the efficiency increased with an increasing amount of crosslinking. However, the nimesulide-loaded microparticles prepared by Method II and produced at lower crosslinking
time (5 min) have shown the least nimesulide content (1.74 % w/w of dry mass of the particles). On the other hand, microparticles produced at 30 min of exposure time to GA have shown the maximum drug content (17.13 % w/w of dry mass of the particles). It may be noted that the particles produced at shorter time of crosslinking leached out higher amount of the drug during methanol washing, but the microparticles produced at higher crosslinking time are more rigid and exhibit reduced leaching of nimesulide from the Na-Alg matrix.

The encapsulation efficiency of the microparticles was further confirmed by studying swelling of the particles from a measurement of the diameter of the particles before and after swelling. The swelling results included in Table X.1 indicate that the microparticles produced at 5 min of exposure to GA exhibited maximum swelling when compared to those particles produced at 30 min of exposure time. The % increase in diameter of the microparticles decrease (i.e., 1.77, 1.30, and 1.28 μm) with an increase in crosslinking for those particles that were exposed to GA at 5, 15 and 30 min, respectively.

X.5. Conclusions

A novel method was adopted for the preparation of Na-Alg microparticles loaded with nimesulide. The morphology of microspheres as examined by SEM indicated smooth surfaces of the particles. The % entrapment efficiency varied significantly depending upon the method adopted to load the drug. The highest efficiency was observed for microparticles loaded with nimesulide without washing than when compared to those microparticles produced by washing.
X.6. References