

# Controlled Release of Diclofenac Sodium and Ibuprofen through Beads of Sodium Alginate and Hydroxy Ethyl Cellulose Blends

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**ABSTRACT:** Controlled release of diclofenac sodium (DS) and ibuprofen (IB) drugs through sodium alginate (NaAlg)-hydroxy ethyl cellulose (HEC) blend polymeric beads has been investigated. Beads were prepared by precipitating the viscous solution of NaAlg and HEC blend in alcohol followed by crosslinking with calcium chloride. Different formulations were developed in bead form by varying the amount of HEC, crosslinking agent, and drug concentration. Swelling studies in water, percent encapsulation of drugs, and release studies were carried out. The DS-loaded beads have shown better release performance than the IB-loaded

beads. Diffusion parameters were evaluated from the Fickian diffusion theory. Mathematical modeling studies and drug release characteristics through bead matrices were studied by solving Fick's diffusion equation. The results are discussed in terms of drug release patterns and theoretical concentration profiles generated through matrices, considering spherical geometry of the beads. © 2006 Wiley Periodicals, Inc. *J Appl Polym Sci* 102: 5708–5718, 2006

**Key words:** sodium alginate; hydroxy ethyl cellulose; diclofenac sodium; ibuprofen; controlled release

## INTRODUCTION

In the literature of pharmaceuticals, a variety of polymers have been used for developing controlled release (CR) formulations to enhance the release rates of drugs. Among various polymers employed, hydrophilic biopolymers are quite suitable in oral applications because of their inherent advantages over the synthetic polymers. Sodium alginate (NaAlg), a natural polysaccharide, can be derived from brown seaweeds. It is composed of D-mannuronic acid and D-guluronic acid. This polysaccharide is extensively used in food industry as a gelling agent and for encapsulating living cells.<sup>1–3</sup> Because the polymer is biodegradable and biocompatible and can be used in drug delivery applications.<sup>4–7</sup> There are many applications of NaAlg in agriculture<sup>2,8,9</sup> when it is crosslinked with glutaraldehyde. Hydroxy ethyl cellulose (HEC), a nonionic water-soluble and water-swella-

ble cellulose, is compatible with a wide range of other water-soluble polymers.<sup>6,10,11</sup> It is commercially used in paints, paper finishes, and membrane designing.<sup>10</sup>

From a perusal of the literature, it is found that no studies have been made on the blends of NaAlg with HEC to study the CR of nonsteroidal antiinflammatory (NASID) drugs. This prompted us to undertake a detailed study on two model drugs, viz., diclofenac sodium (DS), a water-soluble drug, and ibuprofen (IB), a water insoluble drug. Both the drugs have antiinflammatory properties and are used in the treatment of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis for the quick relief of pain.<sup>3,12</sup> Both the drugs are readily absorbed throughout the gastrointestinal tract (GIT). Of these, elimination of IB is somewhat rapid after administration. To avoid the side effects of DS and IB caused by the high plasma peaks, we have attempted here to develop their CR formulations with NaAlg. Earlier, CR of antihypertensive drugs through the tableted microspheres of cellulose derivatives has been reported.<sup>10,12,13</sup> In continuation of our ongoing program of research,<sup>7,12,14</sup> we now report *in vitro* results on the CR of DS and IB drugs through the beads prepared from NaAlg and HEC polymers blends in different combinations. The effect of HEC content, crosslinking agent, and drug concentrations on the release rates of DS and IB are discussed. Mathematical modeling and drug release characteristics have

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been attempted by solving Fick's equation and results are correlated with *in vitro* release data.

## MATERIALS AND METHODS

### Materials

Gift samples of diclofenac sodium (purity 99.39%) and ibuprofen (purity 97.94%) were obtained from Waksman Salesman Pharmaceuticals, Anantapur, India. Sodium alginate, hydroxy ethyl cellulose, calcium chloride, Tween-80, dichloromethane and methanol of AR grade were purchased from s.d. fine chemicals, Mumbai, India. Doubled distilled water was used throughout the study.

### Methods

#### Preparation of beads and formulations

A 4% solution of NaAlg + HEC in distilled water was prepared by gentle heating and stirring on a hot plate with a stirrer (Jenway, model 1103, Essex, UK). To this, the required amount of drug was added and stirred until complete dispersion of the drug in the polymer solution occurred. About 5 mL of the drug-loaded polymer solution was added drop-wise in a short time of 50–75 s into the methanol solution containing the required amount of crosslinking agent (CaCl<sub>2</sub>) using a 25-mL hypodermic syringe having 1-mm diameter under constant stirring condition. The

beads formed were removed from methanol at a particular time and were repeatedly washed with distilled water.

Three placebo beads containing only NaAlg and HEC in the ratio of 50 : 50 were prepared by adding different amounts of crosslinking agent (1.5, 3.0, and 4.5 g of CaCl<sub>2</sub>) and designated, respectively, as P1, P2, and P3. In the first stage of experiments, five formulations were prepared by varying the amounts of NaAlg and HEC in the respective ratios of 90 : 10, 80 : 20, 70 : 30, 60 : 40, and 50 : 50 by keeping DS (0.2 g) and crosslinker (3.0 g CaCl<sub>2</sub>) constant. These formulations were designated, respectively, as DS1, DS2, DS3, DS4, and DS5. In the second stage, three formulations were prepared by keeping the fixed ratio of NaAlg to HEC (50 : 50) and DS (0.2 g), but varying the amount of crosslinker (1.5, 3.0, and 4.5 g of CaCl<sub>2</sub>). These formulations were designated, respectively, as DH1, DH2, and DH3. In the third stage, four formulations were prepared by varying the amount of DS (0.4, 0.6, 0.8, and 1.0 g) while keeping the fixed ratio of NaAlg to HEC (50 : 50) as well as the crosslinker (3 g of CaCl<sub>2</sub>). These formulations were designated, respectively, as DS6, DS7, DS8, and DS9. In the last stage, five formulations were prepared by keeping NaAlg to HEC ratio as 50 : 50 while adding 3 g of CaCl<sub>2</sub> and varying the amount of IB (0.2, 0.4, 0.6, 0.8, and 1.0 g). These formulations were designated, respectively, as IB1, IB2, IB3, IB4, and IB5. The details of all formulations and their codes are given in Table I.

TABLE I  
Formulation Codes

Formulation	Code
Crosslinked placebo beads	
50% NaAlg + 50% HEC with 1.5 g of CaCl <sub>2</sub>	P1
50% NaAlg + 50% HEC with 3.0 g of CaCl <sub>2</sub>	P2
50% NaAlg + 50% HEC with 4.5 g of CaCl <sub>2</sub>	P3
Variation of NaAlg to HEC ratio keeping DS and CaCl <sub>2</sub> constant	
90% NaAlg + 10% HEC with 0.2 g DS	DS1
80% NaAlg + 20% HEC with 0.2 g DS	DS2
70% NaAlg + 30% HEC with 0.2 g DS	DS3
60% NaAlg + 40% HEC with 0.2 g DS	DS4
50% NaAlg + 50% HEC with 0.2 g DS	DS5
Variation of CaCl <sub>2</sub> keeping NaAlg to HEC ratio and DS constant	
50% NaAlg + 50% HEC with 0.2 g of DS and 1.5 g of CaCl <sub>2</sub>	DH1
50% NaAlg + 50% HEC with 0.2 g of DS and 3.0 g of CaCl <sub>2</sub>	DH2
50% NaAlg + 50% HEC with 0.2 g of DS and 4.5 g of CaCl <sub>2</sub>	DH3
Variation of DS keeping NaAlg to HEC ratio and CaCl <sub>2</sub> constant	
50% NaAlg + 50% HEC with 0.4 g DS	DS6
50% NaAlg + 50% HEC with 0.6 g DS	DS7
50% NaAlg + 50% HEC with 0.8 g DS	DS8
50% NaAlg + 50% HEC with 1.0 g DS	DS9
Variation of IB keeping NaAlg to HEC ratio and CaCl <sub>2</sub> constant	
50% NaAlg + 50% HEC with 0.2 g IB	IB1
50% NaAlg + 50% HEC with 0.4 g IB	IB2
50% NaAlg + 50% HEC with 0.6 g IB	IB3
50% NaAlg + 50% HEC with 0.8 g IB	IB4
50% NaAlg + 50% HEC with 1.0 g IB	IB5

### Bead size measurement

Dry bead size was measured using a micrometer screw gauge (Sargent, USA) within an accuracy of  $\pm 0.01$  mm.

### Scanning electron microscopic studies

Scanning electron microscope (SEM) photographs were taken on placebo NaAlg and HEC beads and the DS-loaded as well as IB-loaded beads prepared by cross-linking with 3.0 g of  $\text{CaCl}_2$ . Beads were sputtered with gold to make them conducting and were placed on copper stub. Scanning was done using Leica 400, Cambridge, UK. Thickness of the gold layer obtained with sputtering was  $\leq 1$   $\mu\text{m}$ .

### Differential scanning calorimetric studies

Thermal analysis was performed on the placebo NaAlg and HEC beads, plain drugs, and the drug-loaded beads using Rheometric Scientific, DSCSP, UK. Initially, the moisture was removed by heating the samples at the rate of  $20^\circ\text{C}/\text{min}$  up to  $100^\circ\text{C}$  and then cooled back to  $30^\circ\text{C}$ . The final thermograms were recorded from  $30^\circ\text{C}$  to  $400^\circ\text{C}$  at the heating rate of  $10^\circ\text{C}/\text{min}$ .

### X-ray diffraction studies

The X-ray diffraction (XRD) patterns of placebo beads, plain DS, plain IB as well as DS-loaded and IB-loaded beads were recorded using a Rigaku Geigerflex diffractometer equipped with Ni-filtered  $\text{CuK}\alpha$  radiation ( $\lambda = 1.5418$  Å). Dried beads of uniform size were mounted on a sample holder and the patterns were recorded in the range  $10^\circ$ – $50^\circ$  at the speed of  $5^\circ/\text{min}$  to know the crystallinity.

### Estimation of drug loading and encapsulation efficiency

Dried beads were taken in a separating funnel and drug was extracted with 5 mL of dichloromethane (DCM) under vigorous shaking. About 10 mL of 7.4 pH phosphate buffer containing 0.02% Tween-80 solution was added to the above solution and DCM was evaporated with gentle heating and continuous shaking. The aqueous solution was then filtered and assayed by using UV-vis spectrophotometer (model Anthelie, Secomam, Dumont, France) at the  $\lambda_{\text{max}}$  value of 224 nm. Experiments were performed in triplicates. The percentage of drug loading and encapsulation efficiency were calculated using the equations

$$\% \text{ Drug loading} = \left( \frac{\text{Amount of drug in beads}}{\text{Amount of beads}} \right) \times 100 \quad (1)$$

$$\% \text{ Encapsulation efficiency} = \left( \frac{\text{Drug loading}}{\text{Theoretical loading}} \right) \times 100 \quad (2)$$

### Swelling studies

Dynamic swelling behavior of the beads was studied in water by mass measurements. Beads were soaked in water and at different time intervals, a few beads were taken out and blotted carefully (without pressing hard) to remove the surface-adhered water. The swollen beads were weighed ( $w_1$ ) using an electronic microbalance (Mettler, AT-120, Switzerland). Beads were then dried to constant mass ( $w_2$ ) on an electronic oven maintained at  $60^\circ\text{C}$ . These studies were performed in triplicates for each of the samples, but the average values were considered while data analysis. The percent equilibrium water uptake was calculated as

$$\% \text{ Water uptake} = \left( \frac{\text{Mass of swollen beads } (w_1) - \text{Mass of dry beads } (w_2)}{\text{Mass of dry beads } (w_2)} \right) \times 100 \quad (3)$$

### In vitro release study

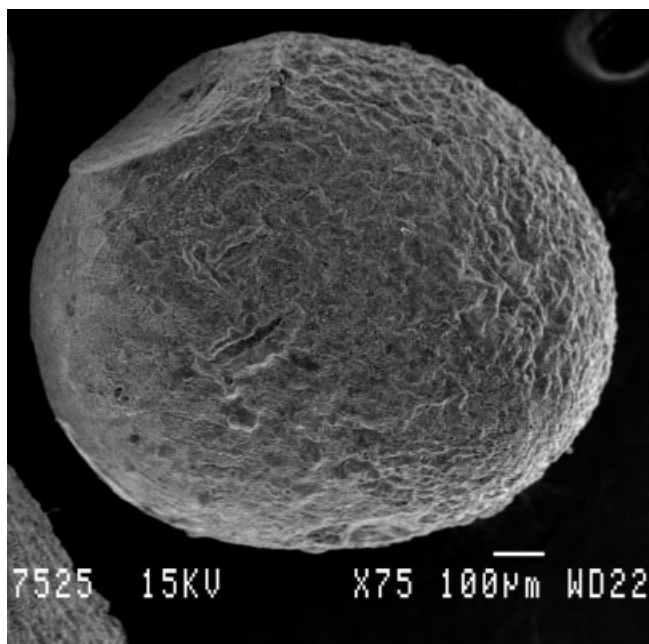
Dissolution was carried out using the fully automated dissolution coupled UCV system (Logan System 888J, NJ) equipped with six baskets. Dissolution rates were measured at  $37^\circ\text{C}$  with 100 rpm speed. About 900 mL of 0.1 HCl (pH = 1.02) was used as dissolution media during the first 3 h and then 7.4 pH phosphate buffer solution was used. In case of IB-loaded beads, a pH 7.4 buffer containing 0.02% Tween-80 was used as the dissolution media to simulate the GIT conditions. Instrument will automatically measure the release of drug through UV

spectrophotometer attached with the instrument at particular time and then replaces the solution back into the dissolution bowl. These studies were performed in triplicates for each of the samples, but the average values were considered for display and data analysis.

## RESULTS AND DISCUSSION

### Morphology and thermal analysis of beads

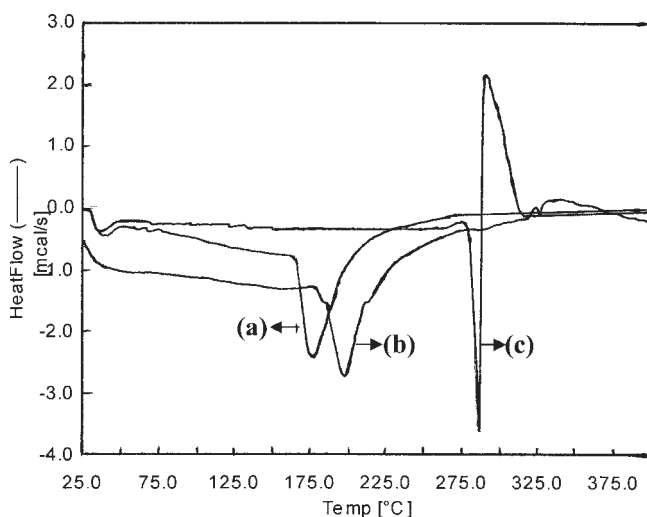
To understand the optimum release characteristics of the drug-loaded beads, we have performed the



**Figure 1** SEM photograph of placebo beads.

experiments by varying the amount of HEC as well as crosslinking agent in the blend bead matrix. The nature of drug molecules (water soluble or insoluble) and the extent of drug loading were also investigated. The formulated beads are all spherical in nature with the smooth surfaces as revealed by SEM photographs shown in Figure 1. Initially, experiments were performed to optimize the geometry of beads to produce noncollapsible and hard beads having sizes ranging from 1.17 to 1.51 mm ( $\pm 0.26$  mm). The particle size varied significantly either by increasing the amount of HEC or by increasing the extent of drug loading into beads.

Differential scanning calorimetric (DSC) curves for placebo NaAlg-HEC beads (a), beads containing DS



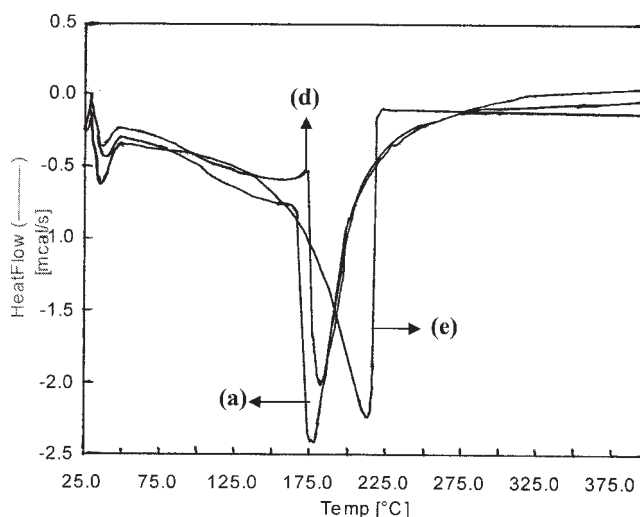
**Figure 2** DSC curves of placebo NaAlg-HEC beads (a), DS-loaded NaAlg-HEC beads (b), and plain DS (c).

(b), and plain DS (c) are shown in Figure 2, whereas DSC curves for the beads containing IB (d) and plain IB (e) are presented in Figure 3. The drugs, DS and IB, exhibit sharp endothermic peaks at 287°C and 230°C, respectively. However, these peaks have not appeared in the curves of DS- and IB-containing beads, suggesting that most of the drug was uniformly dispersed in polymer matrices at molecular level.

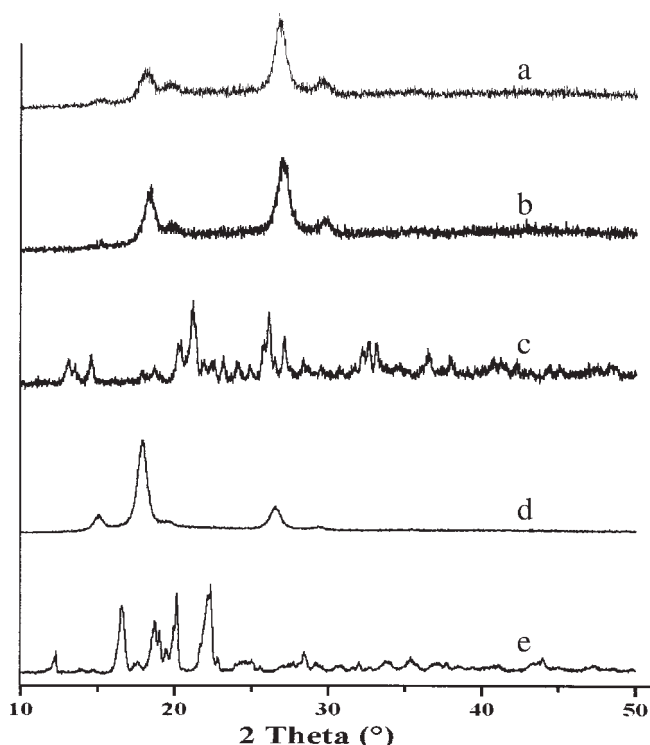
XRD analyses can provide a clue about crystallinity of the drugs in crosslinked beads. XRD patterns recorded for placebo beads (a), DS-loaded beads (b), plain DS (c), IB-loaded beads (d), and plain IB (e) are presented in Figure 4. Here, DS has shown characteristic intense peaks at  $2\theta$  of 20° and 25° because of its crystalline nature, but only the peaks observed in the placebo matrices are observed in the DS-loaded beads. In the case of IB, peaks observed at  $2\theta$  of 16°, 20°, and 22° because of crystalline nature of IB are not found in the IB-loaded beads except those peaks observed in plain placebo beads. This indicates that both DS and IB are dispersed at the molecular level in the polymer matrices since no indication about the crystalline nature of the drugs was observed in the drug-loaded beads.

#### Drug encapsulation and equilibrium water uptake

Results of % drug encapsulation along with the diameter of the beads and % equilibrium uptake data are presented in Table II. It is found that equilibrium uptake data do not seem to bear any relationship with either % encapsulation or size of the beads. The size of the beads increased systematically from 1.45 to 1.51 mm with increasing amount of IB at a constant amount of crosslinking agent in 50 : 50 of NaAlg : HEC matrices. DS, being a water-soluble drug, has somewhat lower bead sizes ranging from 1.28 to 1.35 mm when compared to larger size (1.45–1.51 mm) beads



**Figure 3** DSC curves of placebo NaAlg-HEC beads (a), IB-loaded NaAlg-HEC beads (d), and plain IB (e).



**Figure 4** XRD spectra of placebo NaAlg-HEC beads (a), DS-loaded NaAlg-HEC beads (b), plain DS (c), IB-loaded NaAlg-HEC beads (d), and plain IB (e).

of IB-loaded formulations. Quite adversely, % equilibrium uptake values of DS-containing beads vary in the range of 146.37–149.33 and these values are somewhat higher than those of IB-loaded (138.59–142.36) beads. On the other hand, with the constant loading

of drug and constant amount of crosslinking agent in the matrices and by increasing the amount of HEC, % equilibrium water uptake (147.19–155.23) and the % encapsulation efficiency (32.17–55.46%) increase systematically, but the size of the beads decrease from 1.23 to 1.17 mm with increasing HEC content. This may be due to the fast diffusion of HEC into water. By analyzing the bead size of the DS-loaded matrices with varying amounts of  $\text{CaCl}_2$  at a fixed ratio of NaAlg : HEC (i.e., 50 : 50) and that of DS, we find that the bead sizes are not affected and their diameters are much smaller (1.16–1.18 mm) than those observed for other formulations. The % encapsulation efficiency values are also quite smaller (30–36%), but % equilibrium water uptake increase from 141 to 160, which is a much higher range than observed for other formulations.

#### Drug release kinetics

Drug release kinetics were analyzed by plotting the cumulative release data,  $(M_t/M_\infty)$  versus time by fitting the data to a simple exponential equation<sup>15</sup>

$$\left(\frac{M_t}{M_\infty}\right) = kt^n \quad (4)$$

where  $n$  is diffusional exponent and  $k$  is a constant related to the drug delivery system. Using the least squares procedure, we have estimated the values of  $n$  and  $k$  for all the formulations developed. These results along with correlation coefficients,  $r$  are presented in Table III. If  $n = 0.5$ , the drug diffuses and releases from the polymer matrix following a quasi-Fickian

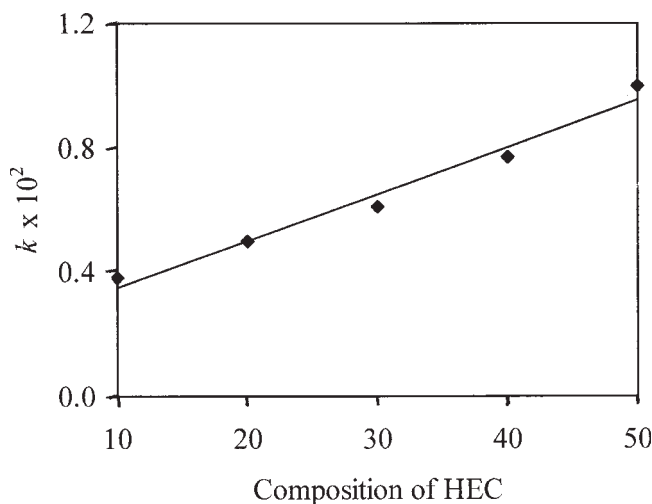
**TABLE II**  
Characteristics of Drug-Loaded Beads for Different Formulations

Formulation code	Bead diameter (mm)	% Encapsulation efficiency	Equilibrium water uptake (%)
Variation of NaAlg to HEC ratio keeping DS and $\text{CaCl}_2$ constant			
DS1	1.23 ± 0.11	55.46	147.19
DS2	1.21 ± 0.56	47.64	149.61
DS3	1.21 ± 0.31	43.56	151.26
DS4	1.19 ± 0.49	38.25	153.51
DS5	1.17 ± 0.23	32.17	155.49
Variation of $\text{CaCl}_2$ keeping NaAlg to HEC ration and DS constant			
DH1	1.18 ± 0.11	35.91	160.38
DH2	1.17 ± 0.23	32.17	155.49
DH3	1.16 ± 0.01	30.05	140.73
Variation of DS keeping NaAlg to HEC ratio and $\text{CaCl}_2$ constant			
DS6	1.28 ± 0.12	54.73	149.01
DS7	1.31 ± 0.35	66.66	148.52
DS8	1.33 ± 0.49	67.94	147.65
DS9	1.35 ± 0.19	72.15	146.37
Variation of IB keeping NaAlg to HEC ratio and $\text{CaCl}_2$ constant			
IB1	1.45 ± 0.43	56.23	142.36
IB2	1.45 ± 0.69	69.79	141.35
IB3	1.46 ± 0.31	73.61	140.65
IB4	1.48 ± 0.57	74.51	139.06
IB5	1.51 ± 0.12	82.32	138.59

**TABLE III**  
**Release Kinetics Parameters for Different Formulations**

Formulation code	$k$ ( $10^2$ )	$n$	Correlation coefficient, $r$
Variation of NaAlg to HEC ratio keeping DS and CaCl <sub>2</sub> constant			
DS1	0.38	0.873	0.9752
DS2	0.50	0.843	0.9893
DS3	0.61	0.855	0.9879
DS4	0.77	0.835	0.9744
DS5	0.89	0.814	0.9966
Variation of CaCl <sub>2</sub> keeping NaAlg to HEC ratio and DS constant			
DH1	1.09	0.820	0.9918
DH2	1.00	0.814	0.9966
DH3	0.97	0.819	0.9928
Variation of DS keeping NaAlg to HEC ratio and CaCl <sub>2</sub> constant			
DS6	0.30	0.747	0.9861
DS7	0.31	0.696	0.9888
DS8	0.57	0.657	0.9815
DS9	0.76	0.655	0.9082
Variation of IB keeping NaAlg to HEC ratio and CaCl <sub>2</sub> constant			
IB1	0.25	1.177	0.9967
IB2	0.34	1.163	0.9999
IB3	0.50	1.136	0.9975
IB4	0.57	1.164	0.9887
IB5	0.78	1.108	0.9795

diffusion. For  $n > 0.5$  an anomalous, non-Fickian drug diffusion occurs. If  $n = 1$ , a non-Fickian Case II or zero-order release kinetics is operative. Values of  $k$  and  $n$  have shown a dependence on the extent of crosslinking, % drug loading, and HEC content in the blend matrix. Values of  $n$  for beads prepared by varying the amounts of NaAlg and HEC in the respective ratios of 90 : 10, 80 : 20, 70 : 30, 60 : 40, and 50 : 50 by keeping DS (0.2 g) and crosslinker (3.0 g CaCl<sub>2</sub>) constant, range from 0.814 to 0.873, leading to a shift of transport mechanism from Fickian to anomalous type.

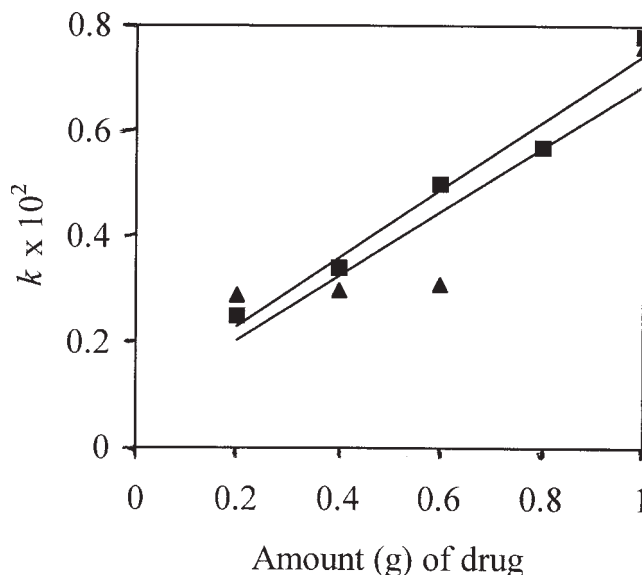


**Figure 5** Values of  $k$  versus composition of HEC in NaAlg + HEC blend beads.

DS-loaded beads have  $n$  values ranging from 0.655 to 0.747, which are slightly smaller than those observed for beads having varying amounts of HEC. On the other hand, for IB-loaded matrices,  $n$  values shift from anomalous type of release to a swelling-controlled, Case II mechanism (Table III). This may be due to a reduction in the regions of low microviscosity and tight closure of microcavities in the swollen state of the beads. Similar findings have been observed elsewhere,<sup>16</sup> wherein effect of different polymer ratios on dissolution kinetics was studied. On the other hand, values of  $k$  are quite smaller for drug-loaded beads, suggesting their lesser interactions than beads having varying amount of HEC. To study the effect of  $k$  on the composition of HEC in the blend, we have plotted values of  $k$  versus HEC composition in Figure 5. A perfect linear increase of  $k$  with increasing amount of HEC is observed, suggesting a systematically varying interaction of drug solution with HEC content of the blend matrix. On the other hand, when values of  $k$  are plotted (Fig. 6) as a function of amount of drug, no strict linearity is observed, suggesting that presence of drugs did not affect the transport much drastically.

**Swelling studies**

Excipients can have a dramatic effect while studying *in vitro* drug release profiles of the formulations prepared with the swellable polymers such as NaAlg or HEC or their blends. Varying the amount and type of coexcipients used in the formulation can influence drug release. Dynamic swelling experiments were performed on DH1 to DH 3 formulations. Results of



**Figure 6** Values of  $k$  versus concentration of (▲) DS and (■) IB.

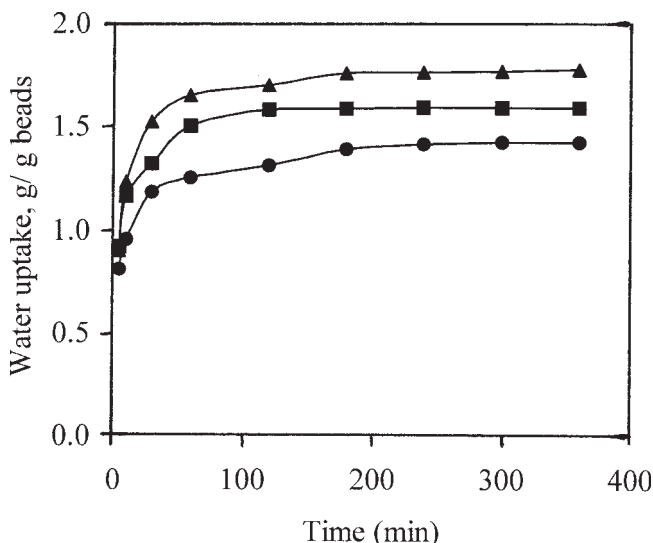
water uptake by beads having different amounts of crosslinking agent are displayed in Figure 7. These data indicate that beads absorb maximum amount of water in the first hour. Also, DH1 beads absorb more water than DH2 and DH3 beads. This is because crosslinking occurs quickly at higher amount of crosslinker. Highly crosslinked beads absorb less water. In an earlier study<sup>14</sup> on chitosan-crosslinked microspheres, encapsulation efficiency for DS was quite smaller than that observed in the present matrices. Similarly, in another previous study,<sup>12</sup> encapsulation efficiency of DS was somewhat smaller for urea-formaldehyde nanocapsules than that of the present systems. It may be noted that results of DS for GA-crosslinked NaAlg beads published earlier<sup>7</sup> are somewhat comparable to the present data.

#### Computation of diffusion coefficients for liquid transport through spherical beads

In the present study, drugs are encapsulated in spherical beads. To study drug diffusion through the bead geometry, we have modeled the diffusion process to compute concentration profiles using sorption data. Mathematical approaches used by Vergnaud were employed<sup>17</sup> to the present problem to describe sorption and desorption processes to compute concentration profiles of liquids inside spherical beads of radius,  $r$  using Fick's equation.<sup>18</sup>

$$F = -D \left[ \frac{\partial C}{\partial r} \right] \quad (5)$$

Here,  $F$  is flux (matter transported/unit area at unit time). To apply these concepts, we assumed that:



**Figure 7** Water uptake versus time for beads containing 50 : 50 ratio of NaAlg : HEC at different amounts of crosslinking agent. (▲) 1.5 g, (■) 3.0 g, and (●) 4.5 g.

1. Dosage formulation is spherical and drug is intimately dispersed in it.
2. Transport is considered in radial direction.
3. Both transports (i.e., liquid enters the polymer, while the drug goes out of the dosage form) are considered simultaneously.
4. Both transports are controlled by transient diffusion, which are related to each other.
5. Diffusion coefficients of these transports depend on concentrations of the drug and the liquid.
6. Concentrations of matter transported (drug, liquid) on the surface attain equilibrium as soon as diffusion takes place.
7. Despite polymer swelling, a frame of reference is fixed with respect to initial dosage form for all calculations.

Considering Fick's equation for radial diffusion with a concentration-dependent diffusivity, we can write

$$\frac{\partial C}{\partial t} = \frac{1}{r^2} \frac{\partial}{\partial r} \left[ D r^2 \frac{\partial C}{\partial r} \right] \quad (6)$$

Diffusion in a spherical bead can be studied in terms of mass % uptake up to equilibrium using the equation

$$\frac{M_t}{M_\infty} = 6 \sqrt{\frac{Dt}{\pi^2}} \left( \frac{1}{\sqrt{\pi}} + 2 \sum_{n=1}^{\infty} \text{ierf} \frac{nr}{\sqrt{Dt}} \right) - 3 \frac{Dt}{r^2} \quad (7)$$

Here,  $M_t$  is the amount of liquid released at time,  $t$ ,  $M_\infty$  is the total amount of liquid in the spherical bead, and  $D$  is diffusion coefficient of the liquid in the polymer bead. Equation (7) is quite complicated to solve. Thus, Baker and Lonsdale<sup>19</sup> derived a simple equation using initial and boundary conditions and following the assumptions (1) and (6)

$$\text{Initial: } t = 0 \quad r < R \quad C = C_{in} \quad \text{inner part}$$

$$\text{Boundary: } t > 0 \quad r = R \quad C = C_{eq} \quad \text{surface}$$

Here,  $R$  is radius of the swollen spherical bead and  $r$  is initial radius of the spherical bead. The solution of eq. (7) can be given as

$$\frac{M_t}{M_\infty} = 6 \sqrt{\frac{Dt}{\pi^2}} - \frac{3Dt}{r^2} \quad (8)$$

Equation (8) is valid for  $M_t/M_\infty < 0.4$ , but at longer times i.e., for  $M_t/M_\infty > 0.6$ , the liquid release profile is given by

$$\frac{M_t}{M_\infty} = 1 - \frac{6}{\pi^2} \exp \left( - \frac{\pi^2 Dt}{r^2} \right) \quad (9)$$

For intermediate times,  $0.4 \leq M_t/M_\infty \leq 0.6$ , and hence, eqs. (8) and (9) can not be computed within  $\pm 5\%$  accuracy of the theoretical profiles given by eq. (7). For constant diffusivity at short-time sorption, amount of liquid or drug transported is low (i.e.,  $M_t/M_\infty < 0.2$ ), and hence,  $M_t$  is proportional to  $t^{1/2}$  so that,

$$\frac{M_t}{M_\infty} = \frac{6}{r} \left[ \frac{Dt}{\pi} \right]^{1/2} \quad (10)$$

The above equation is valid for the first 10–20% of the total release (i.e.,  $M_t/M_\infty \leq 1.0$  to 0.15). Diffusion coefficients can then be calculated for water absorption or drug release by the beads using,

$$D = \left( \frac{r\theta}{6M_\infty} \right)^2 \pi \quad (11)$$

where  $\theta$  is slope of the linear portion of the plot of  $M_t/M_\infty$  versus  $t^{1/2}$ ,  $r$  is radius of the beads, and  $M_\infty$  is maximum (equilibrium) sorption.

**Numerical treatment of the transport problem**

We have solved the complex problem of double transport in bead geometry using the numerical scheme with finite differences.<sup>17</sup> To perform this, bead is divided into concentric spheres of varying radii,  $r + \Delta r$ ,  $r$ ,  $r - \Delta r$ . Number of concentric spheres is related to radial thickness,  $\Delta r$  of each spherical part and to radius,  $R$  of the bead,

$$R = N \Delta R \quad (12)$$

where  $N$  is number of imaginary planes of the sphere created during simulation. Defining each position in the radial direction within the sphere by an integer,  $n$ , we have

$$r = n \Delta r \quad (13)$$

Concentrations of drug and liquid are constant within each spherical part of thickness,  $\Delta r$  located between two adjacent spheres at time,  $t$ . Matter balance is then calculated for short lapse of time,  $\Delta t$  within the spherical part of thickness,  $\Delta r$  at the center position,  $r$  defined by the integer,  $n$  using Fick’s equation. Then, new concentrations within the bead at position,  $r$  (integer,  $n$ ) after lapse of time,  $\Delta t$  expressed in terms of concentration at previous time in the same place and in two adjacent planes are given by,

$$CN_n = C_n + \frac{\Delta t}{n^2(\Delta r)^2} [J_{n-1/2} - J_{n+1/2}] \quad (14)$$

where,  $J$  is a function of diffusivity and concentration, so that we may write

$$J_{n-1/2} = (n - 1/2)^2 D_{n-1/2} (C_{n-1} - C_n) \quad (15)$$

Diffusivity at intermediate position ( $n - 1/2$ ) can be obtained from diffusivities at positions,  $n$  and  $n + 1$  by either way. While computing, the zero concentration ( $C_0$ ) was entered at the center of the sphere. The matter balance was then calculated for sphere of radius,  $\Delta r/2$  located in the middle of the bead.

The concentration of drug or liquid on the surface of beads represents the concentration at equilibrium ( $C_{eq}$ ) as per assumption (4) mentioned before, so that

$$C_0 = C_{eq \text{ liquid, drug}} \quad (16)$$

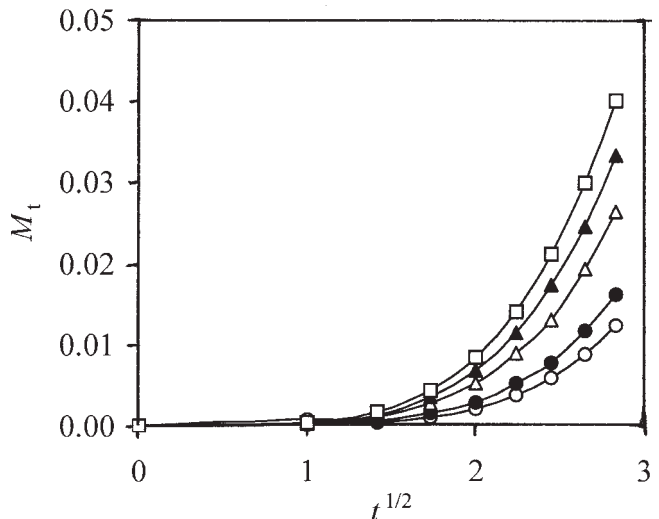
The amount of drug remaining (or liquid entered) in beads at time,  $t$  is obtained by integrating the concentration of drug at this time with respect to space.

$$M_t = 4\pi \int_0^R r^2 C_{rt} dr \quad (17)$$

The above equation is rewritten using finite differences,

$$M_t = 4\pi(\Delta r)^3 \left[ \frac{C_0}{24} + \sum_{n=1}^{n-2} n^2 C_n + \frac{9}{8}(n-1)^2 C_{n-1} + \frac{3}{8}n^2 C_n \right] \quad (18)$$

These equations have been solved to compute concentration at any point and time, either for liquid or drug, if diffusivities are known. Then, theoretical plot of  $M_t$  calculated from eq. (18) versus  $t^{1/2}$  for 0.2, 0.4, 0.6, 0.8, and 1.0 g of drug-loaded or liquid entering can be plotted as shown in Figure 8. It is observed that theoretical curves generated for all the drug loadings even though originate from zero, but they all exhibit some time lag in the beginning. Concentration



**Figure 8** Plots of  $M_t$  calculated from eq. (18) as a function of  $t^{1/2}$  for different drug loadings. (○) 0.2 g, (●) 0.4 g, (△) 0.6 g, (▲) 0.8 g, and (□) 1.0 g.

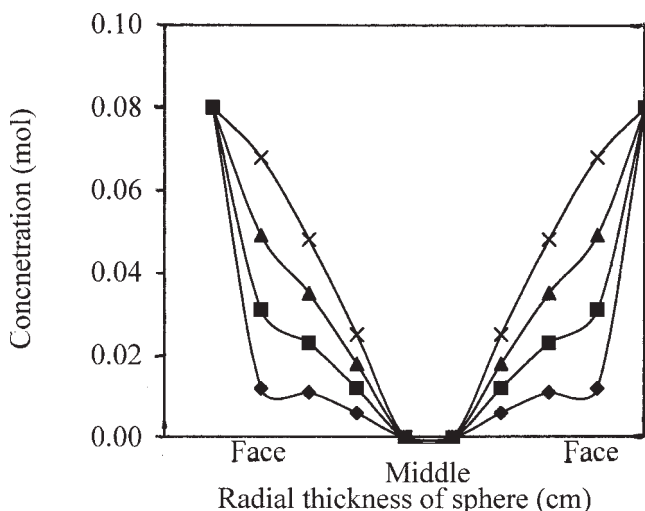


profiles of DS and liquid developed inside the dosage form during diffusion are presented in Figure 9. The steep gradients of concentration of liquid and DS are developed in dosage form, next to the surface. The dosage form swells because rate of transport is higher for liquid than for drug. A constant value is reached on the surface as soon as diffusion starts, following assumption (4). After infinite time, a part of drug remains in the dosage form, probably because of its low solubility.

The value of  $D$  calculated from eq. (11) for all formulations prepared with 50 : 50 (NaAlg : HEC) cross-linked with 1.5%, 3.0%, and 4.5%  $\text{CaCl}_2$  (designated as P1, P2, and P3, respectively) are presented in Table IV. The  $D$  values decrease from  $4.22 \times 10^{-6}$  to  $1.46 \times 10^{-6}$   $\text{cm}^2/\text{s}$ , i.e.,  $D$  values decrease with increasing amount of crosslinking agent from P1 to P3 placebo beads. This is obvious because as the beads are more cross-linked, rigidity of the polymer network increases, thereby allowing lesser transport of water during sorption. Typical  $D$  values for formulations DS3, DS7, and IB3 are also included in Table IV for comparative purpose. The IB-loaded beads have shown higher value of  $D = 2.90 \times 10^{-6}$   $\text{cm}^2/\text{s}$  than the DS-loaded beads.

### *In vitro* drug release

*In vitro* drug release studies were performed in both 0.1N HCl (pH = 1.2) and pH 7.4 buffer solutions. Since no drug release was found in 0.1N HCl even after 3 h, release studies were not carried out in 0.1N HCl solution; also, no swelling of beads occurred in acidic medium because of their hydrophilic nature. However, in pH 7.4 buffer, drug release occurred at the initial stages of dissolution experiments, and thus, *in vitro* drug release studies were performed in pH 7.4



**Figure 9** Penetrant concentration profile plots through the drug-loaded beads as calculated at different arbitrary time intervals.

**TABLE IV**  
Swelling Studies and Diffusion Coefficients of Beads with and without Drug

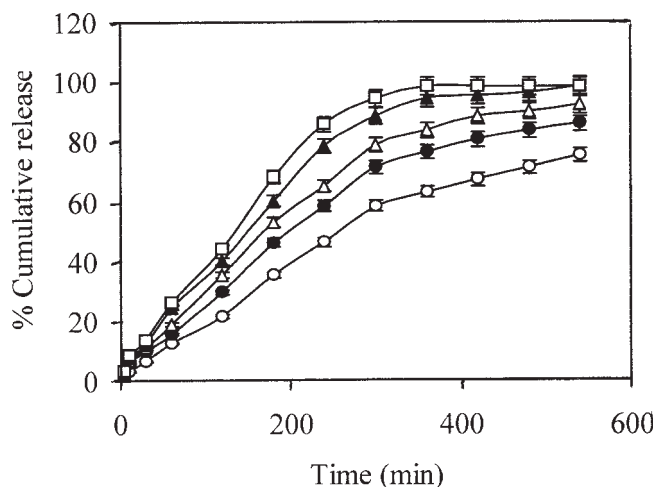
Formulation code	Bead diameter (mm)	% Equilibrium water uptake	$D_{\text{sorption}}$ ( $10^6$ ) ( $\text{cm}^2/\text{s}$ )
P1	$1.11 \pm 0.06$	180.16	4.22
P2	$1.31 \pm 0.42$	161.32	2.82
P3	$1.43 \pm 0.12$	139.86	1.46
DS3	$1.21 \pm 0.31$	151.26	2.13
DS7	$1.31 \pm 0.35$	148.52	2.09
IB3	$1.46 \pm 0.31$	140.65	2.90

buffer for up to 8 h. While studying the CR of DS and IB drugs during dissolution process of NaAlg and HEC beads, several physical and chemical parameters, such as effect of HEC content, effect of crosslinking agent, and % drug loading were studied. Their effects are discussed separately.

### Effect of HEC content in beads

NaAlg and HEC are compatible blends in all compositions.<sup>20</sup> It has been studied earlier<sup>9</sup> that NaAlg can be effectively crosslinked with GA, but crosslinking of NaAlg with  $\text{CaCl}_2$  was done while studying the swelling of NaAlg beads in pH 1.0 and pH 7.4 media.<sup>21</sup> In the present research,  $\text{CaCl}_2$  was employed to crosslink NaAlg and HEC blends, but we realized that  $\text{CaCl}_2$  could crosslink only NaAlg, but not HEC component of the blend. Thus, it was possible to obtain uniform size beads with the blends of NaAlg and HEC. The HEC might be responsible to give dimensional strength to the beads formed during high-speed stirring (250 rpm speed). The effect of HEC composition in the blend of NaAlg and HEC was studied at a constant drug loading (i.e., 0.2 g DS), wherein it was found that 50 : 50 containing NaAlg : HEC blended beads produced almost 100% cumulative drug release in about 6 h, whereas 10% HEC containing beads produced up to 60% cumulative release at about the same time.

From the release data displayed in Figure 10, a systematic increase in % cumulative release with increasing composition of HEC is observed; but the release time remains the same for all compositions. The reason for this effect could be that, during dissolution, a general trend was observed in all formulations, i.e., the blend polymer systematically swelled more with increasing amount of HEC, probably due to the loose crosslinked network of HEC chains in the blend. Microscopically speaking, there is a relaxation response of the polymer chains due to stresses induced in the presence of dissolution media. This might result in an increase of dimension (radius of gyration) of the polymer coil, thereby causing a significant increase in molecular volume of the overall hydrated polymer blend. However, the nature of release profiles remains

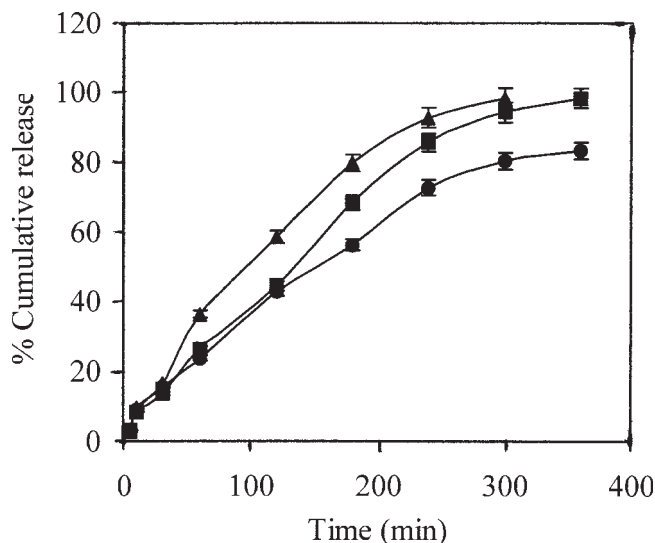


**Figure 10** % Cumulative release of DS through the beads of NaAlg + HEC with different HEC compositions. (○) 10%, (●) 20%, (△) 30%, (▲) 40%, and (□) 50%.

almost identical for all the blends containing different amounts of HEC, indicating that swelling of HEC has a linear relationship with their release profiles.

Effect of crosslinking agent

The % of cumulative release data versus time is plotted in Figure 11 for 50 : 50 blend of NaAlg : HEC at the varying amounts of CaCl<sub>2</sub> (1.5–4.5 g) and at the fixed amount of DS. The % of cumulative release is quite fast and large at the lower amount of CaCl<sub>2</sub> (i.e., 1.5 g), whereas the release becomes quite slower at higher amount of CaCl<sub>2</sub> (i.e., 4.5 g), but the cumulative release value is somewhat smaller than that observed when smaller amount of CaCl<sub>2</sub> was used. This can be

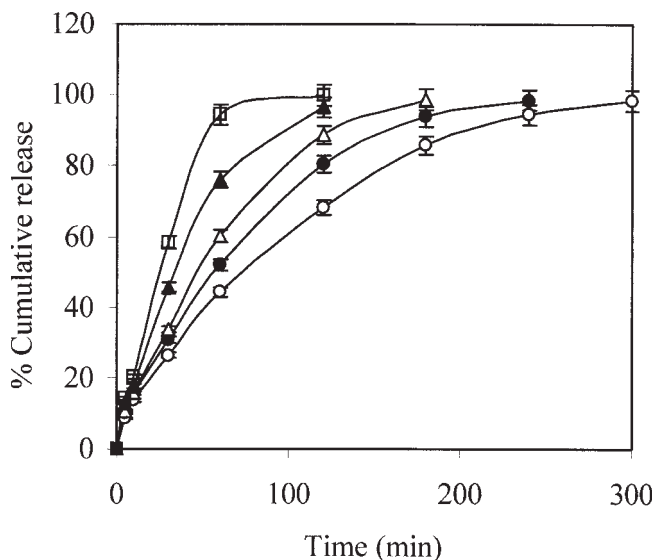


**Figure 11** % Cumulative release of DS through the beads containing 50 : 50 ratio of NaAlg : HEC at different amount of crosslinking agent. (▲) 1.5 g, (■) 3.0 g, and (●) 4.5 g.

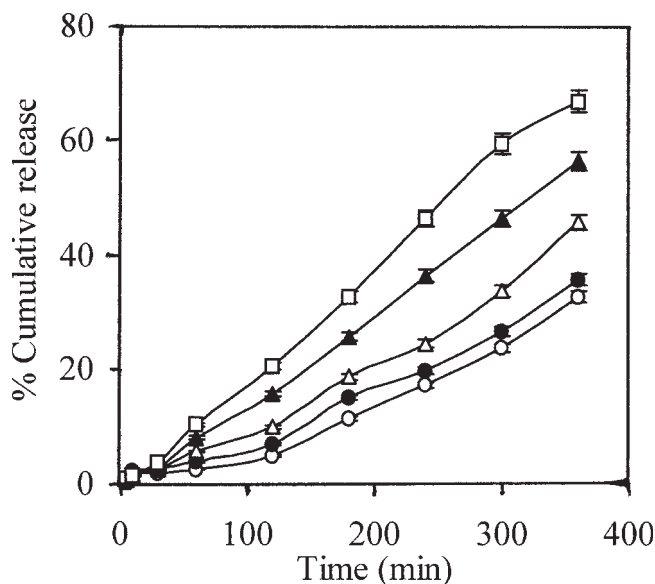
explained in terms of the free volume concept of polymeric matrices; at higher concentration of crosslinking agent, polymeric matrix becomes more rigid because of the closure of microvoids, thereby decreasing the % cumulative release of DS. The release becomes slower at the higher amount of CaCl<sub>2</sub> and *vice versa*.

Effect of percent drug loading

Figure 12 shows the release profiles of DS-loaded beads at different % loading of the drug for 50 : 50 beads of NaAlg : HEC at the constant amount of CaCl<sub>2</sub> (i.e., 3.0 g). The release data showed that formulations containing highest amount of DS (1.0 g) displayed fast and higher release rates than the formulations containing a small amount of DS. The prolonged release was observed for the formulation containing lower amount of DS. In other words, with the decreasing amount of drug in the blend matrix, a shift from anomalous type of release to Case II type release is observed. The release rates become quite slower at lower amount of drug in the matrix. This is due to the availability of more free void spaces through which lesser number of drug molecules will transport through. Similar data for IB-loaded beads are displayed in Figure 13. As the concentration of IB increases in the beads, the release rates also increased. In case of IB-loaded beads, a complete release of the drug was not observed even after 350 min. The nature of release curves are also quite different than those observed for DS-loaded formulations shown in Figure 12. However, the release shifts from Fickian to Case II trans-



**Figure 12** % Cumulative release of DS through beads containing 50 : 50 ratio of NaAlg : HEC with different amount of DS. (○) 0.2 g, (●) 0.4 g, (△) 0.6 g, (▲) 0.8 g, and (□) 1.0 g.



**Figure 13** % Cumulative release of IB through beads containing 50 : 50 ratio of NaAlg : HEC with different amount of IB. (○) 0.2 g, (●) 0.4 g, (△) 0.6 g, (▲) 0.8 g, and (□) 1.0 g.

port as seen in Figure 13 and the values of  $n > 1$  are shown in Table III.

### CONCLUSIONS

Novel drug-loaded beads were prepared by different combinations of NaAlg and HEC polymers, cross-linked with  $\text{CaCl}_2$  to investigate the slow release of two representative drugs, viz., DS and IB. The beads formed were smooth with nonporous surfaces as seen by SEM micrographs. Particle size varied slightly depending upon the formulation parameters like either by changing the blend ratio or drug content as well as crosslinking agent. The % encapsulation efficiency varied significantly with the polymer blend ratio and the amount of drug present in the beads. Greater encapsulation efficiency was observed for IB than DS. As demonstrated, Fickian diffusion may not be the predominant factor while studying the release characteristics from NaAlg and HEC blends. Our results are based on the assumption that drug molecules are dispersed homogeneously in solid matrices

as confirmed by DSC. Mathematical modeling studies confirmed the dependence of release parameters on concentration profiles obtained for the spherical beads.

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