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Research paper

In-vitro release kinetics of cefadroxil-loaded sodium alginate interpenetrating network beads

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Abstract

This paper reports the development of new interpenetrating polymeric networks of sodium alginate with gelatin or egg albumin cross-linked with a common cross-linking agent, glutaraldehyde, for the in-vitro release of cefadroxil. The beads formed were characterized by Fourier transform infra-red spectroscopy, scanning electron microscopy and differential scanning calorimetry. Swelling/drying experiments were performed to compute the diffusion coefficients and the molecular mass between cross-links of the beads. The release results were evaluated using an empirical equation to understand the transport mechanism. The extent of cross-linking was studied in terms of the size and release characteristics of the beads. The experimental and derived quantities have been used to study their dependencies on the nature of the polymeric beads, transport mechanism, encapsulation efficiency and drug diffusion, as well as the cross-linking abilities of the polymers.

Keywords: Sodium alginate; Cefadroxil; Interpenetrating network; Beads

1. Introduction

The ability of hydrogels to swell and regulate the release of encapsulated drugs by controlling cross-linking makes them attractive as materials in the controlled release (CR) of drugs [1–3]. Recently, our polymer research group has been actively involved in developing new polymers useful in the CR applications of drugs and pesticides [4–12]. Sodium alginate (Na-Alg) is a bioerodible polymer that has been widely used in CR applications [13–16] because it forms strong gels in aqueous media and is bioerodible. From a polymer chemistry view-point, the development of interpenetrating network polymers (IPNs) of Na-Alg is attractive because, by definition, the IPNs contain two polymers, each in a network form, which can be cross-linked in the presence of each other to give a three-dimensional network structure producing free volume for the easy encapsulation of drugs.

In this paper, we report the preparation of IPNs of Na-Alg with two other biodegradable polymers, such as egg albumin and gelatin. These matrices were used to study the CR of cefadroxil, an antibiotic used in the treatment of bacterial infections. Cefadroxil has a biological half-life of 1.2–2.0 h for a dose containing between 0.5 and 1.5 g of the drug. Its short half-life can be enhanced by using the new IPNs developed in this research. In an earlier study by Schneider et al. [17], the cephalexin antibiotic was formulated as an oral prolonged-release tablet and evaluated by in-vivo studies. However, to the best of our knowledge, no previous studies have been made on the IPNs of Na-Alg with gelatin or egg albumin for the CR of cefadroxil. The in-vitro release data of cefadroxil from the IPN beads of Na-Alg with gelatin or egg albumin are presented. Their release characteristics in terms of encapsulation efficiency, polymer morphology, drug diffusion coefficients, and the extent and time of cross-linking have been investigated.

2. Experimental

2.1. Materials

Cefadroxil (USP grade) was received from Bio-ethicals, Hubli, India. The USP grade samples of Na-Alg (molecular mass, 240 000), egg albumin and gelatin were purchased from s.d. Fine Chemicals, India. Glutaraldehyde (GA;

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25% w/v) solution and AR grade methanol, were procured from s.d. Fine Chemicals, Mumbai, India.

2.2. Preparation of the beads

The Na-Alg and its IPN beads were prepared by adopting a slight modification of the procedure published earlier [8,9]. In the new procedure, a 4% Na-Alg solution in distilled water or its IPN with gelatin or egg albumin (5 and 10% of dry mass of Na-Alg) was prepared by gentle heating. A weighed amount of cefadroxil in 20% of dry mass of Na-Alg or its IPN was added and mixed homogeneously using a magnetic stirrer. The polymer solution containing cefadroxil was then added drop-wise into methanol containing 1% GA and 1% of 1 N HCl using a 25 ml hypodermic syringe through a needle (number 21) under constant stirring. Experimental conditions, such as the distance between the syringe and water level, number of drops/min and temperature were maintained constant. The beads thus formed were removed from water at the selected time intervals of 5 and 10 min; the beads were washed with water and then allowed to dry. When Na-Alg solution was dropped into methanol (non-solvent), the beads were hardened by cross-linking with GA.

2.3. Drying rate study of the beads

A weighed amount of the beads was placed in open glass bottles and kept in an incubator (WTB Binder, Germany) maintained at 37°C. Initially, the beads were removed at short intervals of time (5, 10, 15, up to 100 min) and later, at longer time intervals (200, 300, up to 550 min). These measurements were continued until attainment of constant mass indicating the complete equilibration. All the masses were measured within an accuracy of ± 0.01 mg using an electronic Mettler microbalance (Model AE 240, Switzerland).

2.4. Measurement of bead size

The particle size was measured by taking 5–10 particles on a glass slide under polarized light. The mean diameter was calculated by measuring the number of divisions of the ocular micrometer covering the microspheres. The stage micrometer was previously used to standardize the ocular micrometer.

2.5. Swelling of the beads

Swelling of the individual beads was done by measuring the percentage water uptake by the beads at a pre-selected time interval. The beads were incubated with distilled water on a watch glass. Then, the mass of all the beads was measured using a Mettler microbalance (Model AE 240, Switzerland) with an accuracy of ± 0.01 mg, and the average value was calculated. During this procedure, the swollen beads should be handled carefully in order to avoid any mass loss due to breaking or erosion of the beads.

2.6. Content assay and entrapment efficiency

The beads were evaluated for cefadroxil content by incubating the known mass of the beads with 5 ml of water for complete swelling. The swollen beads were crushed in an agate mortar with a pestle, and the homogeneous solution thus formed was sonicated (Ikasonic U50, IKA Labortechnik, Germany) for 2 min at 60 MHz of frequency. About 20 ml of methanol was added to precipitate Na-Alg, which was removed from methanol by using a high-speed centrifuge (Remi, R24, India) for 5 min at a rotation speed of 10 000 rev./min. Cefadroxil was analyzed by a UV spectrophotometer (Secomam, Anthielle, France) at a λ_{max} value of 230 nm. The percentage entrapment efficiency was calculated as in practical drug loading $\times 100$/theoretical drug loading.

2.7. Dissolution experiments

Dissolution experiments were performed at 37°C using a dissolution tester (Dissotest, LabIndia, Mumbai, India) equipped with six paddles at a paddle speed of 100 rev./min. A 900 ml solution of phosphate buffer solution (pH 7.4) was used as a dissolution medium in order to simulate the gastrointestinal tract (GIT) conditions, and a 10 ml aliquot was used for analyzing the cefadroxil content at a fixed interval of time. Whenever necessary, the samples were diluted before assaying cefadroxil. The dissolution media was always replenished with a fresh stock solution. The cefadroxil released was analyzed by a UV spectrophotometer.

2.8. Fourier transform infra-red measurements (FTIR)

FTIR measurements were taken at ambient temperature using a Nicolet, Model Impact 410 (USA). About 2 mg of the samples were ground thoroughly with KBr and pellets were formed under a hydraulic pressure of 600 kg/cm^2.

2.9. Scanning electron microscopy (SEM)

The sample was deposited on a brass holder and sputtered with gold. The SEM photographs were then taken with a JSM 6400 scanning electron microscope (Japan) at the required magnification at room temperature. The working distance of 39 mm was maintained and the acceleration voltage used was 20 kV, with the secondary electron image (SEI) as a detector. These experiments were performed at RSIC, Indian Institute of Technology, Mumbai (courtesy of Miss Bharathi).

2.10. Differential scanning calorimetric (DSC) analysis

DSC experiments were performed on the beads, pure cefadroxil and the cefadroxil-loaded beads using a DuPont-2000 microcalorimeter (made in USA). The samples were heated at a rate of 5°C/min under a constant flow of nitrogen gas.

3. Results and discussion

In the literature, beads have been developed to achieve an efficient and site-selective drug delivery [18]. Kim and Lee [19] studied the gel erosion problems associated with Na-Alg beads. In order to circumvent this problem, Murata et al. [20] treated the alginate beads with chitosan, and found that chitosan helped to suppress the gel erosion of alginates. Erosion studies on the calcium-induced alginate gel matrix for the release of brilliant blue have also been reported [21]. In the present research, egg albumin and gelatin were found to be compatible for forming blends with Na-Alg, which were then cross-linked with GA to give IPNs. Both egg albumin and gelatin are stable, non-antigenic, metabolizable and are capable of encapsulating a wide variety of drugs. GA is also biodegradable, and, at the same time, it can serve as a good cross-linking agent [22]. Conventionally, microparticles in dosage forms have been prepared by the emulsion/solvent evaporation technique using liquid paraffin as the dispersion medium, followed by rigidization and washing of the microparticles with large volumes of organic solvents [23]. However, the present method avoids the use of any hazardous solvents.

FTIR spectra indicated that the characteristics of peaks of cefadroxil were not altered after encapsulation, indicating no chemical interactions between the drug and GA. The spherical beads ranged in size from 750 to 850 μm. SEM photographs of the Na-Alg beads given in Fig. 1 indicate smooth surfaces without any pores. DSC thermograms of cefadroxil (Fig. 2A), the Na-Alg beads containing cefadroxil (Fig. 2B) and the empty Na-Alg beads (Fig. 2C) are shown in Fig. 2. Cefadroxil exhibits sharp endothermic peaks at 207.3°C, but cefadroxil-loaded beads do not show this feature. The thermograms of Na-Alg beads containing cefadroxil are almost identical to those of the empty beads, indicating that most of the drug was molecularly dispersed within the beads.

The exposure time to GA limits the extent of cross-linking, and this was found to be optimized 5–10 min after a series of preliminary experiments. However, increasing the exposure time did not show any significant ($P < 0.01$) effect on particle size, without much difference between the SD of individual groups of beads (±35) and the mean particle size (48 μm) among beads formed at 5 and 10 min of exposure to GA. On the other hand, the percentage encapsulation efficiency depends upon the type of matrix material and the extent of the cross-linking agent. These data are presented in Table 1. The percentage encapsulation efficiency was high because bead formation was carried out in methanol, in which cefadroxil is insoluble, with a lesser possibility of leaching of the drug during encapsulation. In the case of neat Na-Alg beads formed at 5 min of exposure to GA, the encapsulation efficiency was 83.7%, whereas for beads formed with a 10 min exposure time to GA, this was 82.42%. This indicates that the percentage encapsulation efficiency decreased with an increase in the time of exposure to GA. However, there was a higher percentage of encapsulation efficiency for the IPN beads of gelatin or egg albumin formed at 5 min when compared with neat Na-Alg beads formed at 5 min of exposure to GA, indicating an increased rigidity of the matrices of IPNs when compared with the neat Na-Alg beads. This helped towards a slow release of cefadroxil.

Polymer swelling and cross-linking are intimately connected to the release kinetics of the drugs from the swollen matrix. In order to investigate this effect, swelling results were obtained. Swelling of the beads was measured in terms of their percentage of water uptake at a selected time inter-

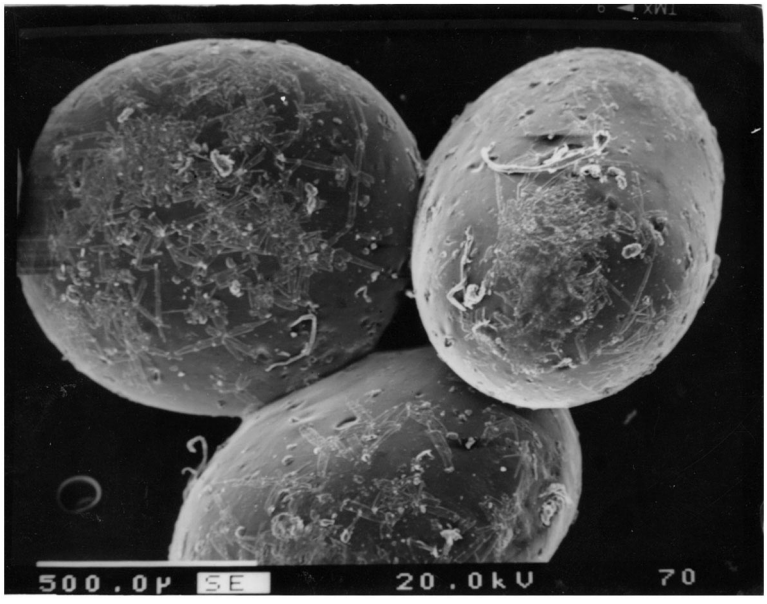

Fig. 1. SEM photograph of Na-Alg beads.

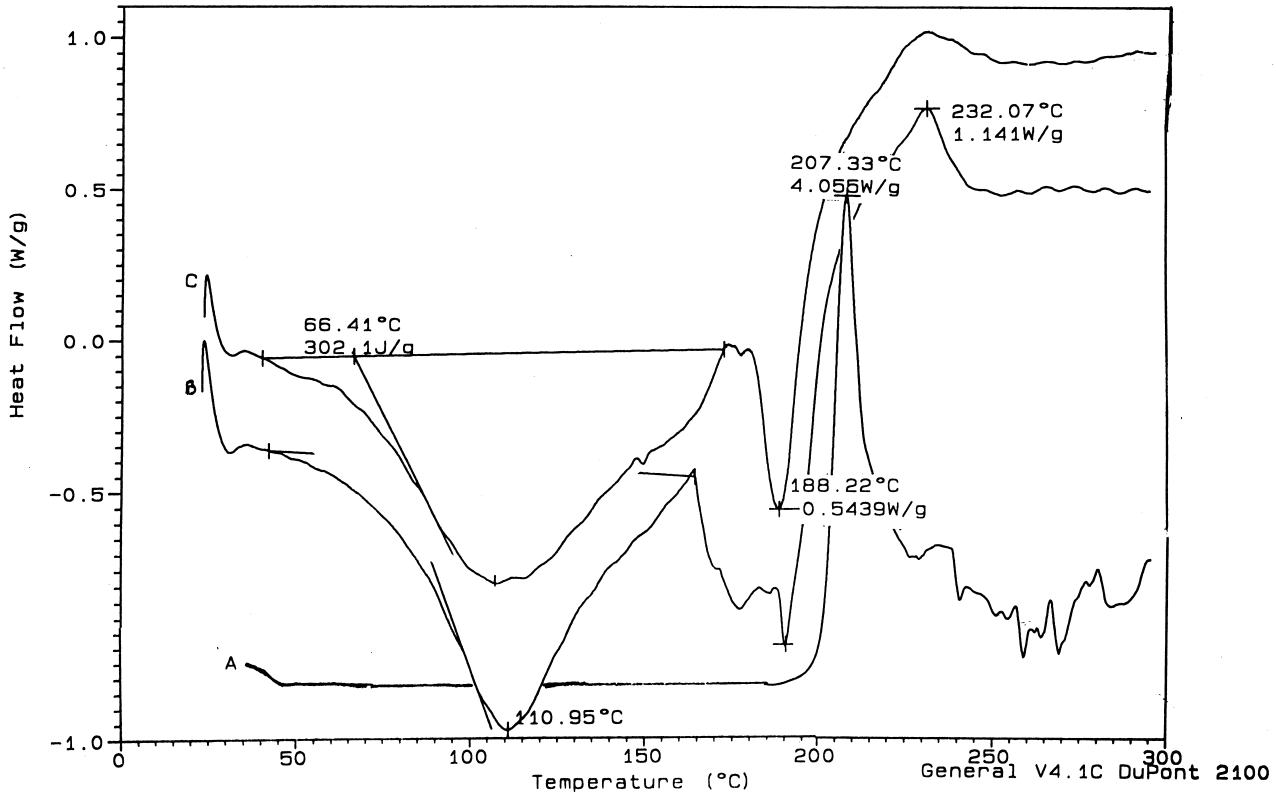

Fig. 2. (A) DSC thermograms of cefadroxil; (B), Na-Alg beads containing cefadroxil; and (C), empty beads of Na-Alg.

val. Using these data, we have attempted to calculate the molecular mass, M_C, between cross-links using the Flory–Rehner equation (Eq. (1)) [24]

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

The volume fraction, ϕ of the swollen polymer was calculated as in Eq. (2)

$$\phi = \left[1 + \frac{\rho_P}{\rho_S}\left(\frac{M_a}{M_b}\right) - \frac{\rho_P}{\rho_S} \right]^{-1} \quad (2)$$

In the above equations, ρ_P and ρ_S are the densities of polymer and solvent, respectively; M_b and M_a, respectively are the masses of the polymer before and after swelling; V_S is the molar volume of the solvent used. The interaction parameter, χ, was calculated using Eq. (3), the procedure published by Aithal et al. [25,26]

$$\chi = \left[\phi(1-\phi)^{-1} + N\ln(1-\phi) + N\phi \right] \times \left[2\phi - \phi^2 N - \phi^2 T^{-1} (d\phi/dT)^{-1} \right]^{-1} \quad (3)$$

where N is as follows in Eq. (4)

$$N = \left(\frac{\phi^{\frac{2}{3}}}{3} - \frac{2}{3} \right) \left(\phi^{\frac{1}{3}} - \frac{2\phi}{3} \right)^{-1} \quad (4)$$

and $d\phi/dT$ is the slope of the line obtained by plotting the volume fraction vs. temperature (in Kelvin).

The M_C values were calculated from the equilibrium swelling data at three different temperatures. The calculated M_C values are presented in Table 2. For the Na-Alg beads, the M_C values range from 208 to 241, and for the gelatin and egg albumin-based IPNs, the M_C values range between 280–337 and 120–137, respectively. The M_C data exhibited an

Table 1
Results of percentage entrapment efficiency, estimated values of k and n for various systems calculated from Eq. (6) for 20% cefadroxil-loaded beads

Polymer	Time of exposure to GA (min)	Bead size (μm)	% Encapsulation efficiency	k (10^2)	n	$D_{sorption}$ ($\times 10^6$ cm^2/s)	$D_{desorption}$ ($\times 10^8$ cm^2/s)
Na-Alg	5	801 ± 35	83.71 ± 0.11	0.016	0.69	5.37	6.11
	10	849 ± 01	82.41 ± 0.03	0.016	0.66	2.05	7.02
Na-Alg + 5% gelatin	5	841 ± 53	88.22 ± 0.52	0.032	0.56	1.57	9.11
Na-Alg + 10% gelatin	5	792 ± 57	83.84 ± 0.08	0.028	0.51	0.15	5.71
Na-Alg + 5% egg albumin	5	752 ± 88	84.35 ± 0.84	0.027	0.59	1.74	3.32
Na-Alg + 10% egg albumin	5	822 ± 25	83.61 ± 0.50	0.027	0.54	1.05	6.02

Table 2
Values of ϕ, (and M_C calculated from Eqs. (2)–(4) for the 20% cefadroxil-loaded beads at different temperatures

Temp. (°C)	System	ϕ	χ	M_C
25	Na-Alg	0.557	0.597	208
30		0.545	0.596	226
35		0.538	0.598	241
25	Na-Alg + 5% gelatin	0.600	0.727	280
30		0.587	0.720	308
35		0.575	0.713	337
25	Na-Alg + 5% egg albumin	0.745	0.873	120
30		0.738	0.864	129
35		0.727	0.855	137

effect on the drug release characteristics, i.e. drug release decreased with an increase in M_C, with the exception of the egg albumin-based IPN. We found that the water uptake of the egg albumin-based IPN was higher than the gelatin-based IPN. Hence, decreased M_C values for the egg albumin-based IPN are observed. A lower cross-link density lead to a higher swelling of the matrix, thereby giving a slow release. Thanoo et al. [27] also observed similar effects on the CR of cross-linked chitosan microspheres. Even though the polymeric beads used in this study were hydrophilic, their drug release characteristics appeared to depend upon the M_C values of the IPNs.

The results presented in Fig. 3 show that all the Na-Alg beads absorbed the maximum amount of water at about 3 h, but the Na-Alg IPN beads absorbed water during the first 2 hours. The IPN formation with gelatin or egg albumin appears to be responsible for reducing the swelling of Na-Alg beads. However, the gelatin-based IPNs are more rigid than the egg albumin-based beads in view of their smaller swelling. These results also support the higher percentage of encapsulation observed for the IPNs of gelatin or egg albumin when compared with the neat Na-Alg beads. This is attributed to an increased rigidity of the matrix after the formation of IPN, thus minimizing the leaching effect of cefadroxil into the external medium. The χ values for the encapsulated Na-Alg beads ranged from 0.596 to 0.598, whereas for the egg albumin-based IPNs, these values ranged between 0.713 and 0.727, and from 0.855 to 0.873 for the gelatin-based IPNs. This suggests mild interactions between the drug and the matrix material.

To calculate the drying rates, some samples of Na-Alg and the IPN beads were selected such that the initial masses were nearly equal. These data are presented in Fig. 4. The IPN beads exhibited a longer drying time than Na-Alg beads. Sezer and Akbuga [28] also observed reduced release rates of a macromolecular drug through chitosan treated Na-Alg beads. The gelatin-based IPNs exposed for 5 min to GA dried more quickly than the egg albumin-based IPNs. This is due to an increased rigidity of the wall polymer [29].

The values of diffusion coefficients, D, for the transport of aqueous drug solution from the beads were calculated using the sorption and desorption results as in Eq. (5) [30]

$$D = \left(\frac{r\theta}{6M_\infty}\right)^2 \pi \tag{5}$$

where θ is the slope of the linear portion of the plot of M_t/M_∞ vs. $t^{1/2}$, and r is the radius of the beads; M_∞ is equilibrium sorption. To calculate D from desorption experiments, θ was computed from the initial linear portion of the desorption plot, i.e. $\ln(1 - M_t/M_\infty)$ vs. time, t. The calculated values of D from Eq. (5) for sorption and desorption runs are also presented in Table 1. The D values for desorption were smaller than those observed for sorption, and these ranged from 3.32×10^{-8} to 9.11×10^{-8} cm^2/s. However, no systematic dependence of D on the nature of the polymer was observed. The values of D for gelatin or egg albumin-based IPNs were lower than those for the neat Na-Alg beads. Higher values of D for sorption ranging between 2.05×10^{-6} and 5.37×10^{-6} cm^2/s for the Na-Alg beads and lower values, ranging between 0.15×10^{-6} and 1.57×10^{-6} cm^2/s, for the gelatin-based IPN were

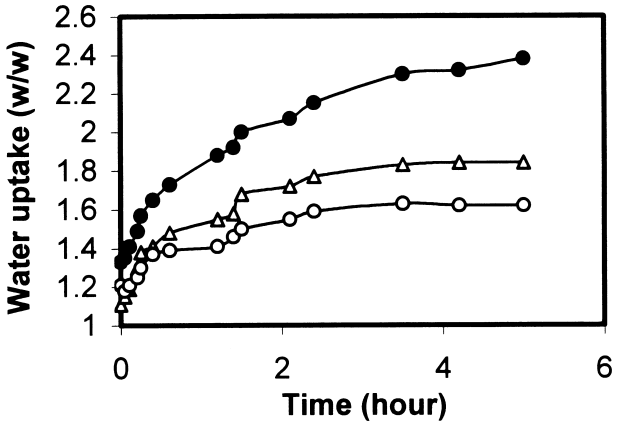

Fig. 3. Effect of IPN formation on percentage uptake of water for: (●), Na-Alg; (△), egg albumin; and (○), gelatin beads.

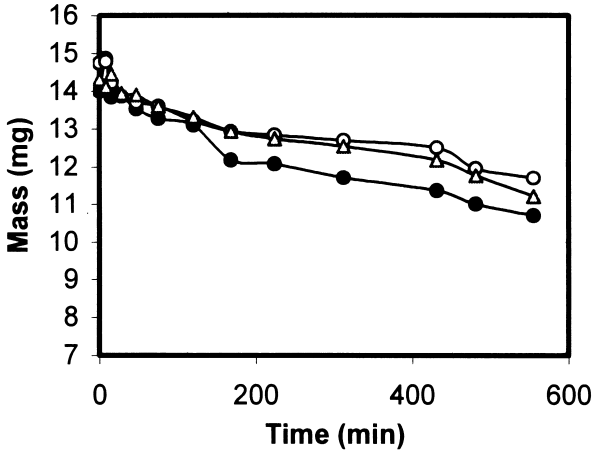

Fig. 4. Effect of IPN formation on drying of: (●), Na-Alg; (△), egg albumin; and (○), gelatin beads.

found. Intermediate values, i.e. ranging between 1.05×10^{-6} and 1.74×10^{-6} cm^2/s, were observed for the egg albumin-based IPNs.

The release of cefadroxil from the beads was dependent upon temperature and the stirring rate. In order to study the effect of the nature of networking (i.e. the IPNs) on the release kinetics, the beads containing 20% of cefadroxil were selected, and these results are displayed in Fig. 5. The release rates of cefadroxil were much faster for the Na-Alg beads than for the IPNs of gelatin or egg albumin. This is due to an increased rigidity of the polymeric beads. Furthermore, the release of cefadroxil from the gelatin-based IPNs was slower than from the egg albumin-based IPNs. Approximately 80% of cefadroxil was released from the Na-Alg beads at 6 h (about 400 min), but only about 63 and 75% of release occurred for the gelatin- and egg albumin-based IPNs, respectively. Our results follow similar trends to those of the release of timolol maleate from the chitosan treated alginate beads [31]. However, the bead sizes in [31] were in the size range of 0.78–1.16 mm with an encapsulation efficiency of 67%, which is lower than our results.

Diffusion-CR of the drug-loaded beads is intimately related to the molecular transport of drugs through the polymeric matrices. Therefore, in order to understand the type of transport phenomenon, we have analyzed the release data, i.e. M_t/M_∞ (before 60% release), using an empirical relationship as in Eq. (6) [32,33].

$$\left(\frac{M_t}{M_\infty}\right) = kt^n \tag{6}$$

Here, k is a kinetic constant related to the drug–polymer interaction, n is the exponent parameter, which gives an indication about the type of transport phenomenon. The values of k and n have been calculated by the least squares method at the 95% confidence limit. The results of the above calculations are included in Table 1. Eq. (6) is valid up to the initial 60% release of the drug, and Fickian diffusion is defined for the value of $n = 0.5$; for the non-Fickian diffusion, $n > 0.5$. With spherical beads, the $t^{1/2}$ dependence of Fickian diffusion is only valid for the first 10–15% of the total drug release. Thus, for non-planar geometries, the diffusional limits of n for Fickian diffusion are based on the first 60% of the fractional release. For these cases, a value of $n = 0.43$ has been suggested for swellable and non-swellable matrices [32]. The values of n calculated for all the systems varied between 0.51 and 0.69, indicating a slight variation from Fickian transport [25,26]. Lower values of n (0.51–0.56) were observed for the gelatin-based IPNs than for the egg albumin-based IPNs, for which n varied between 0.54 and 0.59. On the other hand, for the Na-Alg beads, n varied between 0.66 and 0.69. The lower k values for all the systems indicate a lesser interaction between the bead materials and cefadroxil.

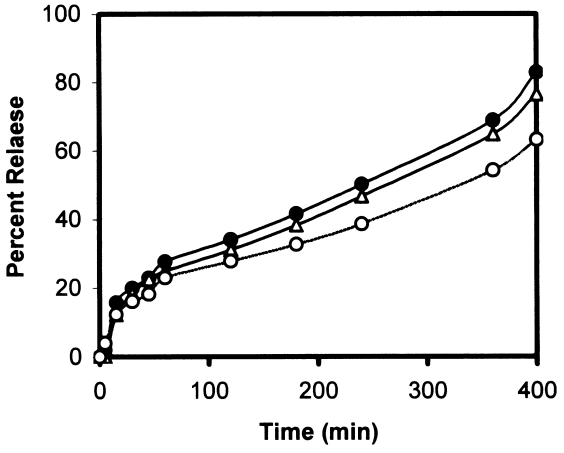

Fig. 5. Effect of IPN formation on the release of: (●), Na-Alg; (△), egg albumin; and (○), gelatin beads.

4. Conclusions

New IPNs of Na-Alg with gelatin or egg albumin are prepared and used in the CR of cefadroxil. Cross-linking was done using GA, and all the materials used are environmentally friendly. We have demonstrated that it is possible to prepare cefadroxil-loaded beads with high encapsulation efficiencies (up to 88%) and low burst release rates. The method developed is simple, fast and reproducible. A remarkable delay in the release of cefadroxil was observed for Na-Alg IPN beads when cross-linked with another cross-linked system, such as albumin or gelatin. Higher M_C values were observed for the cefadroxil-loaded gelatin IPNs when compared with other beads. The size of the beads was not affected by network formation or by increasing the exposure time to the cross-linking agent. The results of in-vitro dissolution and release kinetics indicated an anomalous transport mechanism.

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