EVALUATION OF FUROSEMIDE-LOADED ALGINATE MICROSPHERES PREPARED BY IONOTROPIC EXTERNAL GELATION TECHNIQUE

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Abstract: Alginate microspheres containing furosemide were prepared by the ionotropic external gelation technique using Ca\(^{2+}\), Al\(^{3+}\) and Ba\(^{2+}\) ions. The incorporation efficiency of the prepared microspheres ranged between 65 % and 93 %. The effect of sodium alginate concentration, cross-linking ions and drying conditions was evaluated with respect to entrapment efficiency, particle size, surface characteristics and in vitro release behavior. Infrared spectroscopic study confirmed the drug-polymer compatibility. Differential scanning calorimetric analysis revealed that the drug was molecularly dispersed in the alginate microsphere matrices. Scanning electron microscopic study of microspheres showed the rough surface due to higher concentration of drug molecules dispersed at molecular level in the alginate matrices. The mean particle size and entrapment efficiency were found to be varied by changing various formulation parameters. The in vitro release profile could be altered significantly by changing various formulation parameters to give a sustained release of drug from the microspheres. The kinetic modeling of the release data indicate that furosemide release from the alginate microspheres follow anomalous transport mechanism after an initial lag period when the drug release mechanism was found to be Fickian diffusion controlled.

Keywords: Sodium alginate, microspheres, furosemide, external gelation technique, Fickian diffusion

Alginates, which are naturally occurring substances, found in brown algae have received much attention as a vehicle for controlled drug delivery (1-4). Alginates can be considered as block polymers which mainly consist of mannuronic acid (M), guluronic acid (G) and mannuronic-guluronic (MG) blocks. Dropwise addition of aqueous alginate solution to the aqueous solution containing calcium ions and/or other di- and polyvalent cations cause spherical gel formation termed as “alginate bead”. Alginate is known to be nontoxic when taken orally and also has a protective effect on the mucous membranes of the upper gastrointestinal tract (1). The dried alginate beads have the property of reswelling and thus can act as controlled release system. This property is susceptible to pH, which protects the acid-sensitive drug from gastric juice (5).

Furosemide, a potent loop diuretic, is used in the treatment of edema of hepatic, cardiac, pulmonary and renal failures and in chronic hypertension (6). The dose related adverse effects have been observed and the treatment with conventional tablets produced short period of maximum diuresis, which is inconvenient to the patients. But the treatment with sustained release tablets produces the same diuretic effect as produced by conventional tablets eliminating brief and intense diuresis. Thus the use of sustained release tablets are well tolerated due to the avoidance of discomfort associated with the short period of maximum diuresis (7). However, such single unit sustained release tablets could be disastrous if they fail to release the drug at the desired rate and in the desired amount, or if they release the entire amount of drug so as to cause dose dumping. The multiunit microparticulate oral drug delivery systems can be distributed widely throughout the gastrointestinal tract providing a possibility of achieving a longer lasting and reliable release of drug at the desired rate. Unwanted intestinal retention of the polymeric material and local irritation which may occur with non-disintegrating polymeric matrix tablets can also be avoided (8).

As previously reported, the furosemide microspheres prepared by emulsion-solvent evaporation method utilize a larger volume of organic solvents (9), which are costly and hazardous because of the possibility of explosion, toxicity and air pollution. The water-based ionotropic external gelation tech-
nique may provide characteristic advantages over conventional microsphere preparation methods. In the present study, the above procedure was applied in order to prepare furosemide-loaded alginate microspheres. The effects of factors, such as sodium alginate concentration, cross-linking agents, drying conditions, on morphology of microspheres and drug release from them were studied. Drug-polymer interactions in the solid state were examined by infrared spectrophotometry (IR) and differential scanning calorimetric analysis (DSC) and the surface characteristics were evaluated by scanning electron microscopy (SEM).

MATERIALS AND METHODS

Materials

Furosemide was received as a gift sample from Cipla Ltd., Mumbai. Sodium alginate was procured from Loba Chemie, Mumbai. Calcium chloride (fused), barium chloride and aluminium sulfate were purchased from Ranbaxy Laboratories Ltd., New Delhi. All other chemicals and solvents were of analytical grade satisfying pharmacopoeial specifications.

Methods

Formulation of alginate microspheres

The microspheres were prepared by ionotropic external gelation technique using the formulations as shown in Table 1. The alginate solutions comprising 2.5 % to 4 % w/v sodium alginate were prepared by initially dissolving the polymer in deionized water using gentle heat and magnetic stirring. On complete solution, an accurately weighted quantity of furosemide was added to each solution to afford homogeneous dispersions. The dispersions were sonicated for 30 min to remove any air bubbles that may have been formed during the stirring process. The sodium alginate-drug dispersions (25 mL) were added dropwise via a 20-gauge hypodermic needle fitted with a 10 mL syringe into 50 mL of 5 % w/v solution of gelling agents [CaCl₂, Al₂(SO₄)₃ and BaCl₂ for Ca²⁺, Al³⁺ and Ba²⁺, respectively], being stirred at 200 rpm for 10 min. The droplets from the dispersions instantaneously gelled into discrete furosemide-alginate matrices upon contact with the solution of gelling agents. The formed alginate microspheres were further stirred in the solution of gelling agents for an additional 1 h. On expiration of this period the solutions of gelling agents were decanted and the microspheres were washed with 3 × 50 mL volumes of deionized water. The microspheres were thereafter dried at 80°C for 2 h in a hot-air oven. Similarly, air-dried alginate microspheres (formulation code C1, E1 and F1) were prepared in the same way as the formulations C, E and F, respectively, by drying in air at room temperature.

Morphology and size distribution

The shape and surface morphology of the alginate microspheres were investigated using JEOL, JSM-6360, scanning electron microscope at 15 kV. Prior to examination the samples were gold coated under vacuum (Fine coat, Ion sputter, JFC-1100) to render them electrically conductive. The samples included various alginate microspheres prepared using different gelling agents before release study. The alginate microspheres were not subjected to SEM studies after release study because they converted to gel type of matrix when dissolution was overed.

Size and size distribution of the alginate microspheres were measured by sieve analysis. The alginate microspheres were separated into different size fractions (% weight fraction) by sieving for 5 min using standard sieves having nominal mesh apertures of 1.4 mm, 1.2 mm, 1.0 mm, 0.85 mm and 0.71 mm (sieve no. 12, 14, 16, 18 and 22, respectively). The particle size distributions of the microspheres were determined and the mean particle size of microspheres were calculated using the following formula (10):

\[
\text{Mean particle size} = \frac{\sum (\text{mean particle size of the fraction} \times \text{weight fraction})}{\sum \text{weight fraction}}.
\]

Determination of drug incorporation efficiency

Thirty mg of drug-loaded alginate microspheres from each batch was placed in 100 mL conical flask containing 50 mL of phosphate buffer of pH 7.4. The microspheres were magnetically stirred to promote swelling and break up of the cross-linked structure. This afforded liberation and subsequent dissolution of furosemide. The solution was filtered through a 0.45 mm membrane filter. Then the drug was quantified spectrophotometrically at 276.5 nm after appropriate dilution with phosphate buffer of pH 7.4. The incorporation efficiency was determined by the following empirical relationship:

\[
\text{Drug incorporation efficiency (\%)} = \left(\frac{\text{AQ}}{\text{TQ}}\right) \times 100
\]

where AQ is the actual quantity of drug present in the microspheres and TQ is the 100 % theoretical quantity of drug present in the microspheres (i.e. actual initial loading dose).

Infrared spectroscopy (IR)

The drug-polymer interactions were studied by infrared spectroscopy. The IR spectra were recorded
between 500 and 4000 cm⁻¹ for pure furosemide, blank alginate microspheres and furosemide-loaded alginate microspheres in KBr pellets using Perkin Elmer-883 IR spectrophotometer.

Differential scanning calorimetry (DSC)

The DSC thermograms were recorded on a Universal V 2.5 H differential scanning calorimeter. The DSC studies on the samples were performed by heating samples at a heating rate of 10°C/min over a temperature range of 50-300°C in closed aluminium pans. The samples included pure furosemide and furosemide-loaded alginate microspheres.

In vitro dissolution testing

The dissolution studies were performed in a fully calibrated six station dissolution test apparatus corrected for sampling effect using the following formula (11):

\[ C_n = C_{n-1} \frac{V_t}{V_t - V_s} \left( \frac{C_{n-1}}{C_{n-1}} \right) \]

where, \( C_n \) is the corrected concentration of the \( n \)th sample, \( C_{n-1} \) is the measured concentration of furosemide in the \( n \)th sample, \( C_{n-1} \) is the corrected concentration of furosemide in the \((n-1)\) sample, \( V_t \) is the total volume of the dissolution medium and \( V_s \) is the volume of the sample withdrawn.

Kinetic modeling

In order to investigate the release mechanism, the release data (≤ 60 %) were fitted to the following power law expression (12):

\[ M_t / M_\infty = K t^n \]  

Table 1. Formulation of alginate microspheres.

<table>
<thead>
<tr>
<th>F.N. Code</th>
<th>Furosemide (% w/v)</th>
<th>Sodium alginate (% w/v)</th>
<th>Gelling agent (5% w/v)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>2.5</td>
<td>2.5</td>
<td>CaCl₂</td>
</tr>
<tr>
<td>B</td>
<td>2.5</td>
<td>3.0</td>
<td>CaCl₂</td>
</tr>
<tr>
<td>C</td>
<td>2.5</td>
<td>3.5</td>
<td>CaCl₂</td>
</tr>
<tr>
<td>D</td>
<td>2.5</td>
<td>4.0</td>
<td>CaCl₂</td>
</tr>
<tr>
<td>E</td>
<td>2.5</td>
<td>3.5</td>
<td>Al₂(SO₄)₃</td>
</tr>
<tr>
<td>F</td>
<td>2.5</td>
<td>3.5</td>
<td>BaCl₂</td>
</tr>
</tbody>
</table>

Table 2. Interpretation of drug release mechanisms.

<table>
<thead>
<tr>
<th>Release exponent (n)</th>
<th>Drug release mechanism</th>
<th>Rate as a function of time</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>Fickian diffusion</td>
<td>( t^{-0.5} )</td>
</tr>
<tr>
<td>0.5 &lt; n &lt; 1.0</td>
<td>Anomalous transport</td>
<td>( t^{n-1} )</td>
</tr>
<tr>
<td>1.0</td>
<td>Case-II transport</td>
<td>Zero order release</td>
</tr>
<tr>
<td>&gt; 1.0</td>
<td>Super case-II transport</td>
<td>( t^{n+} )</td>
</tr>
</tbody>
</table>

(37 ± 0.5°C, 50 rpm) using the USP rotating basket method in phosphate buffer media (pH 7.4, 500 mL). A quantity of alginate beads equivalent to 100 mg furosemide for each formulation was employed in all dissolution studies. The samples of 5 mL each were withdrawn at predetermined time intervals and replenished immediately with the same volume of fresh prewarmed phosphate buffer maintaining sink condition throughout the experiment. The aliquots, following suitable dilution, were analyzed spectrophotometrically at 276.5 nm. The concentrations of furosemide in the test samples were calculated using a regression equation (Absorbance = 0.007 + 0.0709 × concentration, \( R^2 = 0.999 \)) of the calibration curve in phosphate buffer of pH 7.4 and corrected for sampling effect using the following formula (11):

\[ C_n = C_{n-1} \frac{V_t}{V_t - V_s} \left( \frac{C_{n-1}}{C_{n-1}} \right) \]

where, \( C_n \) is the corrected concentration of the \( n \)th sample, \( C_{n-1} \) is the measured concentration of furosemide in the \( n \)th sample, \( C_{n-1} \) is the corrected concentration of furosemide in the \((n-1)\) sample, \( V_t \) is the total volume of the dissolution medium and \( V_s \) is the volume of the sample withdrawn.

Kinetic modeling

In order to investigate the release mechanism, the release data (≤ 60 %) were fitted to the following power law expression (12):

\[ M_t / M_\infty = K t^n \]  

Table 3. Incorporation efficiency of furosemide-loaded alginate microspheres.

<table>
<thead>
<tr>
<th>F.N. Code</th>
<th>Entrapment capacity (% w/w) (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>65.18 ± 5.4</td>
</tr>
<tr>
<td>B</td>
<td>66.10 ± 2.26</td>
</tr>
<tr>
<td>C</td>
<td>72.01 ± 0.28</td>
</tr>
<tr>
<td>D</td>
<td>71.25 ± 1.93</td>
</tr>
<tr>
<td>E</td>
<td>91.00 ± 1.00</td>
</tr>
<tr>
<td>F</td>
<td>91.78 ± 0.233</td>
</tr>
<tr>
<td>Cl</td>
<td>74.25 ± 0.84</td>
</tr>
<tr>
<td>El</td>
<td>91.63 ± 0.021</td>
</tr>
<tr>
<td>Fl</td>
<td>93.00 ± 1.41</td>
</tr>
</tbody>
</table>

\( n = 3 \)
where $M_t$ and $M_\infty$ are the amounts of drug released at time $t$ and the overall amount released, respectively, $K$ is the release rate constant and $n$ is the release exponent indicative of release mechanism. The release data were further analyzed using the modified form of the power law expression (13) to accommodate the lag time ($t_L$) in the beginning of the drug release from the alginate beads:

$$M_t / M_\infty = K(t - t_L)^n \quad (2)$$

Fitness of the data into various kinetic models was assessed by determining the correlation coefficient. The value of $n$ was calculated from the slope of the plot of $\log (M_t/M_\infty)$ vs. $\log (t)$ and $\log (M_t/M_\infty)$ vs. $\log (t-t_L)$ for interpretation of release mechanism using Table 2 (14).

Figure 1. SEM of furosemide-loaded alginate microspheres: (a) calcium alginate microsphere, (b) aluminum alginate microsphere and (c) barium alginate microsphere.
Figure 2. Particle size distribution.

Figure 3. Effect of sodium alginate concentration on release characteristics of furosemide in phosphate buffer pH 7.4. Bars indicate ± SD (n = 3).
RESULTS AND DISCUSSIONS

Morphology and size distribution

Morphology of the various formulations of alginate microspheres prepared was found to be discrete and spherical in shape. The SEM photomicrographs of the dried alginate microspheres are shown in Figure 1. The surface of the alginate microspheres was rough due to higher concentration of drug uniformly dispersed at the molecular level in the alginate matrices. The mean particle size of the various formulations of alginate microspheres were between 0.726 ± 0.007 and 1.2 ± 0.008 mm. It was found that the particle size distribution of each formulation was within a narrow range but the mean particle size was different among the formulations (Figure 2). The results indicated the proportional increase in the mean particle size of the microspheres with increasing amount of sodium alginate in the formulations A, B, C and D. This could be attributed to an increase in the relative viscosity at higher concentration of sodium alginate and formation of large droplets during addition of the polymer solution to the gelling agents. Air-dried microspheres were of a larger size than those oven-dried due to incomplete dehydration as a result of air-drying process. The results also indicated no significant variation in particle size of the microspheres prepared using different gelling agents.

Incorporation efficiency of microspheres

The incorporation efficiency increased progressively with increasing sodium alginate concentration (Table 3). An increase in the alginate concentration resulted in the formation of larger microspheres entrapping greater amounts of the drug. This may be attributed to the greater availability of active calcium-binding sites in the polymeric chains and, consequently, the greater degree of cross-linking as the quantity of sodium alginate increased (15). The incorporation efficiencies were generally higher for the formulations cross-linked with Al³⁺ and Ba²⁺ as compared to the beads cross-linked with Ca²⁺. The results tabulated in Table 3 indicate that the incorporation efficiencies were more than 90 % for both oven-dried and air-dried alginate beads cross-linked with Al³⁺ and Ba²⁺. This may be attributed to the formation of nonporous alginate beads due to an increase in the apparent cross-linking density in presence of Al³⁺ and Ba²⁺ which prevent the diffusion of the drug out of the beads at the time of curing. The low incorporation efficiency of alginate beads cross-linked with Ca²⁺ could be attributed to the formation of porous beads ensuring the diffusion of the drug out of the beads at the time of curing.

In vitro dissolution

To study the effect of sodium alginate concentration on furosemide release, the sodium alginate

![Figure 4. Effect of various cross linking agents at 5 % w/v level on release characteristics of furosemide from alginate beads in phosphate buffer pH 7.4. Bars indicate ± SD (n = 3).](image)
was used at four different concentrations: 2.5 (A), 3.0 (B), 3.5 (C) and 4.0 (D) % w/v. The release profiles for these formulations are shown in Figure 3. The results indicated the more sustained effect with an increase in the concentration of sodium alginate. It is observed from Figure 3 that the steady state release was achieved after an initial lag time and it was directly proportional to the concentration of sodium alginate. This type of release behavior agreed with the pulsatile release pattern. The pulsatile or pulsed drug release is defined as the rapid release of certain amount of drug within a short time period immediately after a lag time (16). This pattern could be controlled by the alginate gel disintegration in phosphate buffer. The alginate disintegration was monitored by the exchange of Ca$^{2+}$ with Na$^{+}$ in the dissolution medium. The first phase (negligible release portion of the release graph, lag time) might be for the negligible dissociation of alginate beads in phosphate buffer and the drug release mainly based on drug diffusion through the small pores and cracks. The second phase exhibited a burst-like release pattern, which was accompanied by alginate disintegration. The sodium alginate concentration in the formulation greatly influenced the steady state release of furosemide from the alginate beads. The

<table>
<thead>
<tr>
<th>F.N. Code</th>
<th>$M_t / M_{∞} = K t^n$ model</th>
<th>$M_t / M_{∞} = K (t - t_L)^n$ model</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>R²</td>
<td>n</td>
</tr>
<tr>
<td>0.9308</td>
<td>1.997</td>
<td>0.9290</td>
</tr>
<tr>
<td>B</td>
<td>0.9910</td>
<td>1.553</td>
</tr>
<tr>
<td>C</td>
<td>0.9350</td>
<td>0.9360</td>
</tr>
<tr>
<td>D</td>
<td>0.9360</td>
<td>0.9160</td>
</tr>
<tr>
<td>E</td>
<td>0.8970</td>
<td>0.3050</td>
</tr>
<tr>
<td>F</td>
<td>0.9600</td>
<td>1.17</td>
</tr>
<tr>
<td>C1</td>
<td>0.8490</td>
<td>0.542</td>
</tr>
<tr>
<td>E1</td>
<td>0.8310</td>
<td>0.20</td>
</tr>
<tr>
<td>F1</td>
<td>0.8480</td>
<td>0.3440</td>
</tr>
</tbody>
</table>

R² is the correlation coefficient and $n$ is the release exponent.

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Figure 5. *In vitro* release profiles of furosemide from air-dried alginate beads prepared with CaCl$_2$, Al$_2$(SO$_4$)$_3$, and BaCl$_2$ at 5 % w/v level. Bars indicate ± SD (n = 3).
principle of gelation or cross-linking of sodium alginate with calcium chloride is based on the formation of tight junction between the guluronic acid residues (4). The number of the apparent cross-linking points within the formed calcium alginate gel beads increased with increasing alginate concentration in the formulation. This increase in the apparent cross-linking density delayed the alginate gel disintegration in phosphate buffer due to the retardation of Ca\(^{2+}\) exchange with Na\(^+\) and eventually increasing lag time. Increased alginate gel density per unit volume was also thought to affect the decreased pore size within the gels, and thus furosemide release becomes slow.

The release behavior of alginate microspheres, produced by ionotropic external gelation with different gelling agents depend upon the valency and size of the cations of the respective cross-linking agent (17). To investigate this aspect, the sodium alginate (3.5% w/v) beads were prepared via crosslinking in 5% w/v solution of CaCl\(_2\) (C), Al\(_2\)(SO\(_4\))\(_3\) (E) and BaCl\(_2\) (F), respectively. Their release profiles in phosphate buffer of pH 7.4 is depicted in Figure 4. The pulsatile release pattern was observed in all cases. The steady state release was achieved after 2.45 h for Ca\(^{2+}\)-alginate microspheres, 3.5 h for Ba\(^{2+}\)-alginate microspheres and 5.0 h for Al\(^{3+}\)-alginate microspheres. The results obtained can be explained on the basis of the extent of cross-linking
in the microspheres. Ca\(^{2+}\) and Ba\(^{2+}\), being divalent, form two-dimensional bonding structure with sodium alginate inside the alginate matrices. But since Ba\(^{2+}\) has the largest size (1.74 Å) as compared to the other two cations (1.14 Å for Ca\(^{2+}\) and 0.68 Å for Al\(^{3+}\)), it is expected to form strong alginate microspheres with smaller voids and low water uptake (17). Therefore, the exchange of larger Ba\(^{2+}\) in the microspheres with Na\(^{+}\) of dissolution medium (phosphate buffer, pH 7.4) and also their removal in the form of insoluble barium phosphate was hindered, thus resulting in delayed swelling of the microspheres and slow release. In case of Ca\(^{2+}\)-alginate microspheres, the smaller size of Ca\(^{2+}\) as compared to Ba\(^{2+}\) ensure rapid removal of Ca\(^{2+}\) as calcium phosphate from the microspheres due to ion-exchange process with Na\(^{+}\) of phosphate buffer medium and thus leading to greater water uptake and rapid release. In case of Al\(^{3+}\)-alginate microspheres, the delay was due to the ability of Al\(^{3+}\) to form three-dimensional bonding structure with the sodium alginate inside the microspheres. This three-dimensional bonding results in an extended cross-linking through the whole microsphere, producing hard alginate microspheres with low water uptake and thus leading to slow removal of Al\(^{3+}\) due to ion-exchange with Na\(^{+}\) in the phosphate buffer. As a result, the swelling of the beads are delayed leading to slow disintegration.

The influence of the degree of dehydration on the release of furosemide was investigated by drying alginate microspheres (formulation C, E and F) at 80°C for 2 h in a hot air oven, whilst the duplicate batches (formulations C1, E1 and F1) were dried in air at room temperature. The release of furosemide from oven-dried alginate microspheres was observed to take place at a faster rate as compared to the air-dried alginate microspheres (Figure 4 and 5), because the steady state release was achieved after 5 h for air-dried Ca\(^{2+}\)-alginate microspheres, whereas this value was 6 h and 8.3 h for air-dried Ba\(^{2+}\)-alginate and Al\(^{3+}\)-alginate microspheres, respectively. The alginate microspheres that had been heated at 80°C for 2 h appeared to have become fully dehydrated. The complete dehydration of alginate microspheres may develop a small degree of surface cracking which can facilitate the surface erosion of the beads upon rehydration (18) and consequently, furosemide release was more rapid from the oven-dried microspheres as compared to the air-dried microspheres. Air-drying produced partially hydrated alginate microspheres due to incomplete dehydration. The slow release was supposed to increase in the particle size of the microspheres after air-drying, since the dissolution surface area was decreased. Also, the incomplete dehydration may significantly reduce the pore size of the alginate microspheres and may prevent the surface from cracking.

### Kinetic modeling

The in vitro dissolution data were analyzed by different kinetic models in order to find out the $n$ value, which describes the drug release mechanism. The values of $n$ and the coefficient of correlation ($R^2$) obtained for the respective model are listed in Table 4. The best fit with the highest correlation coefficient was shown in modified power law expression (eqn. 2).

$$n = \frac{0.45}{0.8360} = 0.54$$

The values of $n$ for the release of furosemide from the alginate microspheres range between 0.5 and 1.383 (from eqn. 2), indicating that the drug release from the microspheres followed the anomalous transport and super case-II transport mechanism controlled by swelling and relaxation of the polymer chains. For the formulation E, C1, E1 and F1, the $n$ values from power law expression (eqn. 1) range between 0.20 and 0.54, indicating the mechanism of the initial drug release to be diffusion controlled during the lag period, when alginate dissociation was almost negligible in the dissolution medium.

### Infrared spectroscopy

The stability of furosemide in the alginate microspheres was investigated by infrared spectroscopy study (IR). The study of IR spectra of furosemide (Figure 6) demonstrates that the characteristic absorption bands for N-H stretching vibration of secondary amine, C=O stretching vibration and S=O stretching vibration of sulfonamide group and C-Cl stretching vibration appeared at 3398, 1675, 1593, 1325 and 578 cm\(^{-1}\), respectively. The almost identical absorption bands were obtained from furosemide-loaded alginate microspheres, but with lower intensity as shown in Figure 6. The above observed absorption bands were similar to the reported values (7). Thus, the IR study indicates the stable nature of furosemide in the freshly prepared alginate microspheres.

### Differential scanning calorimetry

The DSC thermograms of pure drug and drug-loaded alginate microspheres prepared with different gelling agents are shown in Figure 7. Furosemide exhibited a sharp endothermic peak at 220.8°C corresponding to its melting point. The peak of the drug did not appear in the thermogram of any type of the prepared microspheres containing...
the drug. It may indicate that the drug was uniformly dispersed at the molecular level in the microspheres as observed by SEM analysis (Figure 1).

CONCLUSIONS

It can be conclude from the above investigation that the proper selection of formulation conditions is very important to achieve high encapsulation efficiency and to control the release of furosemide from alginate microspheres. The pulsatile release pattern was observed from all the formulations investigated. The alginate microspheres swelled and eventually disintegrated in phosphate buffer of pH 7.4. Consequently, 100 % of furosemide was released in the dissolution medium. Therefore, more formulation studies are needed to design the best controlled release formulation.

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