# Controlled Release of Naproxen from Sodium Alginate and Poly(vinyl alcohol)/Sodium Alginate Blend Beads Crosslinked with Glutaraldehyde

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**ABSTRACT:** In this study, polymeric beads of sodium alginate (NaAlg) and its blend with poly(vinyl alcohol) (PVA) were prepared by crosslinking with glutaraldehyde (2.5% v/v) and hydrochloric acid (3% v/v) for the release of naproxen sodium (NS). The prepared beads were characterized with Fourier transform infrared spectroscopy, and pictures of the beads were determined with an optic microscope. The release studies were carried out at three pH values (1.2, 6.8, and 7.4) for 2 h. The effects of the preparation conditions, including the PVA/NaAlg (w/w) ratio, drug/polymer (w/w) ratio, and time of exposure to the crosslinker, on the release of NS were investigated for 10 h at 37°C. The release of NS decreased with the PVA/NaAlg (w/w) ratio and drug/polymer ratio increasing. At the end of 10 h, the highest release of NS was found to be 84% for the 1/2 PVA/NaAlg (w/w) ratio. The swelling measurements of the beads supported the release results. The release kinetics were described with Fickian and non-Fickian approaches.
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**Key words:** blends; drug delivery systems; hydrophilic polymers

## INTRODUCTION

In recent years, controlled release technology has shown important potential in the fields of medicine, pharmacy, and agriculture. Natural and synthetic biodegradable polymeric materials have been used in drug delivery systems.[1,2] Many research studies have contributed to the development of controlled release formulations, which depend on the nature of the synthetic polymer used.[3–6] Generally, natural polymers are preferred to synthetic polymers because of their low cost, free availability, nontoxicity, and biodegradability.[7,8] However, natural polymers have disadvantages, such as poor mechanical strength and uncontrolled water uptake.[6] These problems can be minimized by grafting[9,10] or blending[11–13] with other polymers.

Sodium alginate (NaAlg) is a biodegradable polymer that has been widely used in controlled release applications of pesticides[4,13–15] and drugs.[16–18] Pepperman and Kuan[4] studied the controlled release of alachor from alginate microspheres. Significant control of alachor release rates was obtained with the addition of linseed oil. Fernandez-Perez and coworkers[15] investigated the mobility of isoproturan from an alginate bentonite controlled release formulation in layered soil. They found that the use of the alginate bentonite controlled release formulation produced less vertical mobility of the active ingredient in comparison with the technical product. Işıklan[18] studied the controlled release of the insecticide carbaryl from NaAlg, NaAlg/gelatin blend, and NaAlg/sodium carboxymethylcellulose blend beads and found that the carbaryl release from the beads increased with the increase in the carbaryl/NaAlg ratio.

Poly(vinyl alcohol) (PVA) is also a suitable polymer for drug release because of desirable properties such as nontoxicity and noncarcinogenicity, and it has been used in many studies because of its biocompatibility.[19–22] However, it is difficult to prepare beads from this polymer because of its poor stability and bead-forming ability in an aqueous medium, so the blending technique can be considered a useful tool for the preparation of new alginate beads with PVA. PVA can strongly interact with NaAlg through hydrogen bonding on a molecular level. For this reason, NaAlg and PVA have been chosen for bead formation and successfully crosslinked with gluteraldehyde.[23–25]

Naproxen sodium (NS) is a nonsteroidal antiinflammatory drug with analgesic properties; however, gastrointestinal side effects such as bleeding, ulceration, and perforation have been commonly seen when this drug is used. For this reason, it is important to obtain prolonged or controlled drug delivery to improve the bioavailability or stability and to target the drug to a specific site.

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In this study, we aimed to prepare polymeric beads to obtain a release system for colon-specific drug delivery using NaAlg/PVA blend beads. Although there are several studies on controlled delivery for NS,[26–36] according to our literature survey, this study is pioneering in the release of NS with PVA/NaAlg blend beads.

## EXPERIMENTAL

### Materials

NaAlg (medium viscosity) was purchased from Sigma Chemical Co. (St. Louis, MO). PVA was supplied by Merck (Darmstadt, Germany). The molecular weight and degree of saponification of PVA were 72,000 and greater than 98%, respectively. NS was provided by Novartis (Summit, NJ) as a gift. A glutaraldehyde (GA; 25% w/w) solution, $Na_2HPO_4$, and $NaH_2PO_4$ were all supplied by Merck and were used as received.

### Preparation of the NaAlg beads

An NaAlg (2%, w/v) solution in distilled water was prepared by heating. Different amounts of NS were added and mixed with a magnetic stirrer. The polymer solution containing NS was added dropwise into a 2.5% GA and 3% hydrochloric acid (HCl) solution with a peristaltic pump (Masterflex, L/S Digital Economy Drive, Canada and USA). The formed beads were then removed from the crosslinking solution at selected time intervals of 5, 10, and 15 min. To remove the GA acid that adhered, beads were washed with water repeatedly and then dried completely in an oven at 40°C.

PVA/NaAlg blend beads were prepared in a similar way. Different blend ratios (w/w) and preparation conditions are presented in Table I. To estimate the size of the beads, 10 samples of completely dried beads from the different formulations were selected, and their sizes were measured with a micrometer screw gauge (Aldrich, Germany).

### Swelling of the beads

The equilibrium swelling degree of the crosslinked empty beads was determined by the gravimetric measurement of the extent of their swelling in buffer solutions of pHs 1.2, 6.8, and 7.4 at 37°C. To ensure complete equilibration, the samples were allowed to swell for 48 h. The excess surface-adhering liquid drops were removed by blotting. The swollen beads were weighed with an electronic balance (XB 220 A, Precisa, United States). The beads were then dried in an oven at 40°C until there was no change in the dried mass of the samples. The equilibrium swelling degree (%) was calculated as follows:

$$\text{Equilibrium swelling degree}(\%) = \frac{M_s - M_d}{M_d} \times 100 \quad (1)$$

where $M_s$ and $M_d$ are the masses of the swollen beads and dry beads, respectively.

### Determination of the NS content of the beads

A known mass of beads was crushed in an agate mortar with a pestle, and then polymeric powder was placed in a flask. Water (50 mL) was added and refluxed at 25°C for 1 h to ensure the complete extraction of NS from the beads. At the end of the hour, precipitated NaAlg was filtered, and NS was analyzed with an Unico 4802 ultraviolet–visible spectrophotometer at a wavelength of 271 nm with water as a blank. The entrapment efficiency (%) was then calculated as follows:

**TABLE I**
**Entrapment Efficiencies, Yields, and Bead Diameters for the NS-Loaded Beads**

| Formulation code | Polymer | Drug/polymer ratio (w/w) | Time of exposure to GA (min) | Entrapment efficiency (%) | Yield (%) | Bead diameter (mm) |
|---|---|---|---|---|---|---|
| A1 | NaAlg | 1/1 | 5 | 55 | 86 | 1.19 |
| A2 | NaAlg | 1/2 | 5 | 57 | 83 | 1.17 |
| A3 | NaAlg | 1/4 | 5 | 64 | 85 | 1.14 |
| A4 | NaAlg | 1/2 | 10 | 54 | 86 | 1.08 |
| A5 | NaAlg | 1/2 | 15 | 52 | 81 | 0.98 |
| B1 | PVA/NaAlg (2/1 w/w) | 1/1 | 5 | 63 | 90 | 0.77 |
| B2 | PVA/NaAlg (2/1 w/w) | 1/2 | 5 | 58 | 82 | 0.79 |
| B3 | PVA/NaAlg (2/1 w/w) | 1/4 | 5 | 55 | 81 | 0.76 |
| C1 | PVA/NaAlg (1/1 w/w) | 1/1 | 5 | 64 | 85 | 0.83 |
| C2 | PVA/NaAlg (1/1 w/w) | 1/2 | 5 | 67 | 87 | 0.81 |
| C3 | PVA/NaAlg (1/1 w/w) | 1/4 | 5 | 65 | 86 | 0.78 |
| D1 | PVA/NaAlg (1/2 w/w) | 1/1 | 5 | 68 | 84 | 0.96 |
| D2 | PVA/NaAlg (1/2 w/w) | 1/2 | 5 | 70 | 80 | 0.93 |
| D3 | PVA/NaAlg (1/2 w/w) | 1/4 | 5 | 69 | 83 | 0.85 |

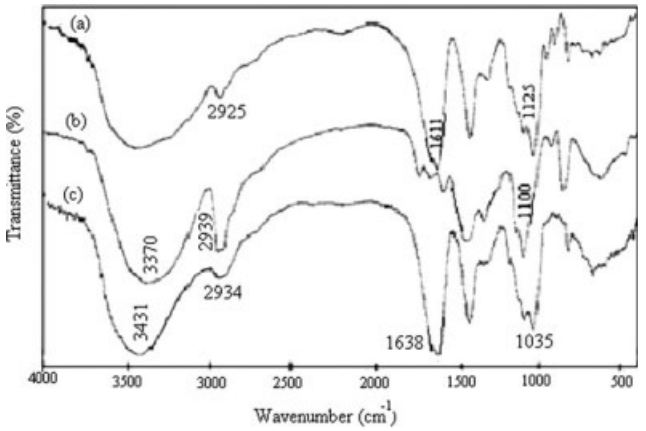



**Figure 1** FTIR spectra of (a) NaAlg, (b) PVA, and (c) PVA/NaAlg blend beads.

$$\text{Entrapment efficiency}(\%) = \frac{\text{Practical NS loading}}{\text{Theoretical NS loading}} \times 100 \quad (2)$$

### Fourier transform infrared (FTIR) measurements

FTIR spectra of the beads and polymer samples were taken with a Mattson 1000 FTIR spectrometer (Welwyn Garden, England).

### Micrographs of the beads

Pictures of the beads were observed with a Leica L2 optic microscope (USA).

### *In vitro* NS release

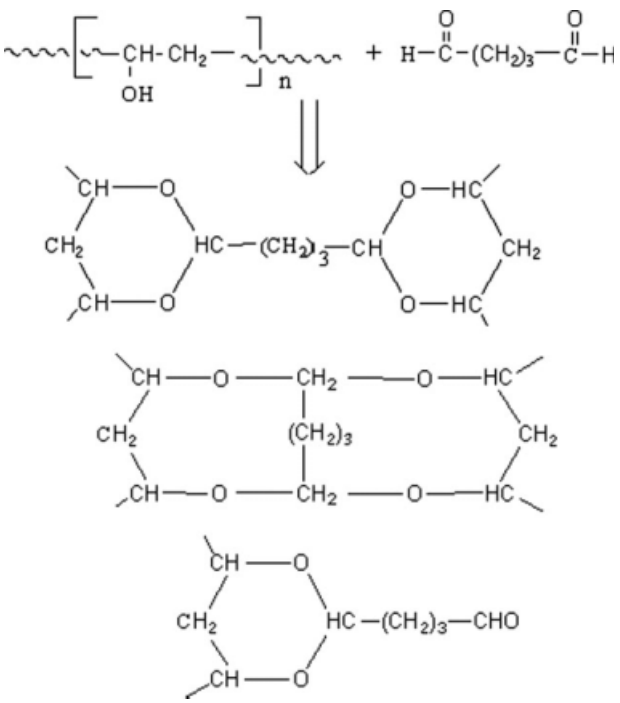
*In vitro* drug release from the beads was studied in a 250-mL HCl solution (pH 1.2) and phosphate buffer solutions (pHs 6.8 and 7.4), and the beads were incubated in a shaking water bath (BS-21, Medline, Hwaseong, Korea) at 37°C at a speed of 50 rpm. At 2-h intervals, the pH of the medium was changed (1.2, 6.8, and 7.4). At specific time intervals, the NS content was determined with an ultraviolet spectrophotometer at 271 nm. The analyzed solution was added back to the dissolution medium to maintain a constant volume. From the absorbance values, the cumulative released amount (%)was determined. All experiments were performed in triplicate to minimize the variation error. The average values were used for further data treatment and plotting.

## RESULTS AND DISCUSSION

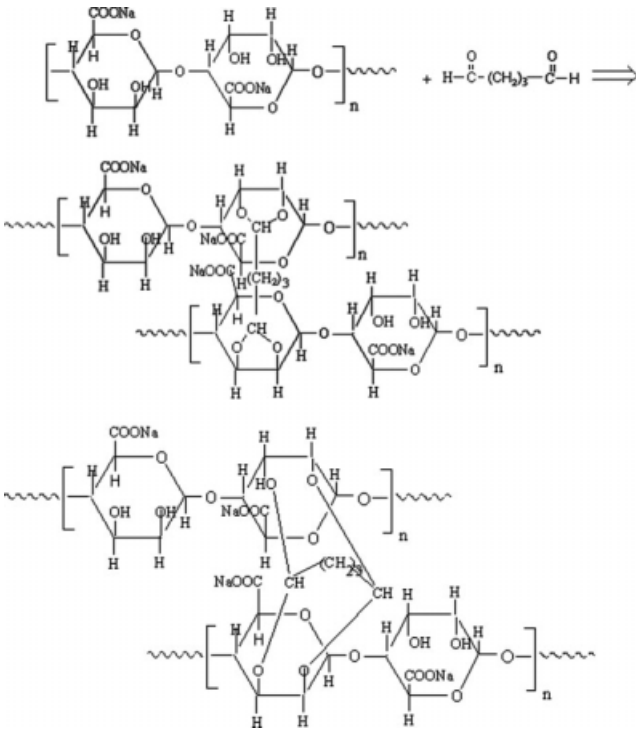
### Characterization of the microspheres

The FTIR spectra of NaAlg, PVA, and empty PVA/NaAlg blend beads are shown in Figure 1. A broad band between 3000 and 3500 $cm^{-1}$ can be attributed to —OH stretching vibrations in the spectrum of NaAlg. This band can be seen at 3370 and 3431 $cm^{-1}$ for PVA and empty PVA/NaAlg blend beads, respectively. The peak at 1611 $cm^{-1}$ in the spectrum of NaAlg is due to the stretching band of carbonyl stretching (C=O). A broad characteristic peak at 1638 $cm^{-1}$ is due to C=O of the NaAlg polymeric chain and the unhydrolyzed part in PVA in the blend. In the spectra of NaAlg, PVA, and PVA/NaAlg, stretching bands of the C—H group at 2925, 2939, and 2934 $cm^{-1}$, respectively, appear. A sharp band at 1125 $cm^{-1}$ corresponds to C—O—C symmetrical stretching (in the acetyl group) present on the PVA backbone because of the unhydrolyzed acetate groups of poly(vinyl acetate). As shown in Figure 1, the —OH peak corresponding to PVA/NaAlg crosslinked blend beads is narrower than that of uncrosslinked NaAlg and PVA and is evidence of crosslinking. Possible reaction mechanisms for the crosslinking of PVA and NaAlg are presented in Schemes 1 and 2.

The FTIR spectra of NS, NS-loaded PVA/NaAlg, and empty PVA/NaAlg beads were also taken, and they are presented in Figure 2. Most of the peaks belonging to NS can be seen in the spectrum of the NS-loaded beads, and this shows that there might be no interaction or a very weak interaction between the drug and the polymeric bead. The band at 2960 $cm^{-1}$ is due to the absorption of —$CH_3$ in the spectrum of NS. This band can be seen at 2950 $cm^{-1}$ in Figure 2(b). The bands at 3435 and 3453 $cm^{-1}$ can be attributed to




**Scheme 1** Expected reaction mechanism of PVA with GA.



**Scheme 2** Expected reaction mechanism of NaAlg with GA.

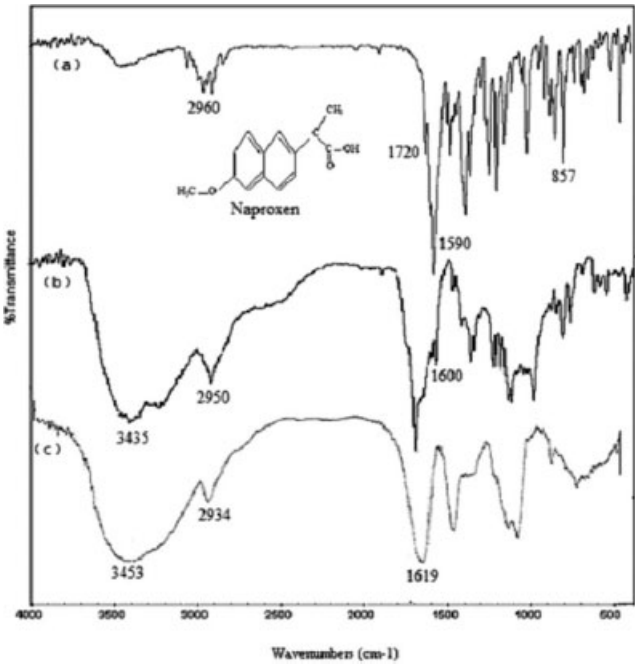



**Figure 2** FTIR spectra of (a) NS, (b) NS-loaded, and (c) empty PVA/NaAlg beads.

the hydroxyl group in Figure 2(b,c), respectively. The peaks at 1720, 1600, and 1619 $cm^{-1}$ can be attributed to the C═O stretching vibration in Figure 2(a–c), respectively. The band at 857 $cm^{-1}$ is due to the C—O—C group.

The shapes of dried empty PVA/NaAlg beads and NS-loaded PVA/NaAlg beads are shown in Figure 3. As reflected by the figure, both empty and NS-loaded beads almost maintain a spherical form under various conditions.

To understand the extent of crosslinking of the polymer, it is necessary to calculate the molar mass between the crosslinks of the polymer ($M_C$). $M_C$ can be calculated from the equilibrium swelling volume of the polymer in a solvent.[37]

The degree of crosslinking of the polymer beads can be calculated with the Flory–Rehner equation:

$$M_C = -\delta_p V_S \phi^{1/3} \left[\ln(1-\phi) + \phi + \chi\phi^2\right]^{-1} \quad (3)$$

where $\delta_p$ is the polymer density, $V_S$ is the molar volume of the solvent, and $\phi$ is the volume fraction of the polymer in the swollen state, and it can be calculated as follows:

$$\phi = \left[1 + \frac{\delta_P}{\delta_S}\left(\frac{M_a}{M_b}\right) - \frac{\delta_P}{\delta_S}\right]^{-1} \quad (4)$$

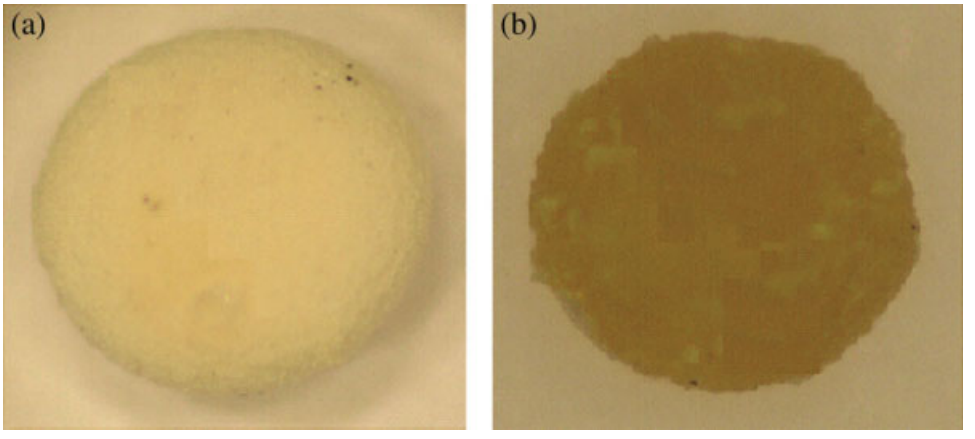



**Figure 3** Microscopic pictures of (a) empty PVA/NaAlg and (b) NS-loaded PVA/NaAlg beads. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

**TABLE II**
**Values of $N$, $\Phi$, $\chi$, and $M_C$ of NS-Containing Polymer Beads Calculated with Eq. (3)**

| Formulation code | Polymer | Drug/polymer ratio (w/w) | Time of exposure to GA (min) | $N$ | $\Phi$ | $\chi$ | $M_C$ |
|---|---|---|---|---|---|---|---|
| A1 | NaAlg | 1/1 | 5 | −1.2930 | 0.1649 | 0.5472 | 1559 |
| A2 | NaAlg | 1/2 | 5 | −1.2850 | 0.1687 | 0.5446 | 1643 |
| A3 | NaAlg | 1/4 | 5 | −1.1654 | 0.1897 | 0.6215 | 1691 |
| A4 | NaAlg | 1/2 | 10 | −1.2647 | 0.1987 | 0.6346 | 1732 |
| A5 | NaAlg | 1/2 | 15 | −1.2298 | 0.1886 | 0.6450 | 1852 |
| B1 | PVA/NaAlg (2/1 w/w) | 1/1 | 5 | −1.2147 | 0.2065 | 0.6654 | 2654 |
| B2 | PVA/NaAlg (2/1 w/w) | 1/2 | 5 | −1.2098 | 0.2198 | 0.7352 | 2580 |
| B3 | PVA/NaAlg (2/1 w/w) | 1/4 | 5 | −1.2015 | 0.2064 | 0.7215 | 2514 |
| C1 | PVA/NaAlg (1/1 w/w) | 1/1 | 5 | −1.2165 | 0.1954 | 0.5645 | 2054 |
| C2 | PVA/NaAlg (1/1 w/w) | 1/2 | 5 | −1.1954 | 0.2098 | 0.6451 | 2168 |
| C3 | PVA/NaAlg (1/1 w/w) | 1/4 | 5 | −1.2068 | 0.1957 | 0.6120 | 2212 |
| D1 | PVA/NaAlg (1/2 w/w) | 1/1 | 5 | −1.2238 | 0.2057 | 0.7115 | 1885 |
| D2 | PVA/NaAlg (1/2 w/w) | 1/2 | 5 | −1.2158 | 0.2759 | 0.7654 | 1916 |
| D3 | PVA/NaAlg (1/2 w/w) | 1/4 | 5 | −1.2089 | 0.3005 | 0.7102 | 1964 |

$\Phi$, volume fraction of the polymer in the swollen state.

where $\delta_P$ and $\delta_S$ are the densities of the polymer and solvent, respectively, and $M_a$ and $M_b$ are the masses of the polymer before and after swelling, respectively. $V_S$ is the molar volume fraction of the polymer in the swollen state.

The interaction parameter ($\chi$) can be calculated with the Flory–Rehner equation:[38]

$$\chi = \left[\phi(1-\phi)^{-1} + N\ln(1-\phi) + N\phi\right] \cdot \left[2\phi - \phi^2 N - \phi^2 T^{-1}\left(d\phi \Big/ dT\right)\right]^{-1} \quad (5)$$

where $N = (\phi^{2/3}/3 - 2/3)(\phi^{1/3} - 2\phi/3)^{-1}$ and $T$ is the temperature (K).

$M_C$ values calculated for the NS-loaded beads are presented in Table II. When the crosslinking of the polymer increases, the rate of diffusion of NS through the beads decreases.

The results for the bead diameter, entrapment efficiency (%), and bead yield (%) are shown in Table I. The beads that formed had particle diameters ranging from 0.76 to 1.19 mm. The size of the beads changed with the PVA/NaAlg (mol/mol) ratio. In general, the diameters of the NaAlg beads were much larger than those of the PVA/NaAlg beads, and as the NaAlg content of the beads increased, the bead diameter increased with the same drug/polymer ratio. The entrapment efficiency percentage, bead yield, and bead diameter were slightly affected by the increase in the NS/polymer ratio. With increasing time of exposure to the crosslinking agent, the entrapment efficiency percentage decreased. Similar results can be observed in the literature. Şanlı et al.[25] prepared PVA/NaAlg and PVA-grafted polyacrylamide/NaAlg blend microspheres for the delivery of diclofenac sodium. They also observed that the entrapment efficiency, bead yield, and bead diameter increased with the drug/polymer ratio increasing.

### Effect of the PVA/NaAlg blend ratio on the release of NS

The *in vitro* release of NS from crosslinked PVA/NaAlg beads was studied in gastric, input intestinal, and intestinal pH conditions at 37°C. Figures 4–6 show the cumulative NS release of beads with different PVA/NaAlg ratios [NS/polymer ratios (w/w): 1/1, 1/2, and 1/4]. The figures show that there was no release of NS under gastric conditions and that release was higher under intestinal conditions than under the input intestinal conditions; also, the release rate of NS beads was much higher for NaAlg beads than for PVA/NaAlg beads. The maximum cumulative NS release of 84% was obtained with NaAlg beads at the end of 10 h with a 1/4 drug/polymer ratio. The lowest cumulative NS release of 16.6% was found with 2/1 PVA/NaAlg beads with a 1/1 drug/polymer ratio. Moreover, as the blend ratio (PVA/

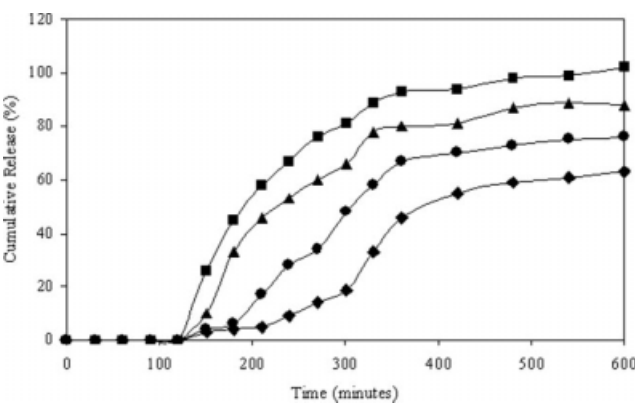



**Figure 4** Effect of the PVA/NaAlg ratio on NS release (drug/polymer ratio = 1/4, concentration of GA = 2.5%, time of exposure to GA = 15 min): (◆) 2/1 PVA/NaAlg, (●) 1/1 PVA/NaAlg, (▲) 1/2 PVA/NaAlg, and (■) NaAlg.

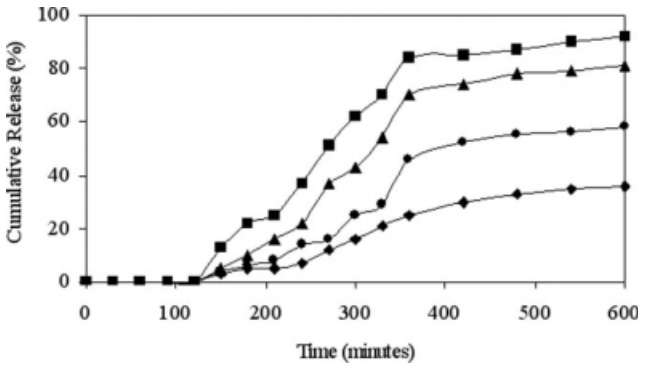



**Figure 5** Effect of the PVA/NaAlg ratio on NS release (drug/polymer ratio = 1/2, concentration of GA = 2.5%, time of exposure to GA = 15 min): (◆) 2/1 PVA/NaAlg, (●) 1/1 PVA/NaAlg, (▲) 1/2 PVA/NaAlg, and (■) NaAlg.

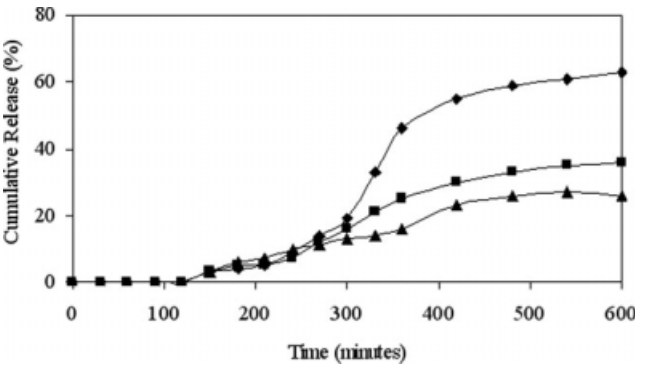



**Figure 7** Effect of the drug/polymer ratio on NS release (PVA/NaAlg ratio = 2/1, concentration of GA = 2.5%, time of exposure to GA = 15 min): (◆) 1/4, (■) 1/2, and (▲) 1/1.

NaAlg) increased from 1/2 to 2/1, the release of NS decreased.

Alginate is a natural water-soluble polymer and contains hydroxyl and carboxyl groups, which impart hydrophilicity to the molecule. On the other hand, PVA is virtually a linear polymer with a small hydrated volume in comparison with alginate, and thus PVA produces a compact network of macromolecular chains in the blend beads. The diffusion of a drug to an external medium is difficult in comparison with the NaAlg beads. Similar observations were found in the literature.[25,39] Bajpai and Giri[39] reported the graft copolymerization of crosslinked polyacrylamide chains onto carboxymethylcellulose and PVA. They observed that the swelling degree and $KNO_3$ release of the prepared macromolecular network decreased with the PVA content.

### Effect of the NS/polymer ratio on the NS release

Another parameter that affects the release of NS from the beads is the drug/polymer ratio. The effect of the drug/polymer ratio on the release of NS is shown in Figures 7–9. The figures show that the cumulative release of NS beads increases with the NS/polymer ratio decreasing from 1/1 to 1/4. A lower NS content might lead to the easier penetration of liquid through beads, and then faster NS diffusion would occur from the beads. In addition, while the NS content of the beads decreases, a loose structure in the polymeric beads forms; the liquid and NS can easily penetrate it and diffuse into it. Similar results were found in the literature.[29] Veronese et al.[29] prepared polyorganophosphazene microspheres for naproxen release. They reported that the lowering of the release rate as the drug content decreases seems to indicate that diffusion through the polymer is the main process in naproxen release. Kumbar and Aminabhavi[40] investigated the controlled release of indomethacin from polyacrylamide-grafted chitosan microspheres. They reported that drug release at lower loadings is quicker than that at higher loadings because of the possibility of the formation of a large pore volume, which might enhance drug release.

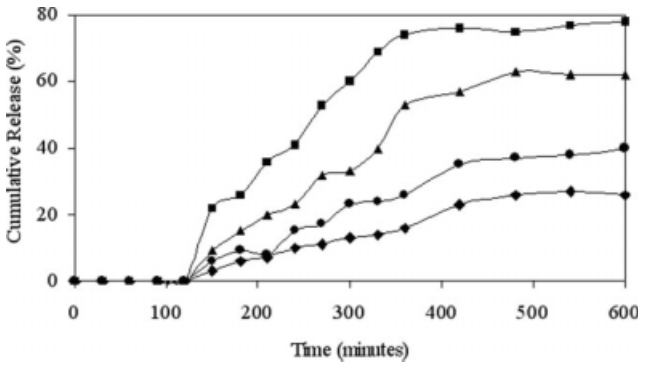



**Figure 6** Effect of the PVA/NaAlg ratio on NS release (drug/polymer ratio = 1/1, concentration of GA = 2.5%, time of exposure to GA = 15 min): (◆) 2/1 PVA/NaAlg, (●) 1/1 PVA/NaAlg, (▲) 1/2 PVA/NaAlg, and (■) NaAlg.

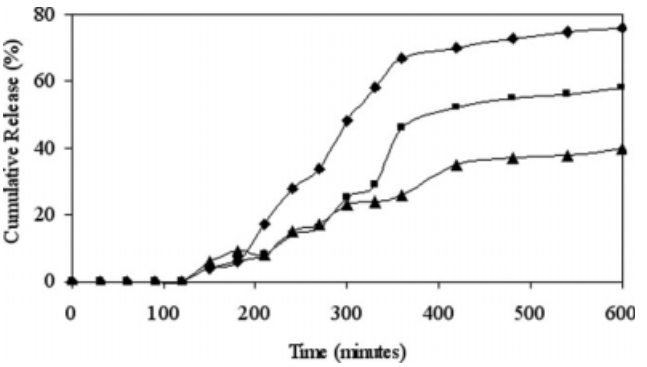



**Figure 8** Effect of the drug/polymer ratio on NS release (PVA/NaAlg ratio = 1/1, concentration of GA = 2.5%, time of exposure to GA = 15 min): (◆) 1/4, (■) 1/2, and (▲) 1/1.

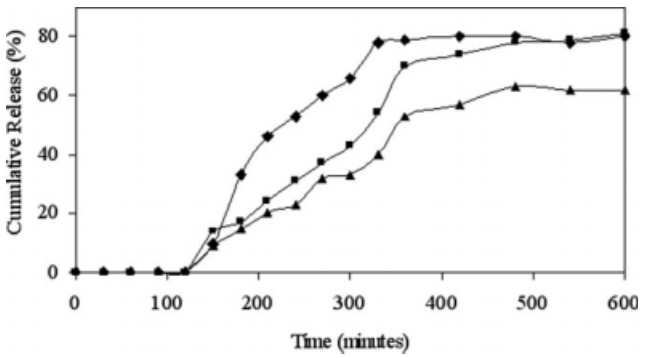



**Figure 9** Effect of the drug/polymer ratio on NS release (PVA/NaAlg = 1/2, concentration of GA = 2.5%, time of exposure to GA = 15 min): (◆) 1/4, (■) 1/2, and (▲) 1/1.

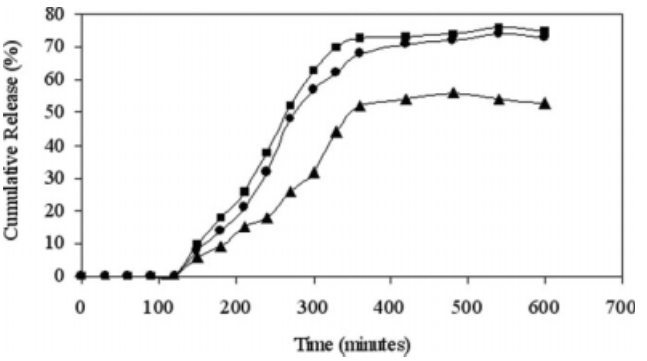



**Figure 10** Effect of the exposure time on NS release (PVA/NaAlg ratio = 1/2, drug/polymer ratio = 1/4, concentration of GA = 2.5%): (■) 5, (●) 10, and (▲) 15 min.

### Effect of the exposure time to GA on the NS release

The release of NS from beads was subjected to a number of physical and chemical parameters, including those related directly to the release medium (water), release conditions (pH and temperature), and preparation conditions and those resulting from changes in the characteristics of the beads. One of the most effective ways of changing the release of beads is to change the crosslinking density of the matrix by the use of various times of exposure to the crosslinking agent. The effect of the time of exposure to GA on the release rate of NS was investigated through the variation of the time of exposure to GA (5, 10, and 15 min). The results are given in Figure 10, which clearly indicates that with increasing exposure time to GA (5–15 min), the cumulative release decreased. Because of that, increasing the exposure time to GA resulted in an increase in the crosslink density of the beads, which gave rise to a compact network of macromolecular chains. The maximum NS release from the 1/2 PVA/NaAlg beads, which were prepared with an exposure time of 5, was found to be 84%.

NS release results were also supported by swelling measurements. Equilibrium swelling experiments were performed in distilled water and in buffer solutions of different pH values (1.2, 6.8, and 7.4) for various empty bead formulations and are presented in Table III. As shown in Table III, decreases in the pH values decreased the swelling percentage. At low pH values, alginate was protonated into insoluble forms of alginic acid; this displayed properties of swelling that explained the small amount of NS released in the first 2 h.

### Analysis of the kinetic results

The event of solvent sorption by a microsphere depends mechanistically on the diffusion of water molecules into the gel matrix and the subsequent relaxation of macromolecular chains of the microsphere.[41] The release data of all the systems were further substantiated by the fitting of the fraction release data ($M_t/M_\infty$, where $M_t$ is the amount of NS released at time $t$ and $M_\infty$ is the drug released at equilibrium time) to an empirical equation proposed by Peppas.[42]

$$kt^n = \frac{M_t}{M_\infty} \tag{6}$$

where $k$ is a constant characteristic of the drug–polymer system and $n$ is the diffusional exponent, which suggests the nature of the release mechanism. Fickian release is defined by an initial $t^{1/2}$ time dependence of the fractional release for slabs, cylinders, and spheres. Analogously, case II transport is defined by an initial linear time dependence of the fractional release for all geometries.[43] A value of $n$;0.5 indicates Fickian transport (mechanism), whereas $n$;1 indicates case II or non-Fickian transport (swelling-controlled).[44] The intermediate values ranging from 0.5 to 1.0 are indicative of anomalous transport. The least-squares estimations of the fractional release

**TABLE III**
**Equilibrium Swelling Degree for the Beads**

| Formulation code | Water | pH 1.2 | pH 6.8 | pH 7.4 |
|---|---|---|---|---|
| A | 1412 ± 1.42 | 112.13 ± 2.07 | 1388.13 ± 1.58 | 1485.83 ± 3.26 |
| B | 101.73 ± 2.06 | 80.87 ± 1.56 | 102.10 ± 3.55 | 128.57 ± 4.30 |
| C | 114.27 ± 1.29 | 89.43 ± 1.12 | 113.50 ± 7.33 | 134.03 ± 1.80 |
| D | 120.20 ± 2.42 | 96.33 ± 2.07 | 119.07 ± 1.56 | 134.40 ± 5.07 |

**TABLE IV**
**Results of *k*, *n*, and *r* Calculated with Eq. (6)**

| Formulation code | $k$ ($\times 10^2$ $min^{-n}$) | $n$ | $r$ | Diffusion mechanism |
|---|---|---|---|---|
| A1 | 0.0073 | 0.8111 | 0.9663 | Anomalous transport |
| A2 | 0.0120 | 0.7328 | 0.9690 | Anomalous transport |
| A3 | 0.0180 | 0.6766 | 0.9875 | Anomalous transport |
| A4 | 0.0198 | 0.6654 | 0.9786 | Anomalous transport |
| A5 | 0.0234 | 0.6578 | 0.1076 | Anomalous transport |
| B1 | 0.0008 | 0.9064 | 0.9910 | Anomalous transport |
| B2 | 0.0008 | 0.9307 | 0.9924 | Anomalous transport |
| B3 | 0.0020 | 0.8108 | 0.9934 | Anomalous transport |
| C1 | 0.0007 | 1.0319 | 0.9970 | Case II |
| C2 | 0.0005 | 1.1238 | 0.9963 | Case II |
| C3 | 0.0038 | 0.7982 | 0.9933 | Anomalous transport |
| D1 | 0.0004 | 1.2652 | 0.9931 | Case II |
| D2 | 0.0007 | 1.1237 | 0.9963 | Case II |
| D3 | 0.0002 | 1.3680 | 0.9980 | Case II |

data along with the estimated correlation coefficient ($r$) values are presented in Table IV. According to these data, the value of $n$ ranged from 0.6578 to 1.3680, indicating that NS from the microspheres slightly deviates from Fickian transport.

## CONCLUSIONS

Studies of NS release from beads prepared from PVA/NaAlg blends crosslinked with GA indicate that the blending of PVA with NaAlg polymers leads to a decrease in the release rate of NS, which is an important factor in controlled release formulations, but increases the entrapment efficiency. It has also been observed that the release of NS is much higher at high pH values versus low pH values, and this shows that the release system is interesting as a controlled release system for colon-specific drug delivery. In addition, NS release from the beads increases with increasing NaAlg content. The highest NS release was found to be 84% for a PVA/NaAlg blend ratio of 1/2 and a drug/polymer ratio of 1/4.

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