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# Sodium Alginate-g-Acrylamide and PEG Blend Beads: Development and Controlled Release of Enalapril Maleate

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***ABSTRACT***

*Development of semi-IPN beads, based on sodium alginate-g-acrylamide (NaAlg-g-AAm), blended with poly (ethylene glycol) were cross-linked with glutaraldehyde and used in controlled release of enalapril maleate (ENM), an anti-hypertensive drug. The beads were characterized by Fourier transform infrared spectroscopy (FTIR) to confirm the grafting and cross-linking reaction, scanning electron microscopy (SEM) for understanding of surface morphology of the beads and differential scanning calorimetry (DSC) and X-RD studies to confirm the uniform distribution of the drug in the polymer matrix. The physicochemical characteristics of the beads (i.e. encapsulation efficiency, in vitro release) were studied. Swelling experiments on the beads give important information on the drug properties. The in vitro release results performed in pH 7.4 affected the release characteristics. The release data have been analyzed with nature of transport of drug solution through the polymeric matrices. The extent of cross-linking was studied in terms of size of beads as well as their release characteristics. Extent of drug loading varies in a linear fashion with the encapsulation efficiency of the drug in polymer matrix. The semi-IPN matrices of this study were able to extend the release rates from the conventional dosage release times to more than 10 h.*

***Keywords:*** *Sodium alginate, poly (ethylene glycol), beads, drug release, Enalapril Maleate.*

## 1. INTRODUCTION

Polymeric beads are one of the multiparticulate delivery systems and are prepared to obtain prolonged or controlled drug delivery, to improve bioavailability or stability and to target drug to specific sites. Drug delivery devises can also offer advantages like limiting fluctuation within therapeutic range, reducing side effects, decreasing dosing frequency and improving patient compliance [1-5]. Controlled drug delivery technology represents one of the most rapidly advancing areas of science in which chemicals and chemical engineers are contributing to human health care. Such delivery systems offer numerous advantages compared to conventional dosage forms including improved efficiency and reduced toxicity [6].

We have developed several controlled release (CR) formulations, we now report the experimental results on modified NaAlg blended with PEG beads containing enalapril maleate. However, in the literature, we find the use of NaAlg as a control release device in medical applications [7, 8] as well as in agriculture [9,5] after crosslinking with GA. The modified NaAlg and poly (ethylene glycol) was successfully crosslinked with glutaraldehyde. Which is an important reagent in biomedical field which has been clinically accepted [10,6]. Enalapril maleate (ENM) is an anti-hypertensive water soluble drug. However, short-acting formulations of ENM should be used with great caution because of their associated problems of increased dose-dependent death from myocardial infection. Therefore, there is a need to develop CR devices of ENM for the effective management of hypertension.

To the best of our knowledge, no previous reports are available on the development of semi-IPNs of sodium alginate-grafted-acrylamide blended with poly (ethylene glycol) matrices for the CR of enalapril maleate in pH 7.4 media. The present investigation therefore, deals with the *in vitro* release studies on semi-IPN bead formulations loaded with different amounts of enalapril maleate. Drug loaded beads were characterized by Fourier transform infrared spectroscopy, scanning electron microscopy, X-ray diffractometry and differential scanning calorimetry. Release characteristics of the formulations were studied for their encapsulation efficiency, polymer morphology, drug diffusion rates as well as extent of crosslinking. *In vitro* drug release from the hydrogels has been studied in pH

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7.4 buffer media. The release kinetics of these systems has been investigated to evaluate the diffusion parameters and the results are present here.

## 2. EXPERIMENTAL

### *2.1. Materials*

Sodium Alginate (NaAlg) (medium viscosity), Acrylamide (AAm), poly (ethylene glycol) (M.W. 6000), acetone (AR), Hydrochloric acid, Potassium per sulphate ($K_2S_2O_8$) and Glutaraldehyde (25 % aqueous solution) (GA) were of AnalaR grade purchased from S.D.Fine chemicals, Mumbai, India. Tween-80 was purchased from Sigma Chemicals; Enalapril maleate was obtained from Waksman Salesman pharmaceuticals, Anantapur, India and was used without purification.

### *2.2. Synthesis of sodium alginate-grafted-acrylamide*

Sodium alginate-g-acrylamide semi-IPN beads, here after designated as NaAlg-g-AAm was prepared by mixing NaAlg with AAm, using potassium per sulphate ($K_2S_2O_8$) as an initiator [11]. In brief, 3% aqueous solution of NaAlg was prepared by dissolving NaAlg in double distilled water for overnight, under constant stirring. The solution was degassed by passing nitrogen gas inlet for 30 minutes. To this solution, different amounts of acrylamide solution were added and stirred thoroughly for 1 hour. The initiator solution containing 50 mg of $K_2S_2O_8$ was added to the earlier mentioned mixture and stirred for 2 hours at the temperature of 70$^o$C. The resulting solution is taken and poured into acetone solution, and then the grafted precipitate was collected and dried within the hot air oven at the temperature of 35$^o$C and stored in a desiccator.

### *2.3. Preparation of NaAlg-g-Am and PEG Beads*

The required amount (w/v %) of sodium alginate-*grafted*-acrylamide was taken into the beaker containing distilled water and stirred for overnight. In another beaker, a required amount (w/v %) of poly(ethylene glycol) solution was added to the above homogeneous solution. To this, the required amount of enalpril maleate, an anti-hypertensive drug was added and stirred until complete dispersion of the drug in the polymer solution is obtained. A 5 mL of drug loaded polymer solution was added drop wise in a short time of 50 to 75 seconds into the acetone solution containing the required amount of cross-linking agent glutaraldehyde (GA) and 1 mL of 0.1 HCl using a 25 ml hypodermic syringe having 1-mm diameter under constant stirring condition. The beads formed were removed from acetone at a particular time and were repeatedly washed with distilled water. The beads were prepared using three different ratios of NaAlg-g-AAm blended with PEG, three different amounts of cross-linker and three different amounts of drug.

### *2.4. Estimation of drug loading and encapsulation efficiency*

Specific amount of dry beads were vigorously stirred in a beaker containing 10 mL of dichloromethane to extract the drug from the beads. A 10 mL of 7.4 pH phosphate buffer containing 0.02 % Tween-80 was added to the above solution to make the drug soluble and dichloromethane was evaporated with a gentle heating and continuous shaking. The aqueous solution was then filtered and assayed by a UV spectrophotometer (Model LabIndia-UV 3000$^+$, UK) at the fixed $\lambda_{max}$ value of 215 nm. The results of % enalpril maleate (ENM) loading and encapsulation efficiency were calculated using Eqs. (1) and (2). These results are compiled in Table.I.

$$\%\ \text{Drug loading} = \left(\frac{\text{Amount of drug in beads}}{\text{Amount of beads}}\right) x100 \quad (1)$$

$$\%\ \text{Encapsulation efficiency} = \left(\frac{\text{Actual loading}}{\text{Theoretical loading}}\right) x100 \quad (2)$$

### *2.5. Swelling Studies*

Dynamic swelling of the NaAlg-g-AAm/PEG beads prepared using three different concentration of cross-linker as well as three different drug loadings was studied in water by mass uptake measurements with time. Swelling experiments performed in pH 7.4 buffer solutions produced no significant changes and hence, we studied the swelling of beads in water. To perform swelling experiments, beads were soaked in water; several of them were removed from the swelling bottles at different time intervals and blotted carefully (without pressing hard) to remove the surface-adhered water. The beads were then weighed ($w_1$) on an electronic microbalance (Mettler, AT 120, Switzerland) accurate to ± 0.0001 g. The beads were then dried to a constant weight ($w_2$) in an oven maintained at 60 $^o$C for 5 h. swelling experiments were repeated thrice for each sample and average values were used in data analysis. The standard deviations (S.D.) in all cases were < 5 %. The weight % water uptake was calculated as:

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

### *2.6. Characterisation*

Fourier transform infrared spectroscopy (Perkin Elmer Spectrum Two, UK) analysis was performed to identify the chemical structure of the NaAlg-g-AAm/PEG beads. Furthermore, to investigate the drug nature in the network of the beeds, DSC

(Model-SDTQ600, USA) analysis was performed for pure Enalapril maleate, Enalapril maleate loaded SA-PAVA hydrogel, and pristine NaAlg-g-AAm/PEG beads. Analysis of the samples was performed at a heating rate of 10 $^{o}$C/min under $N_2$ atmosphere with a purging rate of 100 mL/min. Morphology of the NaAlg-g-AAm/PEG beads was recorded using a scanning electron microscope (MERA\\TESCAN). 10 mg/mL powdered sample of NaAlg-g-AAm/PEG beads was dispersed in DD water under constant stirring. This dispersion was placed on a 400 mesh copper grid and allowed to air dry for 5 min.

## 3. RESULTS AND DISCUSSION

### *3.1. Fourier Transform Infrared spectroscopy (FTIR)*

FTIR Spectra of uncrosslinked NaAlg-g-AAm/PEG beads (A), crosslinked NaAlg-g-AAm/PEG beads (B) and grafted copolymer of NaAlg and AAm (C) is shown in Fig.1. A characteristic broad peak appearing at 3400 $cm^{-1}$ corresponds to -OH stretching vibrations a sharp peak around at 1644 $cm^{-1}$ corresponds to the carbonyl group of -$CONH_2$ (Curve-A). During crosslinking, GA might have reacted with -OH groups of IPN through the formation of ether linkages C-O-C stretching frequency, it explains crosslinking between NaAlg-AAm/PEG, (curve-B) it shows a more intensive broad peak indicates at 1108 $cm^{-1}$. This is further supported by the presence of a sharp high intensity peak due to -$CH_2$ group of alkyl chain as a result of crosslinking. In curve (C), a broad peak both -OH and -NH stretching frequencies at 3416 $cm^{-1}$ and 3199 $cm^{-1}$ respectively. 1126 $cm^{-1}$ shows -CO stretching frequency. A sharp peak appears at 1030 $cm^{-1}$ is due to C-O-C stretching frequency. There it confirms the crosslinking and grafting reactions between NaAlg-AAm and PEG.

### *3.2. Differential scanning calorimetry (DSC) studies*

DSC thermo grams of pure enalapril maleate (A), Plain NaAlg-g-AAm/PEG beads (B) and enalapril maleate (ENM) loaded NaAlg-g-AAm/PEG beads (C) were recorded using Rheometric Scientific differential scanning calorimeter (Model-DSC SP, UK) and shown in Fig.2. The analysis was performed by heating the samples at the rate of 10 $^{o}$C/min under inert atmosphere. Melting peak of ENM was observed at 150.40 $^{o}$C, but in case of drug loaded and plain NaAlg-g-AAm/PEG beads, broad peaks are observed in the range of 50-152 $^{o}$C. However, there is no characteristic peak of ENM in the drug loaded IPN beads. Suggesting that drug is molecularly dispersed in the polymer matrix.

### *3.3. Scanning Electron Microscopic (SEM) studies*

The purpose of SEM study is to obtain a topographical characterization of beads SEM images of the beads were recorded using a Hitachi S520 scanning electron microscope (Japan) at the required magnification. Working distance of the range of 8.5-9.5 mm was maintained and the acceleration voltage used was 20.0 kV with the secondary electron image (SEI) as a detector. Fig.3. shows the SEM micrographs of NaAlg-g-AAm/PEG IPN beads. The ENAM was successfully encapsulated using NaAlg-g-AAm/PEG. The beads formed have been spherical shape with smooth surface as revealed SEM photographs as shown in Fig. 3.

### *3.4. X-RD Studies*

X-RD diffractograms of pure ENM drug (A), plain NaAlg-g-AAm/PEG beads (B), drug loaded NaAlg-g-AAm/PEG beads (C) are displayed in Fig.4. These traces reveal the crystallinity of the drug even after encapsulation in the crosslinked beads. ENM has shown characteristics intense peaks between 2θ of 50 and 300 due to its crystalline nature. However, peaks for the plain drug were marked in the drug loaded IPN matrix. X-RD diffractograms recorded for plain beads and ENM loaded beads did not show any characteristic peak of the drug, indicating that the encapsulated drug in the amorphous state**.**

### *3.5. Estimation of drug loading and encapsulation efficiency*

Three different concentrations of ENM i.e., 5, 10 and 15 wt% were loaded during the crosslinking of the polymeric beads. Results of % encapsulation efficiency included in Table.1 which shows increasing trends with increasing drug loading. Encapsulation efficiency for formulations ranged from 56.6 to 64.8% such smaller values due to a lesser soluble drug in the polymer solution, thus incorporating a lesser amount of ENM into beads. It is noticed that % encapsulation efficiency increased with increasing amount of PEG in the polymeric beads. For beads containing 60/40, 40/60 and 20/80 and 10 wt. % ENM with 2 mL of GA, encapsulation efficiencies were 59, 67.3 and 70.8%, respectively. For the ratios of 60/40 of modified NaAlg and PEG in the matrix, the results of extent of crosslinking on the size have increased, and then the % of encapsulation efficiency decreased (Table.1). For beads crosslinked with 2, 3, and 4 mL of GA, encapsulation efficiencies are 59, 55.5 and 49.3%. Such a decreasing trend is due to an increase in crosslink density, because the beads will become rigid, thereby reducing the free volume spaces with in the polymer matrix and hence, a reduction in encapsulation efficiency is observed.

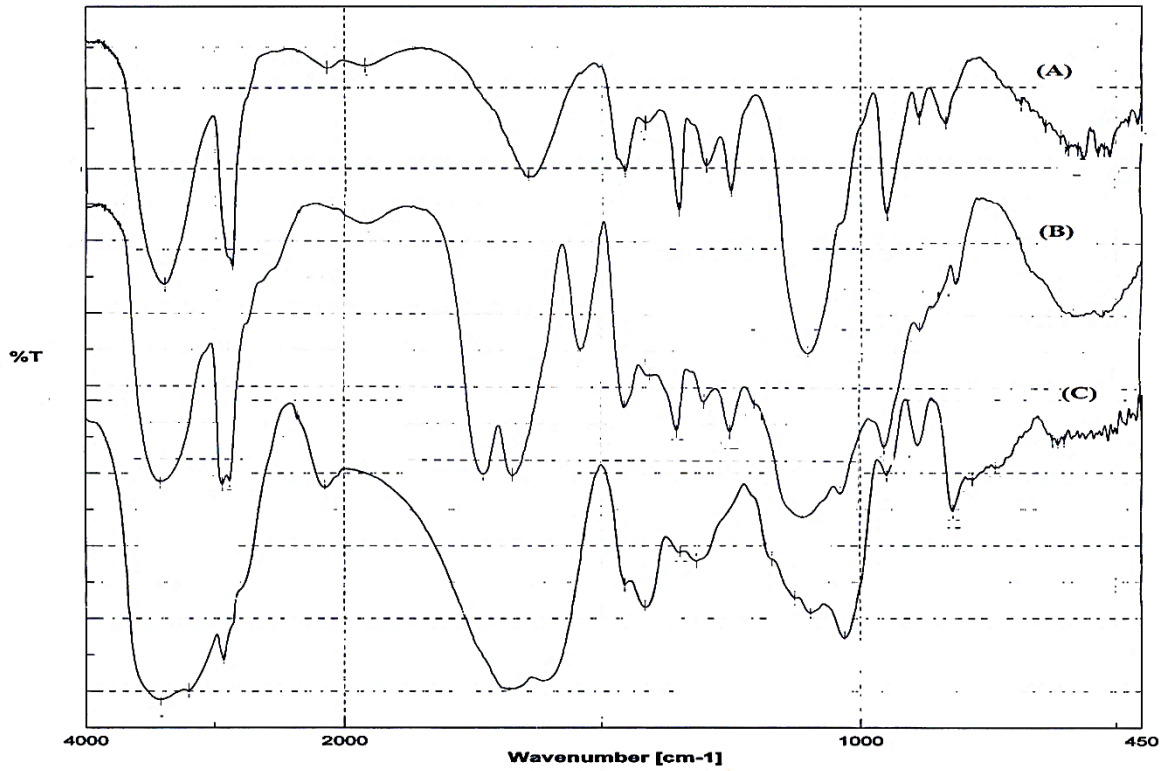


**Figure.1:** FTIR Spectra of (A) Uncross linked NaAlg-g-AAm/PEG beads (B) crosslinked NaAlg-g-AAm/PEG beads (C) Sodium alginate grafted with acrylamide polymer.

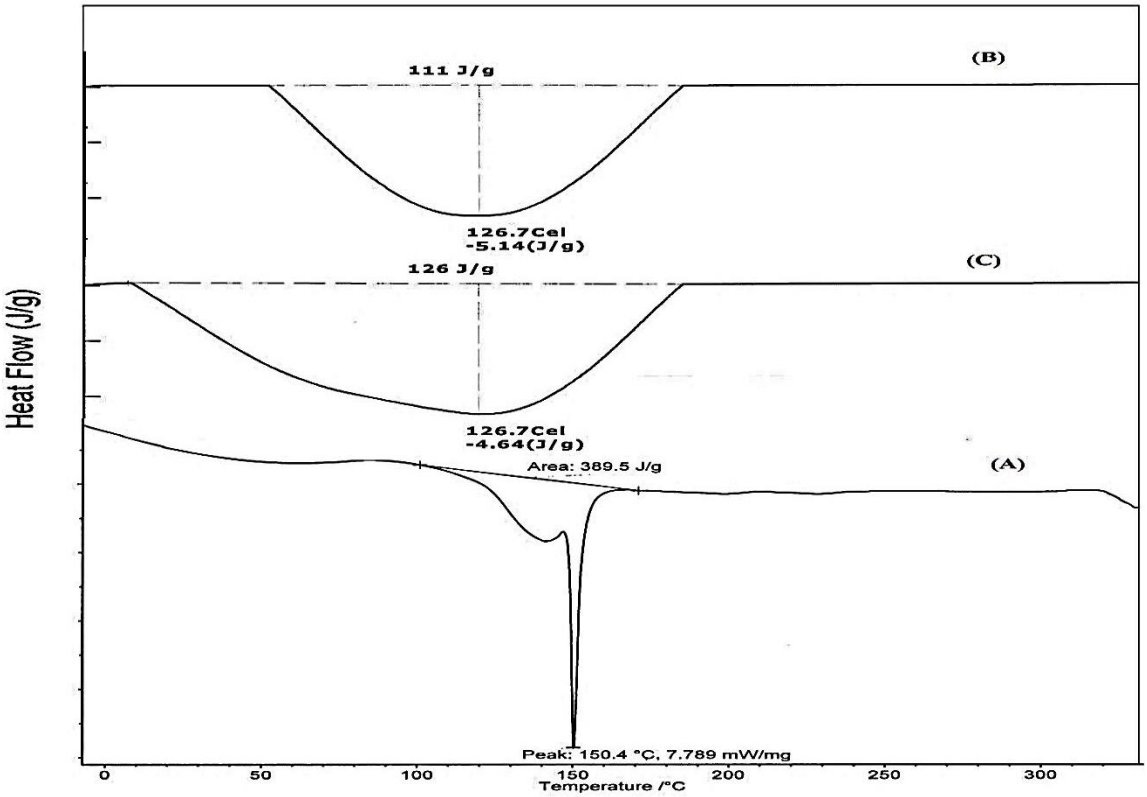


**Figure.2:** DSC Thermographs of (A) Pure ENM drug (B) Plain NaAlg-g-AAm/PEG beads and (C) drug loaded NaAlg-g-AAm/PEG beads.

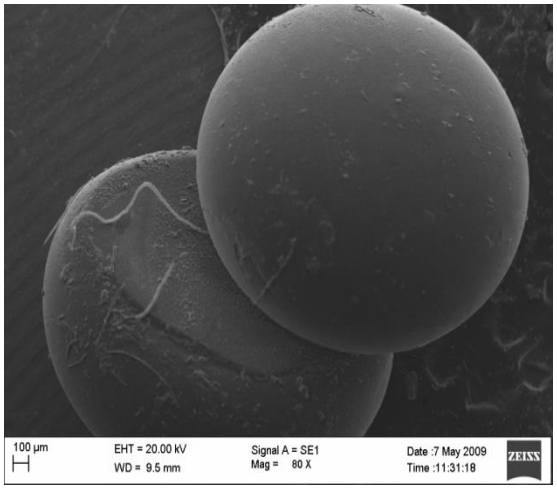


**Figure.3:** Scanning electron microscopy photographs of (A) and (B) NaAlg-grafted-AAm/PEG IPN beads.

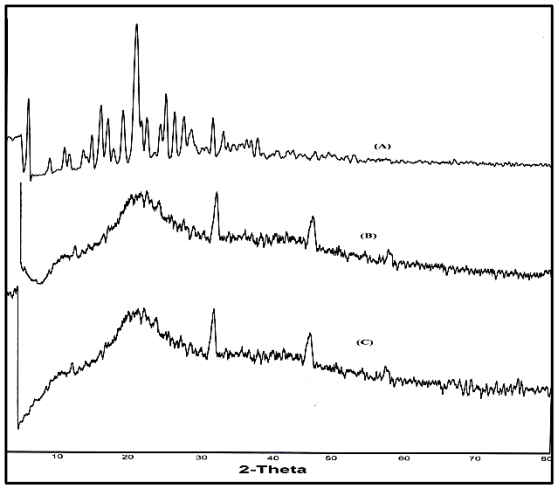


**Figure.4:** X-RD of (A) Pure ENM drug (B) Plain NaAlg-g-AAm/PEG beads and (C) drug loaded NaAlg-g-AAm/PEG beads.

### *3.6. Swelling Studies*

In polymer matrix beads, the extent of crosslinking depends upon the crosslinking agent (GA) used. In the present study, different amounts of GA were added to the IPN beads of NaAlg-g-AAm/PEG containing 10 wt. % of ENM and these data are also included in Table.1. Extent of crosslinking is depends upon the equilibrium swelling. For instance, % equilibrium swelling decreased from 420 to 316 with increasing amount of GA from 2.5 to 7.5 mL. This is due to increased crosslink density and decreased pore volume of the IPN matrix [12] with increasing amount of GA in the matrix. By increasing the drug loading of the matrix, % water uptake also increased i.e., as the drug wt. % loading increased from 5 to 15%, the % equilibrium swelling were 404, 420 and 455, respectively. Such an increasing swelling of the matrix is due the incorporation of hydrophilic modified NaAlg along with PEG chains to form an IPN matrix. The % water uptake (or) % dynamic swelling of the formulated IPN matrix has increased with an increasing amount of PEG in IPN matrix. However, % water uptake (or) % dynamic swelling of the IPN matrix containing 60/40, 40/60 and 20/80 of modified NaAlg and PEG are 420, 440 and 486, respectively. The % water uptake has increased with an increasing amount of PEG in the IPN matrix. This is due to the fact that as the amount of PEG increases in the matrix, hydrophilicity of the matrix could increase slightly due to presence of PEG.

### *3.7. In-vitro release studies: Release kinetics parameters of different formulations*

Drug release kinetics was analyzed by plotting cumulative release data versus time and by fitting these data to the exponential equation of the type [13].

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

Here, $\frac{M_t}{M_\infty}$ 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 seven formulations, and these values are given in Table.2, If $n = 0.5$, the drug diffuses and releases from the polymer matrix following a Fickian diffusion. For $n < 0.5$, 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 [13, 14,].

The values of *k* and *n* have shown a dependence on the extent of crosslinking, % drug loading, and PEG content of the matrix. Values of *n* for beads were prepared by varying the amount of PEG in the polymer matrices of 40, 60, and 80% by keeping ENM (10%) and GA (2 mL GA) constant, ranged from 0.394 to 0.463, leading to a shift of transport from non-Fickian to Fickian transport. The ENM-loaded particles have the *n* values ranging from 0.206 to 0.463 (Table.2), indicating the shift from non-Fickian type release to a swelling-controlled 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 [15], 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 beads containing varying amount of PEG.

### *3.8. Effect of crosslinking agent*

The % cumulative release data vs. time plots for varying amounts of GA i.e., 2, 3 and 4 mL at the fixed amount of the drug (10%) are displayed in Fig.5.a. The % cumulative release is quite fast and large at the lower amount of GA (i.e., 10%), whereas the release is quite slower at higher amount of GA (i.e., 20%). 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 % cumulative release of enalapril maleate drug through the polymeric matrices. As expected, the release becomes slower at higher amount of GA, but becomes faster at lower amount of GA. As shown in Fig.5.a.

### *3.9. Effect of percent drug loading*

Fig.5.b. shows the release profiles of enalapril maleate drug -loaded NaAlg-*g*-AAm/PEG beads at different amounts of drug loadings. Release data showed that formulations containing the highest amount of drug (15%) displayed fast and higher release rates than those formulations containing a small amount of enalapril maleate drug. A prolonged release was observed for the formulation containing lower amount of ENM. In other words, with a decreasing amount of drug in the matrix, it is noticed that the release rate becomes quite slower at the lower amount of drug in the matrix, and this is due to the availability of more free void spaces through which lesser number of drug molecules will transport. For all the ENM loaded formulations, the complete release of ENM was observed up to 8 hours.

### *3.10. Effect of Poly(ethylene glycol)*

Effect of poly (ethylene glycol) content on encapsulation efficiency and *in vitro* release of ENM was investigated. *In vitro* release profiles of enalapril maleate from formulations were prepared by taking different amounts of PEG and 10% of ENM are shown in Fig.5.c. Faster release rates were observed from formulations prepared with the ratios of modified NaAlg and PEG (i.e., 20:80) respectively, observed than those formulations prepared using the ratios of modified NaAlg and PEG (i.e., 60:40) respectively. About 99% of the drug was released within the first 7 hours from the formulations prepared with higher amount of PEG, whereas only 81% of ENM was released within 8 hours from formulations prepared with a lower amount of PEG. Faster drug release observed from formulations prepared with higher amount of PEG is due to the coating of higher amount of PEG onto modified sodium alginate particles.

## 4. CONCLUSION

It describes the preparation of the Inter penetrating

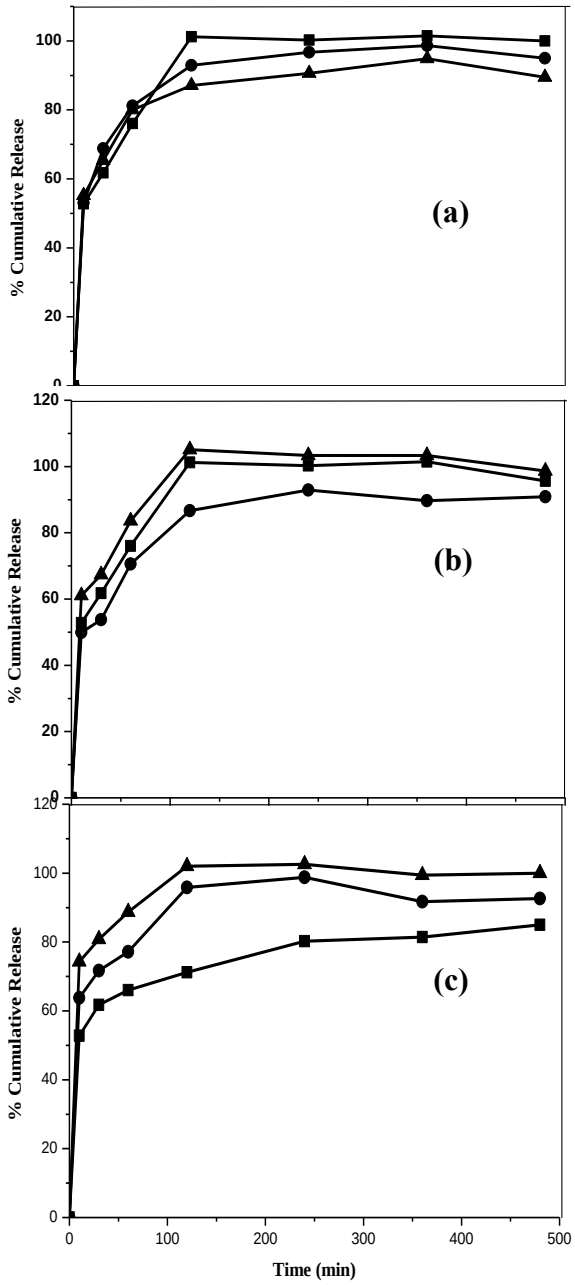


**Figure.5.**% cumulative release of enalapril maleate at **(a)** different amounts of cross- linking agents: (▲) 2 mL GA, (●) 3 mL GA, (■) 4 mL GA; **(b)** different amounts of ENM: (●) 5%, (■) 10%, (▲) 15%; **(c)** different ratios of modified NaAlg and PEG: (■) 60:40, (●) 40:60, (▲) 20:80.

Polymer network (IPN) beads based on sodium alginate-grafted-acrylamide (NaAlg-g-AAm), blend with poly (ethylene glycol) (PEG) loaded with enalapril maleate a hypertensive drug. These beads were characterized by FITR, SEM, X-RD and DSC. The FTIR spectrums confirm the grafting and crosslinking reaction between modified sodium alginate and PEG. The SEM studies explain the smooth surface and nonporous beads properties. A DSC and X-RD study indicates that the drug is

**Table 1:** Results % of encapsulation efficiency and water uptake of different formulations.

| Formulation code | NaAlg (%) | PEG (%) | % o(ENM) loaded | GA (ml) | % EE±S.D | water uptake |
|---|---|---|---|---|---|---|
| NaAlg-g-AAm/PEG-1 | 60 | 40 | 5 | 2 | 56.2±0.4 | 404 |
| NaAlg-g-AAm/PEG-2 | 60 | 40 | 10 | 2 | 58.2±0.2 | 420 |
| NaAlg-g-AAm/PEG-3 | 60 | 40 | 10 | 2 | 64.4±0.4 | 455 |
| NaAlg-g-AAm/PEG-4 | 60 | 40 | 10 | 3 | 54.7±0.8 | 382 |
| NaAlg-g-AAm/PEG-5 | 60 | 40 | 10 | 4 | 48.1±1.2 | 316 |
| NaAlg-g-AAm/PEG-6 | 40 | 60 | 10 | 2 | 66.3±1.0 | 440 |
| NaAlg-g-AAm/PEG-7 | 20 | 80 | 10 | 2 | 70.4±0.4 | 486 |

**EE:** Encapsulation efficiency, **GA:** glutaraldehyde, **S.D:** standard deviation calculated 95% accurately.

**Table.2:** Results of *k*, *n* and correlation coefficient (*r*) values

| Formulation codes | *k* | *n* | *r* |
|---|---|---|---|
| NaAlg-g-AAm/PEG-1 | 60 | 40 | 5 |
| NaAlg-g-AAm/PEG-2 | 60 | 40 | 10 |
| NaAlg-g-AAm/PEG-3 | 60 | 40 | 10 |
| NaAlg-g-AAm/PEG-4 | 60 | 40 | 10 |
| NaAlg-g-AAm/PEG-5 | 60 | 40 | 10 |
| NaAlg-g-AAm/PEG-6 | 40 | 60 | 10 |
| NaAlg-g-AAm/PEG-7 | 20 | 80 | 10 |

dispersed in uniform molecular level in the beads. The extent of crosslinking was studied in terms of size of beads as well as their release characteristics. Extent of drug loading varies in a liner fashion with the encapsulation efficiency of the drug of the polymer matrix. Swelling experiments on the particles gave important information on the drug properties. The IPN matrices of this study were able to extend the release rates from the conventional dosage release times to more than 10 h.

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