Chapter - 5

Glutaraldehyde Crosslinked Chitosan Beads for Controlled Release of Diclofenac Sodium
5.1. INTRODUCTION

Newer controlled release drug delivery systems are being explored in response to changes in environmental conditions, e.g. temperature\textsuperscript{1-3}, pH\textsuperscript{4-6}, electric field\textsuperscript{7-11} and presence of certain chemicals\textsuperscript{12-14}. Many controlled release polymeric drug delivery devices have been developed using a variety of techniques\textsuperscript{15-21}. As most of the commonly used polymers in sustained drug delivery are synthetic materials, their biocompatibility and biodegradability are much more limited than those of natural polymers such as cellulose, chitin, chitosan and other derivatives. In various studies, attempts have been made to overcome these shortcomings by chemical and physical modifications of polymers. Several researchers in recent years have noted hydrogel structures, but crosslinked chitosan beads for a controlled release formulation is a novel approach reported to date\textsuperscript{22-28}.

Use of hydrophilic polymers in the development of CR formulations for the delivery of drugs by the oral route has proven to be advantageous over the conventional systems. Chitosan has been proven to be an ideal polymer not only in biomedical but also has various industrial applications. Chitosan is insoluble in water but soluble in acidic water. Chemical modification of chitosan and its applications have been reported\textsuperscript{29}. Various approaches have been reported over the last decade to develop new methodologies for site-specific drug release, including pH dependent release\textsuperscript{30}, time controlled release\textsuperscript{31} and microbial controlled\textsuperscript{32} releases.
The controlled release non-steroidal antiinflammatory drug (NSAID) formulations have been reported earlier to minimize the side effects. Diclofenac sodium (DS) is widely used in the treatment of chronic inflammatory diseases. Inflammation is defined as a complex vascular and local tissue reaction in higher animals by the presence of microorganisms or other irritants. Due to the rapid systemic clearance of this drug, repeated daily dosing is required. This warrants the use of sustained release formulations to improve the patient compliance. Earlier reports suggest that DS produces side effects such as ulceration, bleeding or perforation of intestinal wall. Since the drug is well absorbed in the colon, colon targeted delivery systems are particularly advisable, as they would avoid drug release in the stomach, thus eliminating local side effects. Colonic drug delivery following administration by the oral route is generally based on a technology, which allows a targeted release to the terminal ileum and proximal colon.

Work on transdermal membranes of DS was amongst the first reported. The membranes were made of ammonium acrylate polymer, glycerin diglycidyl ether and propylene glycol. The drug was found to be readily absorbed into the skin from these films without exhibiting side effects. To increase the bioavailability and decrease the gastric irritation, suppositories containing DS were prepared. These suppositories contained L-arginine hydrochloride, which contributed to the increased absorption of drug in the rectal mucosa. Ointments containing 1-1.5% DS were prepared. There are also reports of
diclofenac sodium eye lotions, spray formulations and gel preparations for topical application[^48-52].

In view of the side effects and short biological half-life, DS was developed as a controlled release formulation using chitosan. Factors like extent of crosslinking, % loading of drug and effect of temperature on crosslinking of beads were studied to optimize the formulation conditions.

According to the suspension cross-linking technique used for preparation of chitosan microspheres, different types of bifunctional agents (glutaraldehyde, terephthaloyl chloride, hexa methylene diisocyanate) can be used as the crosslinkers[^53-54]. Release of an active agent from the polymer matrix depends upon the extent of crosslinking[^55]. From the sorption and desorption experiments, the concentration dependent diffusion coefficient D, for water absorption as well as desorption were calculated[^56-57].

**Drug data[^58]**

Diclofenac sodium (DS) is an analgesic and antiinflammatory.

Chemical name : Sodium 2-[(2,6-dichlorophenyl)-amino] phenyl acetate

Molecular formula : C_{14}H_{10}NCl_{2}NaO_{2}

Molecular weight : 318.13

Color : Yellowish white.

Description : Crystalline powder; slightly hygroscopic.

Solubility : Soluble in *methanol* and *ethanol*; sparingly soluble in *water* and in glacial acetic acid; practically insoluble in *ether.*
Chemical structure:  

![Chemical Structure Image]

Storage: Stored in well-closed, light resistant containers.

Dose: Orally or by intramuscular injection, 25-75 mg.

5.2. EXPERIMENTAL

Materials

The gift sample of DS was supplied by Sun Pharma, Baroda and used as received. Chitosan was purchased from Aldrich Chemical Company, USA. Analytical grade samples of glutaraldehyde (GA) and acetic acid were purchased from s.d.Fine-Chem Ltd. Mumbai, India and used as received.

Methods

5.2.1. Preparation of beads

Chitosan (2 g) was dissolved in 1% acetic acid solution and stirred for 3 hours. Varying quantities (30, 40, 50 and 60% w/w of dry weight of polymer) of diclofenac sodium (an analgesic drug) was added to the above solution and mixed homogeneously. The mixture was added dropwise into methanol–HCl solution (20:1), containing 1% glutaraldehyde (GA), a crosslinking agent (Scheme III).
Scheme III

\[ \text{MeOH} : \text{HCl} \quad 25^\circ \text{C/40}^\circ \text{C} \quad 20:1 \]

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Finally, the chemically reacted crosslinked beads were removed by filtration from the mixture, washed with water and allowed to dry in an oven\textsuperscript{59}.

The bead formation was optimized by carrying out the experiments at two different temperatures (25°C and 40°C) and different exposure time to the crosslinking agent (5 and 10 minutes). Experimental conditions such as distance between syringe and water level, and number of drops per minute were maintained.

5.2.2. Measurement of bead size

Five samples of completely dried beads were randomly selected and their sizes were measured using a micrometer screw gauge (Sargent Co., USA) within an accuracy of ±0.01mm.

5.2.3. Swelling study

Five beads crosslinked with glutaraldehyde, with a known weight were placed on a watch glass containing distilled water. The swollen beads were removed from the watch glass, blotted with the filter paper to remove any adsorbed water on the surface and weighed at regular intervals of time (every 30 minutes) to calculate the percentage water uptake\textsuperscript{60}. The results are shown in Fig. 5.7.
5.2.4. Drying study

After formation of the beads, they were allowed to dry in an oven maintained at 40°C. Initial mass of the beads should be nearly equal for easy comparison. The beads were weighed at an hourly interval until, a constant weight was achieved (Fig. 5.8)\textsuperscript{61}.

5.2.5. Drug content

Beads were evaluated for the drug content and this was done by incubating a known mass of beads with 5 ml of water. The swollen beads were crushed in mortar with a pestle and the solution thus formed was sonicated for 2 minutes. Water was evaporated to form a thick paste, to which about 10 ml of methanol was added to extract the entire drug. The precipitated polymer was separated from methanol by centrifugation. Then the absorbance of methanol, containing diclofenac sodium was taken at 284 nm\textsuperscript{62} using UV spectrophotometer\textsuperscript{63}. The results are given in Table 5.6.

5.2.6. \textit{In vitro} dissolution study

Dissolution of beads was carried out using the dissolution tester equipped with six pedals. The dissolution rates were measured at 37°C under 100 rpm paddle speed. A 900 ml of 0.1N HCl was used during the first 3 hours and then the medium was drained off and replaced with phosphate buffer solution (pH 7.4). A 10 ml of aliquot was taken from the vessel at an interval of every 30 minutes and replaced with an equal volume of corresponding dissolution medium. If necessary, the samples were diluted before the assay. These samples
were analyzed using UV spectrophotometer at 284 nm and concentration of DS was calculated using the calibration curves constructed from the reference standards. The results are shown in Fig. 5.9.

5.2.7. Stability study

Various beads were placed in screw capped glass containers and stored under ambient humidity conditions at different temperatures such as 60°C, 37°C, room temperature and 5°C for a period of 3 months. The samples were analysed for the drug content at regular intervals of 2 weeks and the results obtained are shown in Fig. 5.11.

5.3. RESULTS AND DISCUSSION

A simple and inexpensive method was adopted for the preparation of chitosan beads for the controlled release of DS. Beads were prepared by crosslinking the polymer with GA. Free amino groups of chitosan were reacted with GA to form a crosslinked polymeric matrix, in which DS was embedded to provide a sustained release action. Elemental analysis, melting point and percentage yield of GA crosslinked chitosan is given in Table 5.1.
Table 5.1. Elemental analysis, melting point and percentage yield of GA crosslinked chitosan

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>R</th>
<th>Nature</th>
<th>m.p. (°C)</th>
<th>Yield (%)</th>
<th>Molecular formula</th>
<th>Elemental analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>-CH₂CH₂CH₂CH=N-Chitosan</td>
<td>Yellow flakes</td>
<td>350 &gt;</td>
<td>67</td>
<td>C₁₇H₂₆O₈N₂</td>
<td>C  (52.11) (52.84)  H 6.26 (6.73)  N 7.01 (7.25)</td>
</tr>
</tbody>
</table>
5.3.1. Spectral studies

FTIR spectral data were used to confirm the chemical intactness of drug in the polymeric membranes. FTIR spectra of pure DS, GA crosslinked chitosan and DS loaded GA crosslinked chitosan beads were compared (Fig. 5.1).

The results of FTIR spectral data are presented in Table 5.2. Amino groups of chitosan were converted into imine group (C=N), when treated with GA. A sharp peak observed at 1640 cm\(^{-1}\) was due to the presence of imine group (C=N). FTIR spectra of DS showed a band at 3079 cm\(^{-1}\) due to N-H stretching. The peaks observed at 1579 cm\(^{-1}\) and 1455 cm\(^{-1}\) were due to C=C aromatic stretching. A sharp peak observed at 707 cm\(^{-1}\) was due to –Cl group attached to the aromatic moiety.

When the drug was incorporated into GA crosslinked chitosan, along with all the characteristic peaks of the crosslinked chitosan, additional bands have appeared due to the presence of diclofenac sodium. IR spectra of DS loaded crosslinked beads showed principal peaks at 3036 cm\(^{-1}\) due to N-H stretching and at 690 cm\(^{-1}\) due to C-Cl. The peak at 1449 cm\(^{-1}\) was due to C=C aromatic stretching. No extra peaks were seen, indicating there was no interaction of the drug either with the polymer or the crosslinking agent.
Table 5.2. FTIR spectral data of GA crosslinked chitosan

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Name of the compound</th>
<th>C=N</th>
<th>N-H</th>
<th>O-H</th>
<th>C-Cl</th>
<th>C=C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Diclofenac sodium (DS)</td>
<td>--</td>
<td>3079</td>
<td>--</td>
<td>707</td>
<td>1455</td>
</tr>
<tr>
<td>2</td>
<td>GA crosslinked chitosan</td>
<td>1640</td>
<td>--</td>
<td>3412</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>3</td>
<td>DS loaded GA crosslinked chitosan</td>
<td>1640</td>
<td>3036</td>
<td>--</td>
<td>690</td>
<td>1449</td>
</tr>
</tbody>
</table>
Fig. 5.1. FTIR spectra of (1) DS, (2) GA crosslinked chitosan and (3) DS loaded GA crosslinked chitosan
\textbf{\textsuperscript{13}C NMR Spectral studies}

The crosslinking of chitosan with GA was further confirmed by \textsuperscript{13}C NMR spectroscopy (Fig. 5.2). The peaks at δ values 103.3, 53, 74.2, 84.6 and 80.9 were due to C\textsubscript{1}, C\textsubscript{2}, C\textsubscript{3}, C\textsubscript{4} and C\textsubscript{5} carbons of chitosan respectively. The signal due to C\textsubscript{6}- (CH\textsubscript{2}OH) carbon appeared at 55.6. The peaks observed at 28.8, 23.1 and 28.8 were attributed to C\textsubscript{8}, C\textsubscript{9} and C\textsubscript{10} carbons of the crosslinking agent.

The presence of a peak at 162.1 was due to C\textsubscript{7} and C\textsubscript{11} carbons of imine (C=N) group, which confirmed the crosslinking of chitosan with GA (Table 5.3).

\begin{table}[h]
\centering
\caption{\textsuperscript{13}C NMR Spectral data (Chemical shift, in δ ppm)}
\begin{tabular}{|c|c|c|c|c|c|c|c|c|c|}
\hline
C\textsubscript{1} & C\textsubscript{2} & C\textsubscript{3} & C\textsubscript{4} & C\textsubscript{5} & C\textsubscript{6} & C\textsubscript{7} & C\textsubscript{8} & C\textsubscript{9} & C\textsubscript{10} & C\textsubscript{11} \\
\hline
103.3 & 53.0 & 74.2 & 84.6 & 80.9 & 55.6 & 162.1 & 28.8 & 23.1 & 28.8 & 162.1 \\
\hline
\end{tabular}
\end{table}
Fig. 5.2. \(^{13}\)C NMR Spectrum
DSC studies

The DSC thermograms of pure diclofenac sodium, GA crosslinked chitosan beads and DS loaded crosslinked beads were studied (Fig. 5.3). The polymorphism of drug and transition temperature of the polymer were studied before and after drug loading.

After reacting with GA, the endothermic peak of chitosan has shifted from 50°C to 68.7°C, indicating the crosslinking of polymer with an aldehyde. Diclofenac sodium showed a sharp peak at 287.5°C due to its melting point (Table 5.4). This did not appear in the DSC thermogram of DS loaded GA crosslinked chitosan beads. The enthalpy values and the endothermic peaks responsible for the drug clearly indicated the uniform distribution of drug and its intactness in the formulation.

Table 5.4. Thermal analysis data

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Name of the compound</th>
<th>DSC peaks (°C)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Endothermic</td>
<td>Exothermic</td>
</tr>
<tr>
<td>1</td>
<td>DS</td>
<td>287</td>
<td>291</td>
</tr>
<tr>
<td>2</td>
<td>GA crosslinked chitosan</td>
<td>68.7</td>
<td>310</td>
</tr>
<tr>
<td>3</td>
<td>DS loaded GA crosslinked chitosan</td>
<td>65</td>
<td>No heat changes were observed at the temperature of m.p. of DS</td>
</tr>
</tbody>
</table>
Fig. 5.3. DSC thermograms of (1) DS, (2) GA crosslinked chitosan and (3) DS loaded GA crosslinked chitosan
TGA studies

Effect of crosslinking and drug loading on thermal decomposition of polymer was studied by thermogravimetry. TGA experiments were carried out on pure DS, GA crosslinked chitosan and DS loaded GA crosslinked chitosan beads and the results are presented in Table 5.5.

TGA curves and the corresponding data indicate that the compounds decompose in two steps (Fig. 5.4). GA crosslinked beads showed a lesser weight loss (55%) as compared to chitosan (60%) at the same temperature indicating, the crosslinking decreases the rate of degradation and increases the stability. The first step involves a small weight loss indicating a loss of few fragments attached at the periphery. The destruction of chitosan moiety occurs in the second step. Diclofenac sodium undergoes decomposition at 280°C and above 300°C, only 1% of char residue remains.

Drug loaded beads showed decomposition at the same temperature as that of pure drug. Since the melting point of drug was not altered, indicates the absence of any chemical interaction of DS with the polymer or the crosslinking agent.
Table 5.5. TGA data of GA crosslinked chitosan

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Name of the compound</th>
<th>Decomposition temperature</th>
<th>Mass loss</th>
<th>Probable mode of decomposition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>% Found</td>
<td>% Calcd.</td>
</tr>
<tr>
<td>1</td>
<td>DS</td>
<td>63-205</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>205-329</td>
<td>99.48</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>GA crosslinked chitosan</td>
<td>38-218</td>
<td>7.12</td>
<td>8.80</td>
</tr>
<tr>
<td></td>
<td></td>
<td>218-465</td>
<td>55.17</td>
<td>55.59</td>
</tr>
<tr>
<td>3</td>
<td>DS loaded GA crosslinked chitosan</td>
<td>45-150</td>
<td>10.52</td>
<td>12.47</td>
</tr>
<tr>
<td></td>
<td></td>
<td>150-465</td>
<td>56.4</td>
<td>64.58</td>
</tr>
</tbody>
</table>
Fig. 5.4. TGA curves of (-----) DS, (-----) GA crosslinked chitosan and (-------) DS loaded GA crosslinked chitosan
Characterization of beads

5.3.2. Size of beads

Microscopic observations revealed that the GA crosslinked chitosan beads were in the size range of 500-700 \( \mu \text{m} \) (Fig. 5.5). The beads were further evaluated by SEM, to investigate the morphology of the beads. They were found to be spherical in shape with smooth surface. A SEM view of sample is shown in Fig. 5.6. It has been observed that the particle size did not vary significantly either by increasing the exposure time to the cross-linking agent or by increasing the amount of the drug.

5.3.3. Swelling study

Chitosan is a hydrophilic polymer. Transport of water through the polymer depends upon the rigidity of the polymer and extent of its cross-linking ability. The results of water uptake by the beads exposed to GA, for different time intervals and different temperatures are displayed in Fig. 5.7.

Results of % water uptake indicate that all the beads absorb maximum amount of water during the first hour. The beads prepared by exposing to the crosslinking agent only for 5 minutes, absorbed more amount of water than those prepared by extended exposure time (10 minutes). Water uptake was also dependent upon the temperature. Beads formed at higher temperature (40°C) absorbed less amount of water than those formed at lower temperature (25°C). The increased porosity and decreased crystallinity of the polymer enhance the
Fig. 5.5. Glutaraldehyde Crosslinked Chitosan Beads

Fig. 5.6. SEM View of Glutaraldehyde Crosslinked Chitosan Bead
Fig. 5.7. Rate of water uptake by beads prepared at different temperatures and different exposure time to crosslinking agent

- (■) for 5 min at 25°C
- (▲) for 5 min at 40°C
- (♦) for 10 min at 25°C
- (♦) for 10 min at 40°C
water uptake and swelling ability. Crosslinking occurs fast at higher temperature and highly crosslinked beads absorb very small amount of water.

The drug is dispersed in almost spherical shaped beads. Therefore, it is possible to model the diffusion process and study various factors like effect of extent of crosslinking and % drug loading. The diffusion process involves immersion of polymeric beads into the medium of interest and thereby provoking the process of absorption of the liquid by the polymer. Mathematical models have been built to describe the process of absorption and desorption\textsuperscript{60,67}. The diffusion coefficient (D) for water absorption can be calculated using Eqn. (5.1)

\[ D = \left( \frac{r \theta}{6M_\infty} \right)^2 \pi \]  

(5.1)

where \( \theta \) is slope of the linear portion of the plot of \( M_t/M_\infty \) Vs \( t_t \), \( r \) is radius of the beads and \( M_\infty \) is the maximum value for sorption.

The diffusion coefficient (D) values show dependence on the extent of crosslinking in terms of time of exposure and temperature of methanol, but not significantly on the pH of methanol. The results are given in Table 5.6.

5.3.4. Drying study

In order to optimize the drying conditions, some of the beads with different process variables were selected with approximately equal initial mass.
Fig. 5.8. Rate of drying of beads prepared at different temperatures and different exposure time to crosslinking agent

(■) for 5 min at 25°C  (•) for 10 min at 25°C
(▲) for 5 min at 40°C  (♦) for 10 min at 40°C
The results of drying (Fig. 5.8) indicated that both the time of exposure to GA and the temperature of methanol influenced the drying rate of the beads.

Beads exposed to GA for longer time required higher drying time than those exposed for short period of time. On the other hand, for the beads prepared at higher temperature, time of drying was more than those beads prepared at lower temperature. The beads exposed to GA only for 5 minutes and at 25°C were rapidly dried (within 21 hours) as compared to the beads exposed to the crosslinking agent for 10 min at 40°C (25 hours). This may be due to an increased rigidity of the polymer by increased exposure to the crosslinking agent and at high temperature.

For calculating diffusion coefficient (D) from desorption experiments, the slope $\theta$ was calculated from linear plot of

$$\ln 1 - \frac{M_t}{M_\infty} \text{ vs time } t.$$

The results are presented in Table 5.6. It is observed that the D values for sorption are higher than those observed for desorption by several orders of magnitude. This is attributed to the slow drying of beads. However the D values for desorption did not show any systematic dependence on the type of matrix. In majority of cases, the lower D values are observed for the matrix produced at high temperature with longer exposure time than for those produced at low temperature with lesser exposure time.
5.3.5. Drug content study

To optimize the parameters affecting the formation of beads, experiments were carried out under different conditions viz., time of exposure to cross-linking agent, temperature of methanol, pH of methanol and % loading of drug. These results are compiled in Table 5.6.

It has been observed that the content of drug decreased drastically with a decrease in the amount of HCl added to methanol. Beads prepared in 1% HCl, at 25°C and exposed to the cross-linking agent for 5 minutes, showed highest entrapment efficiency (72.11%). The lowest drug content (28.17%) was observed for beads prepared in 0.1% HCl, at 40°C and exposed to the cross-linking agent for 5 minutes. Diclofenac sodium, being a salt of weak acid, is insoluble in acidic media and hence, an increase in drug content was observed with an increase in % HCl content in methanol.

Drug content is the amount of drug entrapped within the matrix with respect to the total drug introduced into the polymer solution. The drug content in the beads reflects the composition and rigidity of the beads, because % drug content depends upon the space available within the matrix.

5.3.6. In vitro dissolution studies

Release of DS from the beads can be influenced by a number of physico-chemical parameters including those related to the pH, temperature, rate of stirring and change in the characteristics of the CR devices (beads). The effect of time of exposure to the crosslinking agent and temperature of
Table 5.6. Results of % Drug content of 50% DS loaded beads

<table>
<thead>
<tr>
<th>Time of exposure to GA (min)</th>
<th>Temperature of methanol (°C)</th>
<th>% HCl (v/v) in methanol</th>
<th>Drug content</th>
<th>(D_{\text{Sorption}}) (cm(^2)/s)</th>
<th>(D_{\text{Desorption}} \times 10^{-8})</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>25</td>
<td>0.1</td>
<td>43.07 ± 0.14</td>
<td>5.73 x 10(^{-7})</td>
<td>5.11</td>
</tr>
<tr>
<td>5</td>
<td>25</td>
<td>0.5</td>
<td>48.58 ± 0.30</td>
<td>5.29 x 10(^{-7})</td>
<td>4.49</td>
</tr>
<tr>
<td>5</td>
<td>40</td>
<td>0.1</td>
<td>28.17 ± 0.41</td>
<td>4.78 x 10(^{-7})</td>
<td>3.39</td>
</tr>
<tr>
<td>5</td>
<td>40</td>
<td>0.5</td>
<td>37.51 ± 0.51</td>
<td>4.34 x 10(^{-7})</td>
<td>3.10</td>
</tr>
<tr>
<td>5</td>
<td>25</td>
<td>1.0</td>
<td>72.11 ± 0.24</td>
<td>5.81 x 10(^{-7})</td>
<td>5.04</td>
</tr>
<tr>
<td>10</td>
<td>25</td>
<td>1.0</td>
<td>70.32 ± 0.54</td>
<td>5.02 x 10(^{-7})</td>
<td>4.8</td>
</tr>
<tr>
<td>5</td>
<td>40</td>
<td>1.0</td>
<td>68.14 ± 0.34</td>
<td>4.19 x 10(^{-7})</td>
<td>3.78</td>
</tr>
<tr>
<td>10</td>
<td>40</td>
<td>1.0</td>
<td>57.27 ± 0.19</td>
<td>7.86 x 10(^{-8})</td>
<td>2.02</td>
</tr>
</tbody>
</table>
methanol ultimately affects the degree of crosslinking of chitosan. Kinetics of DS release is depicted in Fig. 5.9.

To investigate the effect of crosslinking on the release kinetics, the beads exposed to GA for different time intervals (5 and 10 minutes), at different temperatures (25°C and 40°C) and loaded with 50% DS were selected. The time selected was between 5 and 10 minutes because less than 5 minutes, the beads formed were not hardened, whereas more than 10 minutes, the % drug content was very less due to the leaching of drug by slow solubalisation in methanol.

From Fig. 5.9, it may be inferred that the effect of temperature was more prominent than the effect of exposure time for the drug release. From the graph, it is evident that the rate of release of drug is low for the beads formed at higher temperature compared to those, formed at lower temperature under the same exposure time to the crosslinking agent. An increase in the degree of crosslinking resulted in a significant decrease of drug release from the beads. By crosslinking the polymer, the overall matrix becomes denser so that the rate of diffusion of the drug decreases.

Release of the drug from the polymer matrix is a function of the extent of crosslinking. The effect of % loading of drug on drug release is shown by Fig. 5.10. Release rate increased with higher drug loading. The 60% DS loaded beads showed nearly 100% release (250 minutes), whereas 30% DS loaded beads showed only 90% release (300 minutes).
Fig. 5.9. Amount of drug released from beads prepared at different temperatures and different exposure time to crosslinking agent

- (●) for 5 min at 25°C
- (▲) for 5 min at 40°C
- (●) for 10 min at 25°C
- (★) for 10 min at 40°C
Fig. 5.10. Amount of drug released from beads loaded with different concentrations of DS

(■) 60 %,  (♦) 50 %,  (▲) 40 %, and (●) 30%
5.3.7. Stability studies

The beads were observed for any change in color or appearance and drug content during storage. The effect of temperature on stability of beads is shown by Fig. 5.11. Beads were stable at 5°, 27°, 37° as well as 60°C.

Fig. 5.11. Stability studies of DS loaded GA crosslinked chitosan beads at different temperatures

(■) 5°C, (●) 27°C, (▲) 37°C, and (●) 60°C
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