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pH Sensitive Interpenetrating Network Microgels of Sodium Alginate-Acrylic Acid for the Controlled Release of Ibuprofen

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ABSTRACT: pH-Sensitive interpenetrating network (IPN) microgels (MGs) of sodium alginate (NaAlg) and acrylic acid have been prepared by using water-in-oil (W/O) emulsion technique. The MGs were characterized by Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), X-ray diffractometer (X-RD). The release of ibuprofen (IB), an anti-inflammatory drug, from these MGs was studied in pH 1.2 and 7.4 media. MG network consists of NaAlg, which disintegrates in the intestinal fluid, while poly(acrylic acid) provides pH-sensitivity to the

microgel network. The system developed in this study showed a pH-sensitivity for the release of IB, which was attributed to the diffusion controlled release of the drug through the surfaces of MGs that undergo disintegration after swelling, depending upon the chemical composition of MGs and pH of the medium. © 2005 Wiley Periodicals, Inc. *J Appl Polym Sci* 99: 2671–2678, 2006

Key words: sodium alginate; acrylic acid; IPNs; drug delivery

INTRODUCTION

Biodegradable polymers have been extensively used to develop controlled release (CR) formulations^{1–3} to decrease the release rates of the drugs having short plasma life. Among the various polymers employed, hydrophilic biopolymers are quite suitable in oral applications⁴ due to their inherent advantages over the synthetic polymers. Sodium alginate (NaAlg), a natural polysaccharide, composed of D-mannuronic acid and D-guluronic acid is derived from brown seaweeds. This polysaccharide has been used extensively in food industry as a gelling agent and for encapsulation of living cells.^{5–7} NaAlg is a biodegradable polymer that has been used in drug delivery applications.^{8–10} Earlier literature cites many applications of NaAlg in agriculture^{11–13} after when it is crosslinked with glutaraldehyde. From a search of the literature, we find no studies on the use of NaAlg and acrylic acid for the CR of nonsteroidal anti-inflammatory (NASID) drugs. This prompted us to undertake a detailed study on the CR of ibuprofen (IB), a water insoluble drug. Pure IB is a nonsteroidal anti-inflammatory drug used extensively in the treatment of various musculo-skeletal disorders and painful condi-

tions. The drug has proven its therapeutic efficacy, tolerability, and safety in the treatment of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis for the quick relief of pain.¹⁴ However, its short plasma half-life of 1–3 h following oral dosing¹⁵ necessitates frequent administration to maintain the desired constant levels. IB can be readily absorbed throughout the gastro-intestinal tract and can be eliminated rapidly after administration. In this research, we have developed the CR, formulations of IB with NaAlg and acrylic acid. Earlier, CR of antihypertensive drugs through the tableted microspheres of cellulose derivatives have been reported.^{16–18} In continuation of our ongoing program of research,^{19,16} we report here the in vitro CR data for IB through the interpenetrating network (IPN) of microgels (MGs) prepared from NaAlg and acrylic acid in different compositions. Effect of acrylic acid content, crosslinking agent, and drug concentration on the release rates of IB has been investigated.

EXPERIMENTAL

Materials and methods

Acrylic acid, sodium alginate (low viscosity), potassium persulfate, light paraffin oil, and glutaraldehyde (25% aqueous solution; GA) were purchased from s.d. Fine Chemicals, Mumbai, India. Tween-80 was purchased from Sigma Chemical Co. Ibuprofen (purity

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97.94%) was obtained from Waksman Salesman Pharmaceuticals (Anantapur, India).

Synthesis of sodium alginate-acrylic acid (NaAlg-g-AA) IPNs

NaAlg-Acrylic acid IPN, hereafter designated as NaAlg-AA, was prepared by mixing NaAlg with acrylic acid, using potassium persulfate ($K_2S_2O_8$) as an initiator. In brief, 2% aqueous solution of NaAlg was prepared by dissolving NaAlg in water overnight, under constant stirring. The solution was degassed by passing nitrogen gas for 30 min. To this solution, different amounts of acrylic acid were added and stirred thoroughly for 1 h. The initiator solution containing 50 mg of $K_2S_2O_8$ was added to the earlier mentioned mixture and stirred for 1 h at 40°C under vacuum pressure of 10 Torr.

The final polymerization mixture was emulsified into liquid paraffin to form a water-in-oil (w/o) emulsion at 400 rpm using Eurostar (IKA Labortechnik, Germany) high-speed stirrer for 30 min in a separate 500 mL beaker containing 100 mL of light liquid paraffin oil, 2% (w/v) of Tween-80, 1 mL of 0.1M HCl, and the required amount of GA. The MGs formed were filtered, washed repeatedly with hexane and water to remove the oil as well as excess amount of surfactant and unreacted GA, respectively. These MGs were dried under vacuum at 40°C and stored in a desiccator before further analysis. First, MGs with different extent of crosslinking were prepared by taking 2.5, 5.0, and 7.5 mL of GA with 10% of AA and 25% of drug. These are designated as NaAlg-AA (GA1), NaAlg-AA (GA2), and NaAlg-AA (GA3). Secondly, MGs were prepared by varying the amount of AA (i.e., 10, 20, and 30%) and pure NaAlg with 5 mL of GA and 25% of drug, which are designated as NaAlg-AA (GA2), NaAlg-AA (20), NaAlg-AA (30), and NaAlg-AA (00), respectively. In the third set of experiments, MGs were prepared by varying the amount of drug, i.e., 25, 50, and 75% with 10% of AA and 5 mL of GA; these are designated as NaAlg-AA (GA2), NaAlg-AA (IB1), and NaAlg-AA (IB2), respectively. All the eight formulations were prepared by varying three parameters viz., amount of AA, extent of drug loading, and extent of crosslinking.

Fourier transform infrared spectroscopy

Fourier transform infrared spectroscopy (FTIR) spectral measurements were performed using Nicolet spectrophotometer (Model Impact 410) to confirm the presence of crosslinking in NaAlg-AA. The IPN particles were finely ground with KBr to prepare the pellets under a hydraulic pressure of 392.2 dynes/cm² and spectra were scanned between 400 and 4000 cm⁻¹.

Differential scanning calorimetry studies

Differential scanning calorimetry (DSC) curves of the placebo NaAlg-AA MGs, plain drug and drug-loaded MGs were recorded using Rheometric Scientific differential scanning calorimeter (Model-DSC SP, UK). The analysis was performed by heating the samples at the rate of 10°C/min under inert atmosphere.

X-RD studies

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

Particle size analysis

Particle size of the microspheres was measured by using a particle size analyzer (Mastersizer 2000, Malvern Instruments, UK). About 500 mg of MGs were transferred to the dry sample holder and stirred vigorously to avoid the agglomeration of particles during measurements. For measurement of sizes of different formulations/batches, the sample holder was cleaned by vacuum. The particle size was also measured using optical microscopy.

Estimation of drug loading and encapsulation efficiency

Specific amount of dry MGs were vigorously stirred in a beaker containing 10 mL of ethanol to extract the drug from the MGs of IPN. A 10 mL of 7.4-pH phosphate buffer containing 0.02% Tween-80 was added to the earlier mentioned solution to make the drug soluble, and ethanol was evaporated with gentle heating and continuous shaking. The aqueous solution was then filtered and assayed using a UV spectrophotometer (model Anthelie, Secomam, Dumont, France) at the fixed λ_{\max} value of 224 nm. The results of % drug loading and encapsulation efficiency were calculated using eqs. (1) and (2) and these data are compiled in Tables I and II, respectively.

% Drug loading

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

% Encapsulation efficiency

$$= \left(\frac{\text{Actual loading}}{\text{Theoretical loading}} \right) \times 100 \quad (2)$$

TABLE I
Results of % of Encapsulation Efficiency and Mean Size of the IPN MGs with 5 mL GA and at Stirring Speed of 400 rpm

Formulation codes	AA in microspheres (%)	Ibuprofen loaded (%)	Encapsulation efficiency (%)	Mean particle size (μm) \pm SD
NaAlg-AA 00	—	25	50.36	45 \pm 1.9
NaAlg-AA GA2	10	25	51.85	81 \pm 0.6
NaAlg-AA IBI	10	50	76.68	126 \pm 1.5
NaAlg-AA IB2	10	75	83.82	167 \pm 2.3
NaAlg-AA 2	20	25	58.07	90 \pm 0.4
NaAlg-AA 3	30	25	62.67	153 \pm 1.1

SD, Standard deviation.

In vitro release study

Dissolution was carried out using the Tablet dissolution tester (LabIndia, Mumbai, India) equipped with eight baskets. Dissolution rates were measured at 37°C under 100 rpm speed. Drug release from the MGs was studied in both the simulated gastric (0.1N HCl) and intestinal (7.4 pH phosphate buffer) fluids. At regular intervals of time, aliquot samples were withdrawn and analyzed using UV spectrophotometer (Model Anthelie, Secomam, Dumont, France) at the fixed λ_{max} value of 224 nm.

RESULTS AND DISCUSSION

Fourier transform infrared spectroscopy

In case of NaAlg, a characteristic broad peak appearing at 3456 cm^{-1} corresponds to O—H stretching vibrations of NaAlg. A sharp peak at 1610 cm^{-1} corresponds to the carbonyl group of —COONa moiety present in NaAlg. The peak at 1103 cm^{-1} is attributed to C—O stretching mode in PAA, while the peak at 810 cm^{-1} is due to the O—H out of plane motion of the carboxylic acid group in PAA.^{20,21} During crosslinking, GA might have reacted with —OH groups of IPN through the formation of ether linkages (Fig. 1a). Hence, the appearance of a peak at 1263 cm^{-1} in the spectra of crosslinked microspheres confirms the formation of more ether linkages. This is further supported by the presence of a sharp high intensity peak due to —CH₂ group of alkyl chain as a result of crosslinking. The acetal ring formation is a further test of crosslinking of hydroxyl groups of the polymer

with aldehydes of GA, which is shown by the peak observed at 1263 cm^{-1} .

Differential scanning calorimetry

DSC tracings of pure IB, drug-loaded NaAlg-AA MGs, and plain NaAlg-AA MGs are displayed in Figure 2. Melting peak of IB was observed at 78°C, but in case of drug-loaded and plain NaAlg-AA particles, a broad peak was observed in the range of 50–80°C. However, there is no characteristic peak of IB in the drug-loaded IPN MGs, suggesting that drug is molecularly dispersed in the polymer matrix. The observed endothermic peak was close to the reported²² melting temperature, i.e., 75–78°C of IB.

X-ray diffraction (X-RD) studies

X-RD analyses can provide a clue about crystallinity of the drugs in crosslinked MGs. X-RD patterns recorded for plain IB (a), IB-loaded MGs (b), and placebo MGs (c) are presented in Figure 3. Here, IB peaks observed at 2θ of 16, 20, and 22° are due to the crystalline nature of IB. These peaks are not found in the IB-loaded MGs and in plain placebo MGs. This indicates that drug particles are dispersed at molecular level in the polymer matrices since no indication about the crystalline nature of the drugs was observed in the drug-loaded MGs.

Laser particle size analyzer

Results of the mean particle size with standard errors are presented in Table I, while the size distribution

TABLE II
Results of %Encapsulation Efficiency and Mean Size of IPN MGs with Different Amount of Crosslinking Agent for 10% AA and 25% of Drug

Formulation codes	Crosslinking agent (GA in mL)	Ibuprofen loaded (%)	Encapsulation efficiency (%)	Mean particle size (μm) \pm SD
NaAlg-AA GA1	2.5	25	48.36	113 \pm 1.7
NaAlg-AA GA2	5.0	25	51.85	81 \pm 0.6
NaAlg-AA GA3	7.5	25	62.19	58 \pm 1.2

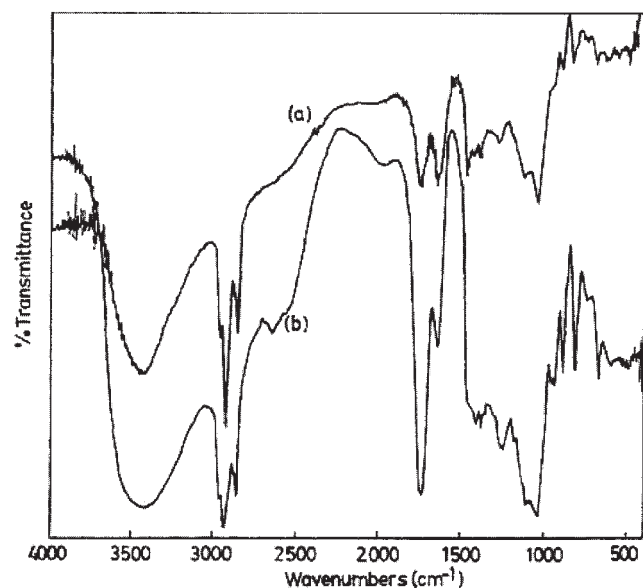


Figure 1 FTIR spectra of (a) NaAlg-AA crosslinked with glutaraldehyde and (b) NaAlg-AA uncrosslinked.

curve for a typical formulation containing 10% AA, 25% IB, and 5 mL of NaAlg-AA (GA2) is displayed in Figure 4. It is obvious that the size distribution is narrow and volume mean diameter of IPN MGs is found to be $178 \mu\text{m}$. However, 90% of population has the size range between 176 and $269 \mu\text{m}$; these results are comparable with the size measurements done by optical microscope. Particle size of different formulations containing different amount of drug, GA, and different amount of AA are presented in Tables I and II.

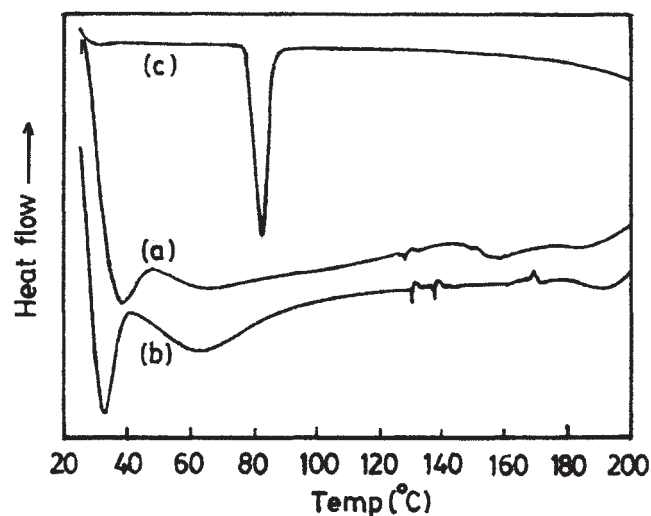


Figure 2 DSC thermograms of (a) plain NaAlg-AA MGs (b) drug-loaded NaAlg-AA MGs, and (c) Ibuprofen.

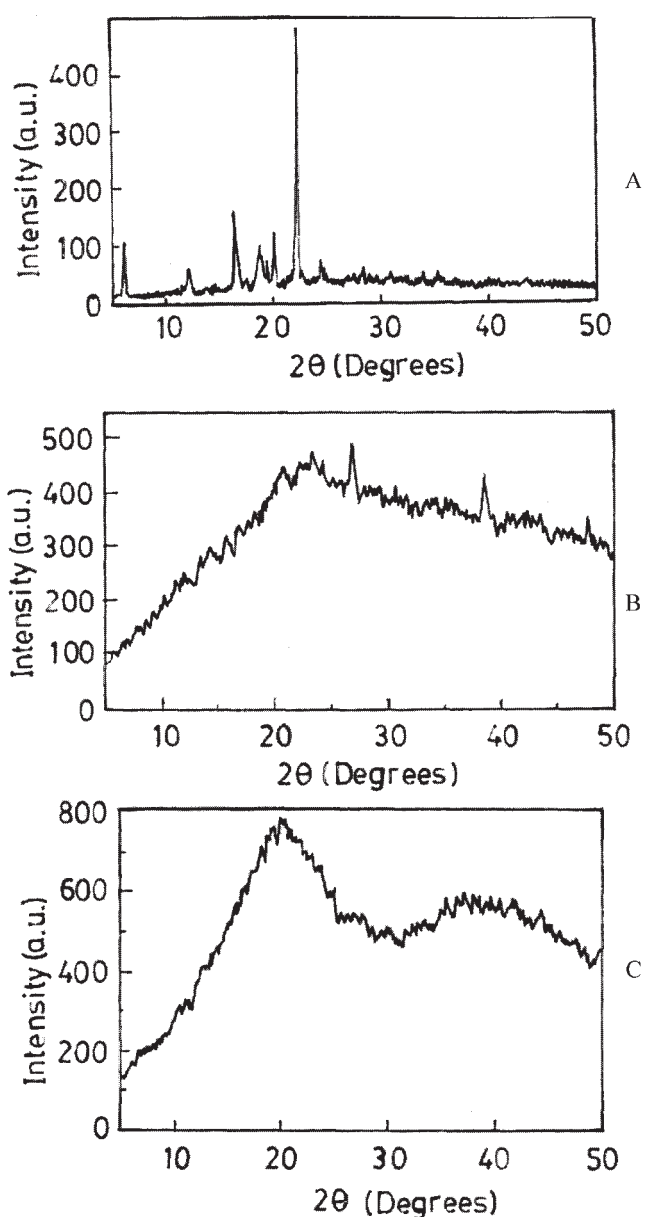


Figure 3 X-RD spectra plain NaAlg-AA IPN MGs (a) plain Ibuprofen, (b) IB loaded NaAlg-AA, and (c) plain NaAlg-AA.

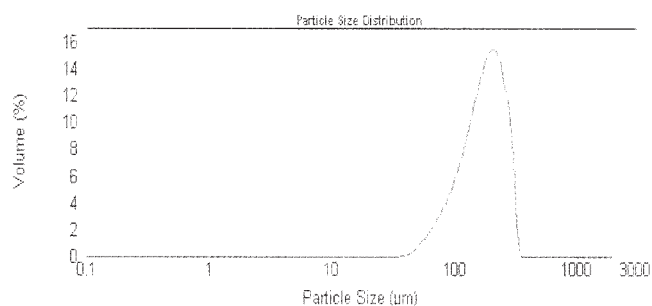


Figure 4 Particle size distribution curve for IPN MGs.

TABLE III
Release Kinetics Parameters of Different Formulations

Formulation code	K	n	D ($10^{-5} \text{ cm}^2 \text{ s}^{-1}$)	Correlation coefficient, r
NaAlg with 5 mL of GA and 25% of drug				
NaAlg-AA 00	0.0111	0.701	0.154	0.963
Variation of IB keeping the amount of AA and GA constant				
NaAlg-AA GA2	0.0154	0.648	0.572	0.893
NaAlg-AA IBI	0.0156	0.589	0.900	0.978
NaAlg-AA IB2	0.0091	0.533	2.000	0.971
Variation of AA by keeping amount of GA and IB constant				
NaAlg-AA GA2	0.0154	0.648	0.572	0.893
NaAlg-AA 2	0.0239	0.681	0.854	0.930
NaAlg-AA 3	0.0385	0.725	2.370	0.948
Variation of amount of GA by keeping the amount of AA and IB constant				
NaAlg-AA GAI	0.0153	0.639	0.130	0.943
NaAlg-AA GA2	0.0154	0.648	0.572	0.893
NaAlg-AA GA3	0.0239	0.589	0.790	0.961

Drug release kinetics

Drug release kinetics was analyzed by plotting cumulative release data versus time and by fitting these data to the exponential equation of the type²³

$$\left(\frac{M_t}{M_\infty}\right) = kt^n \quad (3)$$

Here, M_t/M_∞ represents the fractional drug release at time t , k is a constant characteristic of the drug-polymer system, and n is an empirical parameter characterizing the release mechanism. Using the least squares procedure, we have estimated the values of n and k for all the nine formulations, and these values are given in Table III. If $n = 0.5$, the drug diffuses and releases from the polymer matrix following a Fickian diffusion. For $n > 0.5$, an anomalous or non-Fickian type drug diffusion occurs. If $n = 1$, a completely non-Fickian or Case II release kinetics is operative. The intermediary values ranging between 0.5 and 1.0 are attributed to the anomalous type transport.^{23,24}

The values of k and n have shown a dependence on the extent of crosslinking, % drug loading, and AA content of the matrix. Values of n for beads prepared by varying the amount of AA in the MGs of 10, 20, and 30% by keeping IB (25%) and GA (5 mL GA) constant, ranged from 0.53 to 0.70, leading to a shift of transport from Fickian to anomalous type. The IB-loaded particles have the n values ranging from 0.61 to 0.73 (Table III), indicating the shift from erosion type release to a swelling-controlled, non-Fickian mechanism. This could be possibly due to a reduction in the regions of low microviscosity and closure of microcavities in the swollen state. Similar findings have been observed elsewhere,²⁵ wherein the effect of different polymer ratios on dissolution kinetics was studied. On the

other hand, the values of k are quite smaller for the drug-loaded beads, suggesting their lesser interactions compared with MGs containing varying amount of AA. To study the effect of composition on k of AA in the matrix, we have plotted the results of k versus AA composition in Figure 5. A perfect linear increase of k with increasing amount of AA is observed, suggesting systematically the varying interaction of drug solution with AA content of the blend matrix.

The diffusion coefficient, D , of water in the MGs was calculated¹³ using the equation,

$$D = \left(\frac{r\theta}{6M_\infty}\right)^2 \pi \quad (4)$$

where, θ is slope of the linear portion of the plot of M_t/M_∞ versus $t^{1/2}$, r is radius of the spherical parti-

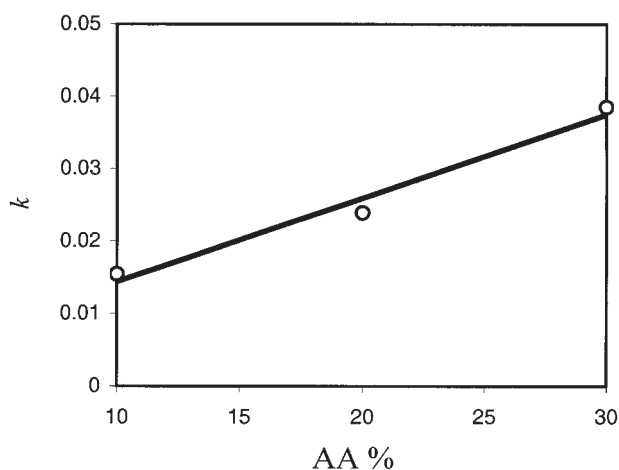


Figure 5 Values of k vs. composition of AA in the IPN MGs.

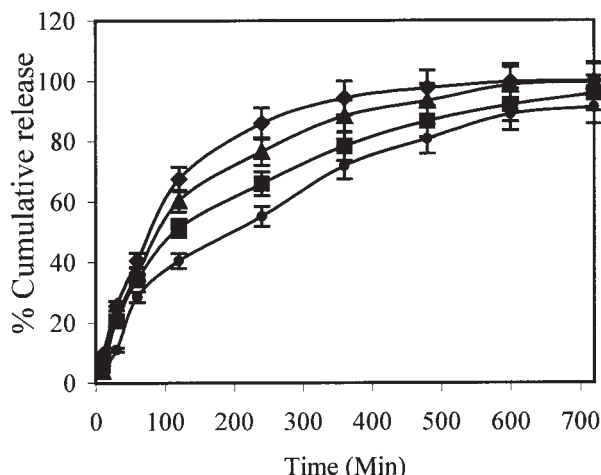


Figure 6 Percentage cumulative release of IB through NaAlg IPN MGs containing different amount of AA at pH 7.4. Symbols: (●) NaAlg, (◆) 10% of AA, (■) 20% of AA, and (▲) 30% of AA.

cles, and M_{∞} is the maximum sorption value. Diffusion coefficients were estimated assuming Fickian diffusion. The D (see Table III) values calculated are in the range of $(0.13\text{--}2.0) \times 10^{-5} \text{ cm}^2/\text{s}$ and are found to depend upon the extent of crosslinking. For instance, D values show a systematic decrease with increasing crosslinking of the matrix in all the formulations. This is obvious because of the increased rigidity of the chain due to increased crosslinking, thereby, prohibiting the transport of more of water molecules.

In vitro drug release

To understand the release kinetics of IB loaded NaAlg-AA IPN MGs, in vitro experiments were carried out. Approximately 100 mg of the drug-loaded MGs were weighed and placed in the phosphate buffer solution and rotated at 100 rpm. The in vitro experiments were performed in triplicate and average values were used for the graphical presentation and data treatment. The Standard deviations are less than 5% in all cases. Figures 6–9 display the release profiles of formulations containing different amount of AA in MGs in pH 7.4 and 1.2 media, crosslinking agent, and drug loading, respectively.

Effect of acrylic acid content in MGs

In the present research, GA was employed to crosslink NaAlg and AA IPNs. However, NaAlg and acrylic acid IPNs gave uniform size MGs probably because GA could crosslink with only NaAlg, but not with AA. The effect of AA composition in the matrix of NaAlg and AA was studied at a constant drug loading of 25%, wherein it was found that NaAlg-AA (GA3)

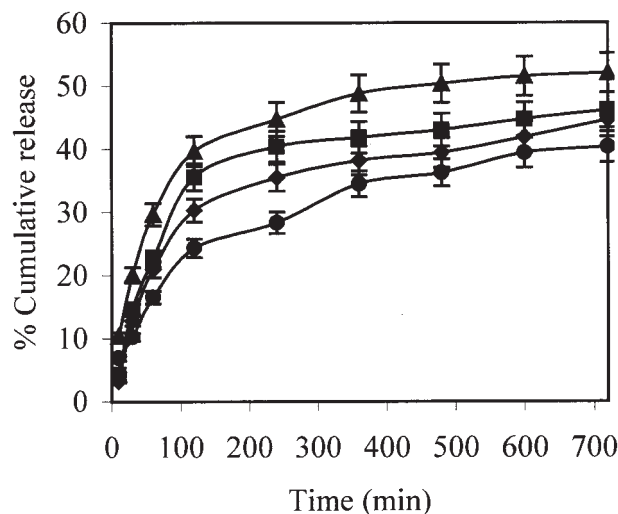


Figure 7 Percentage cumulative release of IB through NaAlg IPN MGs containing different amount of AA at 1.2 pH. Symbols: (◆) NaAlg, (●) 10% of AA, (■) 20% of AA and (▲) 30% of AA.

MGs produced almost 100% cumulative drug release in about 12 h, whereas NaAlg-AA (GA2) MGs produced up to 90% cumulative release at the same time.

Release data of different amount of AA in both pH 7.4 and 1.2 media are displayed in Figures 6 and 7, respectively. A systematic increase in percentage cumulative release with increasing composition of AA is observed, but the release time remains almost the same for all the compositions. The reason for this effect could be that, during the process of dissolution, a general trend was observed in all the formulations, i.e., MGs systematically swelled more with the in-

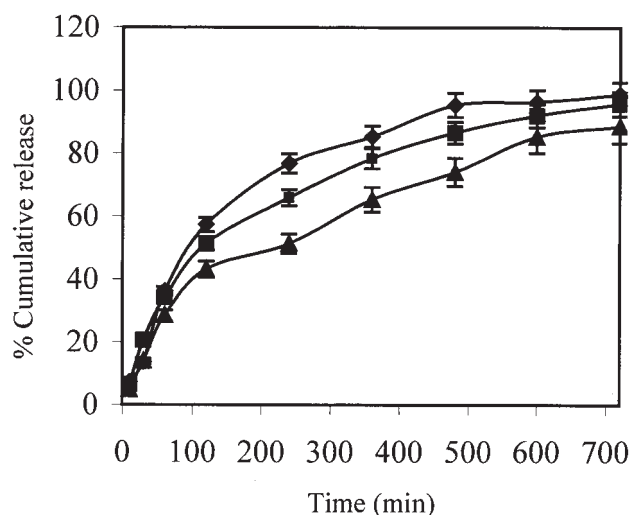


Figure 8 Percentage cumulative release of IB through NaAlg-AA IPN MGs containing different amount of crosslinking agent at pH 7.4. Symbols: (◆) 2.5 mL of GA, (■) 5 mL of GA, and (▲) 7.5 mL of GA.

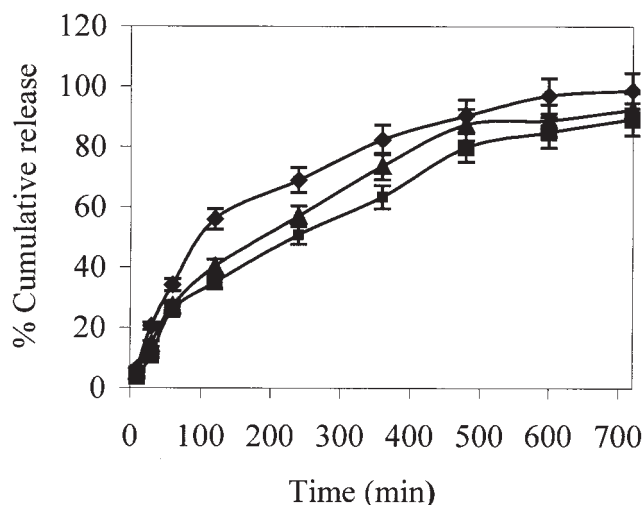


Figure 9 Percentage cumulative release of IB through NaAlg IPN MGs containing different amount of drug at pH 7.4. Symbols: (◆) 25% of IB, (▲) 50% of IB, and (■) 75% of IB.

creasing amount of AA, probably due to the loose crosslinked chains of AA in the MGs. Microscopically speaking, there is a relaxation response of the polymer chains because of the stresses introduced during the process of dissolution, resulting in an increase of dimension (radius of gyration) of the polymer coil, thus, a significant increase in molecular volume of the overall hydrated polymer matrix due to increased swelling of AA component of the blend. This, in turn, might reduce the free volume of the matrix. Note that, the nature of release profiles remains almost identical for all the matrices containing different amount of AA, indicating that swelling of AA has a linear relationship with their release profiles.

Effect of crosslinking agent

The % cumulative release data versus time plots for varying amounts of GA, i.e., 2.5, 5.0, and 7.5 mL at the fixed amount of the drug (25%) are displayed in Figure 8. The % cumulative release is quite fast and large at the lower amount of GA (i.e., 2.5 mL), whereas the release is quite slower at higher amount of GA (i.e., 7.5 mL). The cumulative release is somewhat smaller when lower amount of GA was used, probably because at higher concentration of GA, polymeric chains become rigid due to the contraction of microvoids, thus decreasing percentage cumulative release of IB through the polymeric matrices. As expected, the release becomes slower at higher amount of GA, but becomes faster at lower amount of GA.

Effect of percent drug loading

Figure 9 shows the release profiles of IB-loaded MGs of NaAlg-AA (GA2) at different amount of drug load-

ings. Release data showed that formulations containing the highest amount of drug (75%) displayed fast and higher release rates than those formulations containing a small amount of IB. A prolonged release was observed for the formulation containing lower amount of IB. In other words, with a decreasing amount of drug in the matrix, a shift from anomalous type release to Case II is observed. Note that, the release rate becomes quite slower at the lower amount of drug in the matrix, because of the availability of more free void spaces through which lesser number of drug molecules will transport. For all the IB-loaded formulations, the complete release of IB were not observed even after 600 min, but the release rates were around 700 min.

Effect of pH

To investigate the effect of pH and ionic strength of the external medium on the swelling of MGs, we have measured the percentage cumulative release in both pH 1.2 and 7.4 media. Cumulative release data presented in Figures 7 and 8 indicate that by increasing the pH from 1.2 to 7.4, a considerable increase in the cumulative release is observed for all microgels. At higher pH (above the pK_a of the microgels), the $-\text{COOH}$ groups may dissociate, increasing the osmotic pressure inside the microgels, resulting in higher swelling. Cumulative release in both the pH conditions thus, depends upon the extent of crosslinking. At lower crosslinking, the network is loose with a greater hydrodynamic free volume so that the polymer chains can accommodate more solvent molecules, thereby inducing higher swelling and higher cumulative release. However, cumulative release of the MGs at higher pH depends upon the extent of hydrodynamic free volume, polymer chain relaxation, and availability of hydrophilic functional groups ($-\text{COO}^-$ as in case of ionized polymer) for water to form hydrogen bonds. The release data shown in Figures 6 and 7 obtained in pH 7.4 and 1.2 at the fixed amount of drug (25% IB) and the fixed amount of crosslinking agent (i.e., 5 mL of GA) are different because of the differences in the swelling of MGs in different external media. The percentage cumulative release is quite fast and large in pH 7.4 media, whereas the release rate is quite slow in pH 1.2 media. Note that cumulative release of NaAlg-AA beads in 1.2 pH media is almost half of the cumulative release observed in 7.4 pH media, which is due to lesser swelling of the beads in 1.2 pH media.

CONCLUSIONS

The present study addresses the preparation of novel IPN microgels of sodium alginate and acrylic acid used for the controlled release of IB. By DSC thermo-

grams, it is confirmed that the drug has dispersed at molecular level as supported by X-RD. The percentage cumulative release of IB through MGs indicated that NaAlg-AA matrix is pH sensitive. The IPN of MGs exhibited better encapsulation efficiencies and micromeritic properties for the formation of single unit dosage forms than the plain sodium alginate microspheres. The microspheres have lower densities, and hence, could be retained in gastric environment for more than 12 h, which might help to improve the bioavailability of IB.

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