Available online at www.sciencedirect.com
ScienceDirect
European Journal of Pharmaceutics and Biopharmaceutics 65 (2007) 204–214
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

Release characteristics of diclofenac sodium from poly(vinyl alcohol)/sodium alginate and poly(vinyl alcohol)-grafted-poly(acrylamide)/sodium alginate blend beads

Oya Şanlı [a,*], Nuran Ay [a], Nuran Işıklan [b]

[a] *Gazi Üniversitesi, Fen Edebiyat Fakültesi, Kimya Bölümü, Ankara, Turkey*
[b] *Kırıkkale Üniversitesi, Fen Edebiyat Fakültesi, Kimya Bölümü, Kırıkkale, Turkey*

Received 26 May 2006; accepted in revised form 8 August 2006
Available online 18 August 2006

Abstract

In this study, acrylamide (AAm) was grafted onto poly(vinyl alcohol) (PVA) with UV radiation at ambient temperature. The graft copolymer (PVA-g-PAAm) was characterized by using Fourier transform infrared spectroscopy (FTIR), elemental analysis and differential scanning calorimetry (DSC). Polymeric blend beads of PVA-g-PAAm and PVA with sodium alginate (NaAlg) were prepared by cross-linking with glutaraldehyde (GA) and used to deliver a model anti-inflammatory drug, diclofenac sodium (DS). Preparation condition of the beads was optimized by considering the percentage entrapment efficiency, particle size, swelling capacity of beads and their release data. Effects of variables such as PVA/NaAlg ratio, acrylamide content, exposure time to GA and drug/polymer ratio on the release of DS were discussed at three different pH values (1.2, 6.8, 7.4). It was observed that, DS release from the beads decreased with increasing PVA/NaAlg (m/m) ratio, drug/polymer ratio (d/p) and extent of cross-linking. However, DS release increased with increasing acrylamide content of the PVA-g-PAAm polymer. The highest DS release was obtained to be 92% for 1/1 PVA-g-PAAm/NaAlg ratio beads. It was also observed from release results that DS release from the beads through the external medium is much higher at high pH (6.8 and 7.4) than that at low pH (1.2). The drug release from the beads mostly followed Case II transport.

Keywords: Graft copolymer; Controlled release; Drug delivery systems; Diclofenac sodium; Hydrophilic polymers

1. Introduction

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, reduced toxicity, and improved patient compliance and convenience [1].

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. Beads can also offer advantages like limiting fluctuation within therapeutic range, reducing side effects, decreasing dosing frequency and improving patient compliance [2].

In view of their abundance and biocompatibility, natural polymers like polysaccharides have been used in drug delivery applications [3–5]. Among such natural polymers alginates which are naturally occurring polysaccharides obtained mainly from brown algas belonging to the *Phaeophyceae* and composed of two monomeric units, β-D-mannuronic acid and α-L-guluronic acid [6]. Alginate salts are known to form a reticulated structure when in contact with calcium ions or glutaraldehyde and this characteristic has been used to produce sustained release particulate systems for a variety of drugs, proteins and even cells [6,7].

* Corresponding author. Present address: Gazi Üniversitesi, Fen Edebiyat Fakültesi, Kimya Bölümü, 06500 Ankara, Turkey. Tel.: +90 312 2126030/3052; fax: +90 312 2122279.
E-mail address: osanli@gazi.edu.tr (O. Şanlı).

0939-6411/$ - see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejpb.2006.08.004

Poly(vinyl alcohol) has been used in a wide variety of fields since its discovery in 1924 [8] because of its desirable properties such as nontoxicity and noncarcinogenicity [9]. It finds extensive applications as biomaterials [9–11] such as contact lenses, artificial blood vessels, artificial intestines [8], and artificial kidneys [10]. Studies have been carried out for the drug release with PVA hydrogels; which are biocompatible, chemically stable, and desirable for both bioseparations and cell encapsulations [9,11,12]. However, PVA is a highly hydrophilic polymer and has poor stability in water; thus its solubility must be prevented for use in aqueous systems. To overcome this problem, PVA should be insolubilized by blending [13], copolymerization [14], grafting [15,16], and cross-linking [17,18]. The polymer blending technique can be considered as a useful tool for the preparation of new alginate beads with PVA. NaAlg can be cross-linked using glutaraldehyde, due to the chemical reaction between hydroxyl groups of NaAlg and aldehyde groups of GA [19].

In this study it was aimed to prepare PVA-g-PAAm/NaAlg and PVA/NaAlg blend beads containing diclofenac sodium to achieve a controlled drug release profile suitable for oral administration. DS, a potential non-steroidal anti-inflammatory drug with pronounced analgesic properties, is used in the long-term treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis [20]. Its biological half-life has been reported as 1–2 h [21,22]. Gastrointestinal side effects such as bleeding, ulceration or perforation of intestinal wall are commonly seen [20,23,24]. Due to short biological half-life and associated adverse effects, it is considered as an ideal candidate for controlled drug delivery. There are many controlled delivery studies for diclofenac sodium [20–25].

In our previous work [18], PVA and PVA/PAA membranes at different combinations were prepared for the release of diclofenac sodium under in vitro conditions. In the present study, firstly AAm was grafted onto PVA and then PVA/NaAlg and PVA-g-AAm/NaAlg blend beads were prepared in various blend ratios with GA as a cross-linking agent. Particle size, bead yield, entrapment efficiency, equilibrium swelling degree of the beads and DS release rate were investigated at 1.2, 6.8 and 7.4 pH values. The effects of AAm grafting, blend ratio, extent of cross-linking and drug/polymer ratio on DS release from the beads were researched and discussed.

2. Experimental

2.1. Materials

Sodium alginate with a viscosity of 3500 cps (2% solution, 25 °C) was purchased from Sigma Chemical Co (Louis, USA). PVA and AAm were supplied by Merck (Darmstadt, Germany). The molecular weight and degree of saponification of PVA were 72,000 and greater than 98%, respectively. Diclofenac sodium was kindly provided by Novartis (Summit, NJ). Glutaraldehyde (25% w/w) solution, Na_2HPO_4, NaH_2PO_4, benzophenone, hydroquinone, DMSO and methanol were all supplied from Merck (Darmstadt, Germany) and were used as received.

2.2. Synthesis of the graft copolymer of PVA with AAm

The grafted copolymers of PVA with acrylamide were synthesized via an ultraviolet-initiated photopolymerization technique in the presence of an accelerator (benzophenone). The PVA solution was mixed with acrylamide solution under a slow stream of nitrogen gas for 30 min. After that benzophenone solution was added to this mixture and solution was exposed to UV irradiation (Helios Italquartz, GR.E. 125 W, Italy) for 1, 3 and 6 h at ambient temperature. At the end of specified polymerization period, the reaction was terminated by adding saturated hydroquinone solution. The resultant solution was added into excess amount of acetone to precipitate the polymer, which was then filtered through the suction and dried in vacuum oven (Medcenter, Einrichtungen GmbH, Germany) at 60 °C. The polymer was dissolved in dimethylsulfoxide and filtered to remove the polyacrylamide. The filtrate was concentrated and the dissolved graft copolymer was again precipitated in excess amount of acetone. The graft copolymer was vacuum-dried at 40 °C for 48 h. The percentage grafting was estimated from the elemental analysis using with a LECO CHNS-932 C-, H-, N- analyzer (USA).

2.3. Viscometric measurements

Viscosities of the copolymers solutions were determined using an Ubbelhode viscometer in water thermostated at 25 °C. The intrinsic viscosity $[\eta]$ of polymer solutions was calculated as

$$[\eta] = \lim_{C \to 0} \left(\frac{\eta - \eta_0}{\eta_0 C} \right) \quad (1)$$

where η_0, η and C are the solvent viscosity, solution viscosity, and concentration (g/dL) of the polymer, respectively. Intrinsic viscosity was determined by extrapolating the linear portion of the reduced viscosity vs concentration plot to the zero concentration. From the values of $[\eta]$, the viscosity average molar mass, $\overline{M}_\eta$, was calculated using the Mark Houwink-Sakurada (MHS) relation:

$$[\eta] = k(\overline{M}_\eta)^\alpha \quad (2)$$

The values of the MHS parameters, k and α, were taken as 1.4×10^{-3} dL/g, 0.6, respectively, from the literature [26].

2.4. Preparation of the NaAlg beads

The mixture of NaAlg with PVA or PVA-g-PAAm containing diclofenac sodium in various drug/polymer ratios was prepared and stirred to form homogeneous solution for 12 h. The polymer solution containing DS was then added dropwise into water containing glutaraldehyde and HCl using peristaltic pump (Masterflex, L/S Digital Econ-

omy Drive, USA). The formed beads were then removed from the cross-linking solution at selected time intervals of 2.5, 5 min and were washed with water repeatedly to remove the adhered glutaraldehyde and acid; the beads were then dried completely in oven at 40 °C. Unloaded beads were prepared in a similar way without DS to determine equilibrium swelling degree. Beads, preparation conditions are displayed in Table 1. In order to estimate the size of beads ten samples of the completely dried beads from different formulations were selected and their sizes were measured by using a micrometer screw gauge (Aldrich, Germany).

2.5. Equilibrium swelling study of the beads

The equilibrium swelling degree (ESD) of the cross-linked empty beads was determined by measuring gravimetrically the extent of their swelling in buffer solutions at pH 1.2, 6.8, 7.4 at 37 °C. To ensure complete equilibration, the samples were allowed to swell for 24 h. The excess surface-adhered liquid drops were removed by blotting, and the swollen beads were weighed using electronic balance (Precisa XB 220A, USA). The beads were then dried in an oven at 40 °C until constant weight. The percent equilibrium swelling degree was calculated as follows:

$$\text{Equilibrium swelling degree } (\%) = \frac{(M_s - M_d)}{M_d} \times 100 \quad (3)$$

where M_s and M_d are mass of swollen beads and mass of dry beads, respectively.

2.6. Determination of diclofenac sodium content of the beads

The known mass of beads was crushed in an agate mortar with a pestle and then polymeric powder was refluxed with 50 mL of methanol for 4 h to ensure the complete extraction of DS from the beads. After that, the absorbance of the methanol containing the extracted amount of DS was taken at a wavelength of 280 nm in a UV spectrophotometer (Unicam UV2-100, UK) using pure methanol as a blank. The percentage of entrapment efficiency was then calculated as:

$$\text{Entrapment efficiency}(\%) = \frac{\text{Practical DS loading}}{\text{Theoretical DS loading}} \times 100 \quad (4)$$

2.7. Fourier transform infrared measurements (FTIR)

FTIR spectra of the grafted and ungrafted PVA were taken with a Mattson 1000 FTIR spectrometer (UK). FTIR spectra were taken in the wavelength region 400–4000 cm^{-1} at ambient temperature.

2.8. Differential scanning calorimetry (DSC)

The thermal analysis was performed with a Dupont General V4.1C 2000 differential scanning calorimeter (USA). The sample weights ranged from 5 to 8 mg. The samples were heated from 50 to 250 °C at a heating rate of 10 °C/min. The intercept point of the slopes was taken as glass-transition temperature (T_g).

2.9. Scanning electron microscope (SEM)

SEM photographs were taken with JSM 5600 Scanning Microscope (Japan) to examine the morphology and surface structure of the beads at the required magnification at room temperature. The beads were deposited on brass hold and sputtered with a thin coat of gold under vacuum. Acceleration voltage used was 20 kV with the secondary electron image as a detector.

Table 1
Entrapment efficiency, yield (%) and bead diameter for the DS loaded beads

Code	Polymer	Concentration of GA (%) and HCl (%)	Exposure time to GA (min)	Drug/polymer ratio	Entrapment efficiency (%)	Yield (%)	Bead diameter (mm)
A_1	PVA/NaAlg 3/1	2.5 + 3	5	1/1.5	41.9 ± 0.60	60.47 ± 3.16	1.13 ± 0.010
A_2	PVA/NaAlg 3/1	2.5 + 3	5	1/1.25	44.53 ± 1.16	60.33 ± 0.32	1.23 ± 0.022
A_3	PVA/NaAlg 3/1	2.5 + 3	5	1/1	44.93 ± 0.45	62.32 ± 0.55	1.32 ± 0.023
B_1	PVA/NaAlg 2/1	2.5 + 3	5	1/1.5	42.3 ± 1.15	61.43 ± 1.37	1.06 ± 0.014
B_2	PVA/NaAlg 2/1	2.5 + 3	5	1/1.25	43.17 ± 1.40	63.17 ± 0.85	1.10 ± 0.050
B_3	PVA/NaAlg 2/1	2.5 + 3	5	1/1	46.63 ± 0.32	65.07 ± 1.26	1.15 ± 0.093
C_1	PVA/NaAlg 1/1	2.5 + 3	5	1/1.5	44.23 ± 3.30	62.80 ± 0.46	0.84 ± 0.014
C_2	PVA/NaAlg 1/1	2.5 + 3	5	1/1.25	46.00 ± 2.80	65.48 ± 2.34	0.84 ± 0.016
C_3	PVA/NaAlg 1/1	2.5 + 3	5	1/1	45.80 ± 1.47	65.60 ± 1.87	0.85 ± 0.011
D_1	NaAlg	2.5 + 3	5	1/1.5	37.43 ± 1.50	50.69 ± 1.92	0.64 ± 0.033
D_2	NaAlg	2.5 + 3	5	1/1.25	37.50 ± 2.38	51.54 ± 0.50	0.68 ± 0.015
D_3	NaAlg	2.5 + 3	5	1/1	39.67 ± 0.50	56.28 ± 1.18	0.69 ± 0.009
E	PVA/NaAlg 1/1	1 + 1	5	1/1.5	40.30 ± 0.26	44.87 ± 2.81	0.78 ± 0.033
F	PVA/NaAlg 1/1	1 + 1	2.5	1/1.5	40.97 ± 0.91	42.93 ± 0.40	0.75 ± 0.024
G_1	PVA-g-PAAm1/NaAlg 1/1	1 + 1	5	1/1.5	38.50 ± 1.40	55.20 ± 0.79	0.55 ± 0.009
G_2	PVA-g-PAAm2 /NaAlg 1/1	1 + 1	5	1/1.5	37.00 ± 0.46	53.27 ± 1.10	0.55 ± 0.015
G_3	PVA-g-PAAm3/NaAlg 1/1	1 + 1	5	1/1.5	35.33 ± 1.25	51.95 ± 1.40	0.51 ± 0.015

2.10. In vitro drug release

The in vitro drug release from the beads was studied in 250 mL conical flasks containing pH 1.2, HCl solution, pH 6.8, pH 7.4 phosphate buffer solutions and incubated in a shaking water-bath (Medline BS-21, Korea) at 37 °C, with a speed of 50 rpm. At 2 h intervals DS release medium was changed to be pH: 1.2, 6.8 and 7.4, respectively. Four milliliter solution was withdrawn at specific time intervals and DS content was determined by UV spectrophotometer at 280 nm. Equal volume of fresh HCl or phosphate buffer solution was replaced into the release medium to maintain constant volume. Experiments were performed in triplicate in order to minimize the variational error. Standard deviations from the average values were calculated.

3. Results and discussion

3.1. Synthesis and characterization of the graft copolymer of PVA with AAm

Graft copolymerization of PVA with AAm was achieved in the presence of UV irradiation. The elemental analysis results, percentage grafting and grafting yield are presented in Table 2. As it is seen from the table, grafting percentage and grafting yield (%) increased with the increase in reaction time. Presence of nitrogen in the grafted PVA and increasing content of it with the reaction time confirm the grafting reaction. Fig. 1 shows a possible reaction between PVA and AAm.

IR spectra of PVA and grafted PVA are shown in Fig. 2. A broad band around 3391 cm^{-1} in both cases is attributed to the O—H stretching vibration of hydroxyl group of PVA. Similar O—H stretching can be seen in the grafted copolymer spectra, indicating that all the hydroxyl groups of PVA are not involved in the grafting reaction. A sharp band at 1245 cm^{-1} corresponds to C—O—C symmetrical stretching (in acetyl group) present on the PVA backbone due to the unhydrolyzed acetate groups of poly(vinyl acetate). The peak due to an asymmetric N—H stretching vibration of the primary amide overlaps with the O—H stretching vibrations. The aliphatic C—H stretching vibrations appear at ~2935 cm^{-1}. A characteristic peak at 1645 cm^{-1} is due to the carbonyl (C=O) stretch of the AAm polymeric chain in grafted PVA. Grafting was also confirmed by the presence of strong bands at 1618 cm^{-1} corresponding to asymmetric N—H bending [27].

The results of viscosity measurements along with the viscosity average molecular masses are presented in Table 2, assuming the k and α values do not change with the grafting. The observed increases in intrinsic viscosity and molecular mass of the PVA can be attributed to the grafting. As the reaction time is increased from the 1 h to 6 h, the amount of acrylamide grafted onto PVA increased and thereby viscosity average molecular mass increased relatively.

DSC analyses were performed to understand the thermal behavior of the graft copolymers and results are illustrated in Fig. 3. As it is reflected from Fig. 3 that temperature of the end point of the endotherm peak shifted 117.08 °C to 122.60 °C with the grafting of AAm monomer. T_g values of NaAlg and PVA polymers used in this study were found to be 93 and 96 °C, respectively, whereas the value for PVA-g-PAAm1 was found to be 99 °C. T_g is affected by both the degree of modification and the character of the substituent, for the PVA-g-PAAm copolymer. T_g increases as the bulkiness of the side chain increases, and the presence of the amide side chain imparts rigidity of the polymer. Since the T_g value of polyacrylamide

Table 2
Elemental analysis, AAm grafting (%), grafting yield (%), intrinsic viscosity and viscosity average molar mass of polymers

Polymer	Reaction time (h)	N (%)	C (%)	H (%)	Grafting (%)	Grafting efficiency (%)	[η]	M_v
PVA	–	–	–	–	–	–	0.9870	56,000
PVA-g-PAAm1	1	3.73	54.86	6.97	19	41.0	1.3919	99,000
PVA-g-PAAm2	3	6.89	50.41	8.42	35	75.4	1.5019	112,000
PVA-g-PAAm3	6	8.92	48.76	8.02	45	98.0	1.8202	155,000

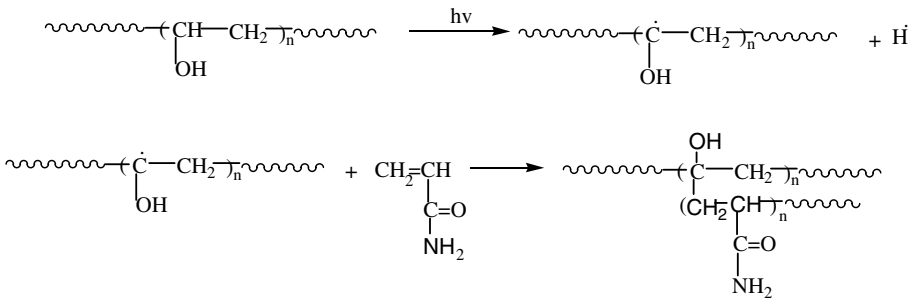

Fig. 1. Postulated grafting reaction mechanism of PVA with AAm.

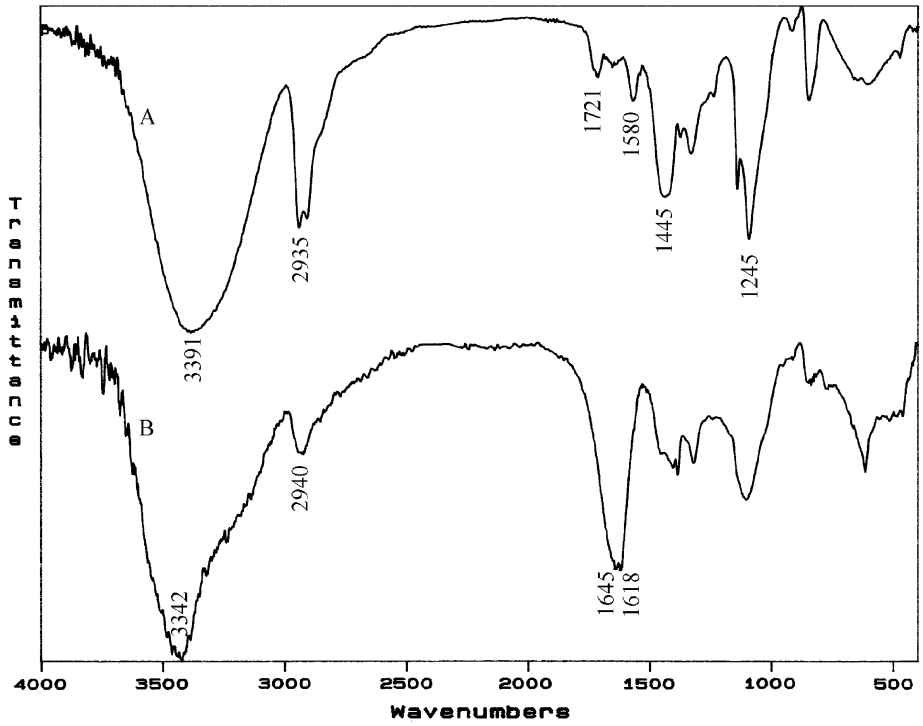

Fig. 2. IR spectra of PVA (A) and PVA-g-PAAm (B).

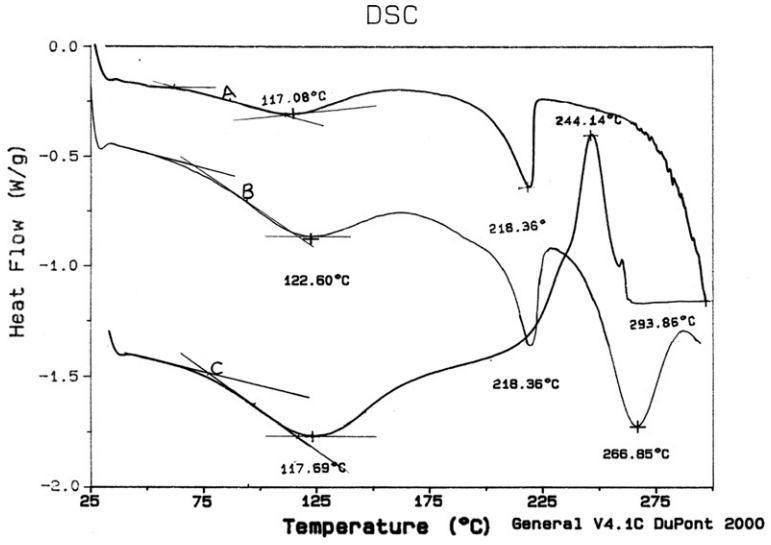

Fig. 3. DSC results of PVA (A), PVA-g-PAAm (B) and NaAlg (C).

($T_g = 165$ °C) is higher than the PVA [26]. Therefore, T_g value of the PVA increases with the grafting of AAm onto PVA. Similar results were found in the literature [28,29].

3.2. SEM study

SEM photographs of a single bead taken at 60x magnification are shown in Fig. 4. As it is seen from the figure, all the beads are almost of spherical shape and empty bead shows smooth surface whereas DS loaded bead shows roughness in surface.

3.3. Particle size, entrapment efficiency and yield value evaluation of beads

The results of bead diameter, entrapment efficiency (%) and bead yield (%) are shown in Table 1. As can be seen from the table, the beads formed have particle sizes ranging from 0.51 ± 0.02 to 1.32 ± 0.02 mm in diameter. The size of the beads changed with PVA/NaAlg (m/m) ratio and acrylamide content whereas it did not vary significantly either with drug/polymer (m/m) ratio or the concentration of GA. In general, diameters of the PVA/NaAlg beads are

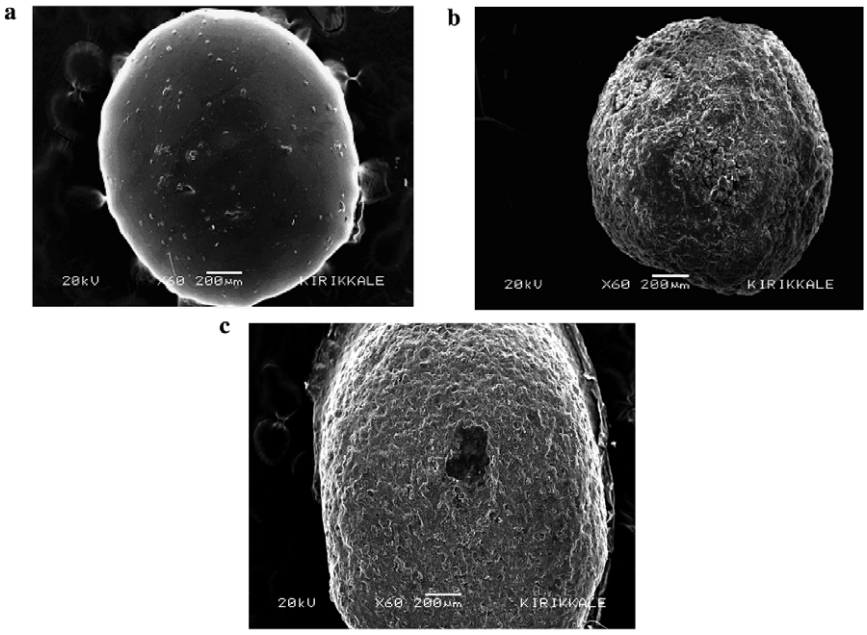

Fig. 4. SEM photographs of empty PVA/ NaAlg bead ×60 (a), DS loaded PVA/ NaAlg bead ×60 (b), DS loaded PVA-g-PAAm/NaAlg bead ×60 (c).

much larger than those of NaAlg beads. In all of the formulations, with increasing PVA content, diameter of the beads increases. Kurkuri and coworker [30] have found similar release from poly(vinyl alcohol) and poly(acrylic acid) interpenetrating network of pH sensitive microspheres.

The grafting ratio played an important role in the particle size. Diameter of the beads also decreased with grafting of acrylamide onto PVA. For instance, diameter of 1/1 PVA/NaAlg beads (E) is found to be 0.78 ± 0.03 mm whereas diameter of 1/1 PVA-g-PAAm1/NaAlg beads (G1) is found to be 0.55 ± 0.01 mm. Similar findings were reported by Kumbar and Aminabhavi [31].

The percentage of entrapment efficiency and bead yield may change depending on the preparation conditions and the type of matrix material of the beads. These values increased slightly with increasing both of the drug/polymer ratio and the PVA/NaAlg ratio. Percentage of entrapment efficiency and yield value of PVA/NaAlg beads were found to be higher than those of pure NaAlg beads (Table 1). When the PVA is added and the amount of it is increased, polymer concentration and viscosity of bead preparation solution increase. As a result, polymer traps more DS molecules and entrapment efficiency increases. The percentage of entrapment efficiency and yield values are also affected by grafting of acrylamide onto PVA. The lowest entrapment efficiency was found to be 35.33 ± 1.25 for the PVA-g-PAAm3/NaAlg bead formulation.

3.4. Effect of PVA/NaAlg ratio on the DS release

To understand the release of DS from cross-linked PVA/NaAlg beads in vitro release study was carried out in gastric, input intestinal and intestinal pH conditions at 37 °C. Figs. 5–7 display the cumulative DS release of beads in different PVA/NaAlg ratios (with 1/1.5, 1/1.25, 1/1 drug/polymer ratios and 2.5% GA, 3% HCl concentration). From the figures, it is observed that release rate of DS is much higher for the NaAlg beads than for the PVA/NaAlg beads. The highest cumulative DS release obtained at the end of 6 h was 81% for NaAlg beads, which have 1/1.5 drug/polymer ratio. On the other hand; the least cumulative DS release obtained was found to be 12% with 3/1 PVA/NaAlg beads, which have 1/1drug/polymer ratio. When the amount of PVA is increased in the PVA/NaAlg beads from 1/1 to 3/1, decreases in the DS release are also observed as it is seen from the figures.

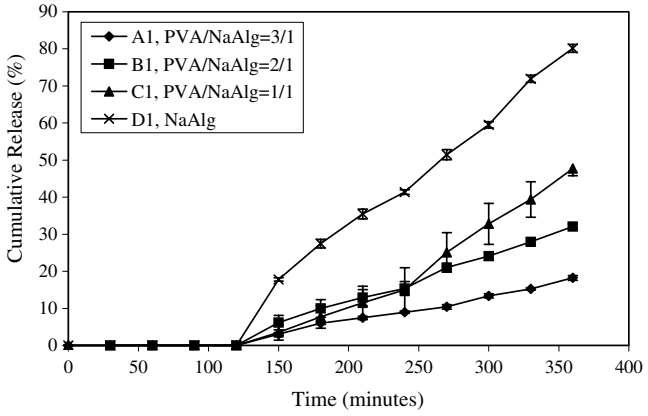

Fig. 5. Effect of PVA/NaAlg ratio on DS release. d/p:1/1.5, concentration of GA: 2.5%, exposure time to GA: 5 min.

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 compared to

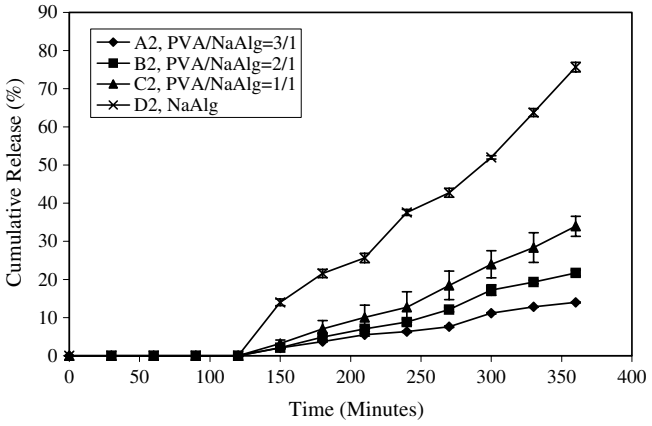

Fig. 6. Effect of PVA/NaAlg ratio on DS release. d/p:1/1.25, concentration of GA: 2.5%, exposure time to GA: 5 min.

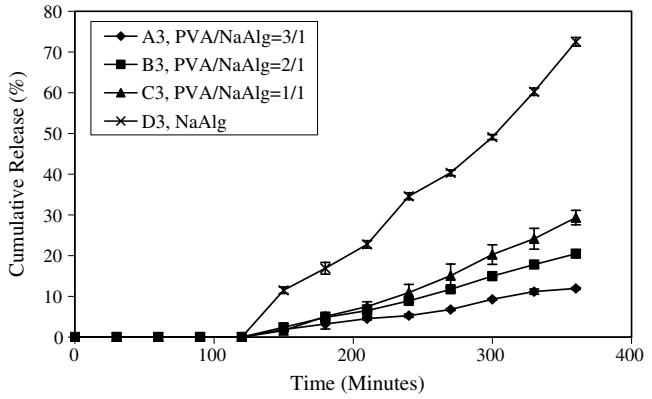

Fig. 7. Effect of PVA/NaAlg ratio on DS release. d/p:1/1, concentration of GA: 2.5%, exposure time to GA: 5 min.

alginate and thus PVA produces a compact network of macromolecular chains in the blend beads. Therefore, penetration of liquid molecules through PVA/NaAlg beads and then diffusion of drug to external medium is difficult compared to the NaAlg beads.

The results obtained show good consistency with the swelling results. Equilibrium swelling experiments were performed in distilled water and in buffer solution of different pH values (pH: 1.2, 6.8 and 7.4) for various empty bead formulations and are presented in Table 3. As can be seen from the table, in all the conditions, equilibrium swelling degree decreases with increasing PVA content of the beads. Furthermore the table shows that ESD values increase with the increase in pH of the external medium. Similar results were found in the literature [32–34].

Bajpai and Giri [32] prepared graft copolymerization of cross-linked polyacrylamide chains onto carboxymethyl cellulose and poly(vinyl alcohol) and studied swelling dynamics and controlled release of KNO_3 of this macromolecular network. They have observed that swelling and KNO_3 release of the network decreases with the PVA content.

A pronounced difference is also observed in the release data between pH of 1.2 and pH of 6.8, 7.4 conditions, which can be attributed to less swelling of alginate in acidic medium [23]. At acidic pH, DS release is low for 2 h. At low pH values the less swelling should reduce the matrix permeability and limit the drug diffusion. At this pH, alginate is protonated into insoluble form of alginic acid; this displays properties of swelling that explains low amount of the release. Moreover, DS exists in its acidic form in an acidic solution such as in gastric fluid and it is practically insoluble in stomach, but soluble in intestinal fluid and water [25]. At pH 6.8 and 7.4 a rapid increase of the release is observed up to 90%. The deprotonation of alginic acid causes disintegration of the bead systems and nearly completes the release of DS as soluble ions.

3.5. Effect of drug/polymer ratio on the DS release

Another parameter that affects the DS release from the beads is drug/polymer ratio. The effect of d/p ratio on DS release is shown in Figs. 8–10. The figures illustrate that DS release from the PVA/NaAlg beads with 1/1.5 d/p ratio is much higher than that of beads 1/1.25 and 1/1 d/p ratio. The maximum DS release for the beads in 1/1.5 d/p ratio with different PVA/NaAlg ratios, 3/1, 2/1 and 1/1, is obtained to be 18%, 32% and 48%, respectively. When the d/p ratio decreases from 1/1 to 1/1.5, DS content of the beads decreases. Lower DS content might be lead to the easier penetration of liquid through beads and then faster DS diffusion occurs from the beads. The other explanation is that while DS content of the beads decreases, loose structure in the polymeric beads has formed in which

Table 3
Equilibrium swelling degree for beads

Code	Water	pH 1.2	pH 6.8	pH 7.4
A	120.20 ± 2.42	96.33 ± 2.07	119.07 ± 1.56	134.40 ± 5.07
B	114.27 ± 1.29	89.43 ± 1.12	113.50 ± 7.33	134.03 ± 1.80
C	101.73 ± 2.06	80.87 ± 1.56	102.10 ± 3.55	128.57 ± 4.30
D	1412 ± 1.42	112.13 ± 2.07	1388.13 ± 1.58	1485.83 ± 3.26
E	146.70 ± 4.61	109.47 ± 1.00	141.90 ± 6.94	198.23 ± 4.38
F	178.30 ± 7.14	140.10 ± 1.65	180.60 ± 7.37	207.53 ± 12.22
G_1	221.3 ± 6.32	170.53 ± 1.56	217.17 ± 5.20	232.93 ± 4.17
G_2	260.64 ± 1.38	136.13 ± 1.83	196.06 ± 1.40	285.99 ± 1.46
G_3	277.29 ± 1.49	154.13 ± 1.960	217.13 ± 1.43	305.06 ± 1.24

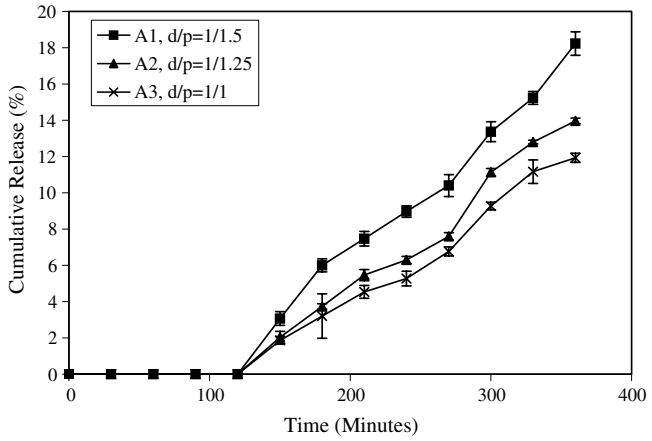

Fig. 8. Effect of drug/polymer ratio on DS release. PVA/NaAlg:3/1, concentration of GA: 2.5%, exposure time to GA: 5 min.

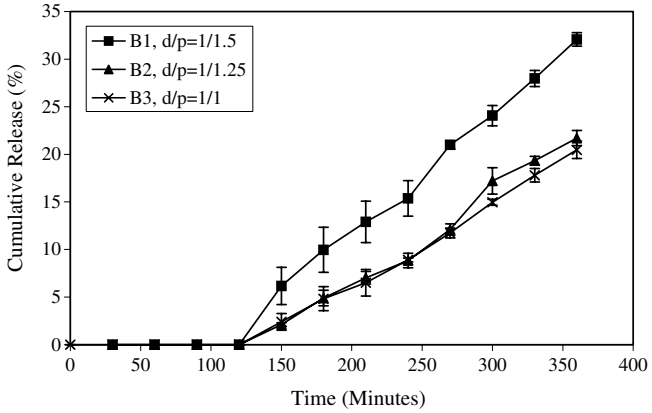

Fig. 9. Effect of drug/polymer ratio on DS release. PVA/NaAlg:2/1, concentration of GA: 2.5%, exposure time to GA: 5 min.

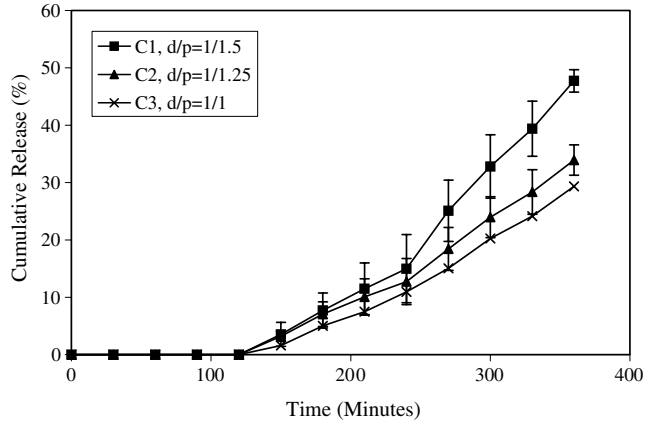

Fig. 10. Effect of drug/polymer ratio on DS release. PVA/NaAlg:1/1, concentration of GA: 2.5%, exposure time to GA: 5 min.

liquid and DS can easily penetrate and diffuse. Similar observations were found in the literature [28,29,31].

Kumbar and Aminabhavi [31] studied controlled release of indomethacin from polyacrylamide grafted chitosan microspheres. They have reported that drug release at lower loadings (<10%) is quicker than that of higher loading due to possibility of formation of a large pore volume, which might enhance the drug release.

3.6. Effect of exposure time to GA and concentration of GA on the DS release

DS release from the beads or microspheres was subjected to a number of physical and chemical parameters including those related directly to the release medium, the release conditions (temperature, pH), preparation conditions and those resulting from the change in the characteristics of the beads. One of the most effective ways to change release rate of beads is to change cross-link density of the matrix by employing varying times of exposure to cross-linking agent and concentrations of the cross-linking agent. The effect of exposure time to GA on the release rate of DS has been investigated at exposure times namely 2.5 and 5 min. The results are shown in Fig. 11, which clearly indicates that with increasing exposure time to GA (2.5–5 min), the release rate decreases at pH of 6.8 and 7.4. The maximum DS release from the 1/1 PVA/NaAlg beads, which were prepared with an exposure time of 2.5 min, was found to be 88%.

Another way to change the cross-link density of the bead is to change the concentration of GA. For this purpose, GA concentration was changed during the bead preparation from 1% to 2.5% and release results from these beads are presented in Fig. 12. As it is seen from the figure as the GA concentration increased from 1% GA to 2.5%, DS release decreased at pH of 6.8 and 7.4.

The observed decreases in the cumulative release are due to the fact that increasing exposure time and concentration of GA result in an increase in cross-link density of the bead which gives rise to a compact network of the polymer. Consequently, the free volume reduces and penetration of water molecules and diffusion of DS molecules become difficult.

DS release results were also supported by swelling measurements. As it is seen from the Table 3, increase in concentration and exposure time to GA decrease swelling

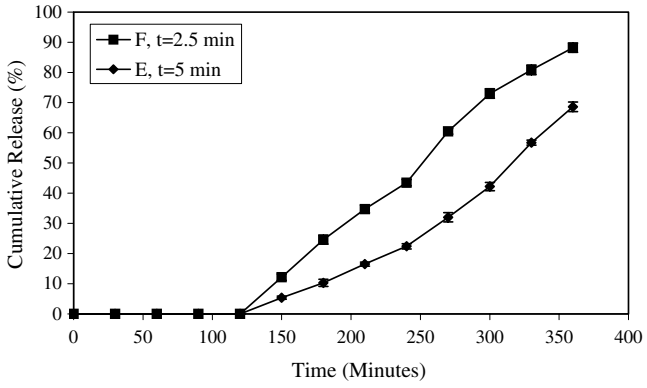

Fig. 11. Effect of exposure time on DS release. PVA/NaAlg:1/1, d/p: 1/1.5, concentration of GA: 1%.

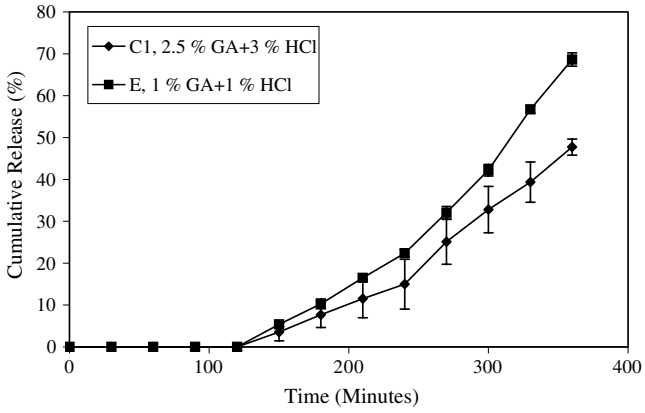

Fig. 12. Effect of GA concentration on DS release. PVA/NaAlg:1/1, d/p: 1/1.5, exposure time to GA: 5 min.

percentage. Similar results were reported by many other workers [4,19,28,29,33,35–38].

Kulkarni and coworkers [35] studied controlled release of diclofenac sodium from cross-linked alginate beads. They have reported that when the exposure to GA increased from 5 to 10 min at 25 °C and 40 °C, DS release significantly decreased.

3.7. Effect of acrylamide grafting on the DS release

In this study DS was also encapsulated by using PVA-g-PAAm and NaAlg matrices. The beads formed in three different percentages of grafting have almost spherical shapes with the rough surfaces as revealed by SEM (see Fig. 4). DS release kinetics from the beads, with different grafting percentages, and in 1/1 PVA-g-PAAm/NaAlg ratios, are presented in Fig. 13. It is reflected from the figure that DS release rate increases with the increasing amount of acrylamide in the PVA polymer. The highest DS release is obtained to be 92% for the beads that are prepared from grafted PVA (45% acrylamide) and NaAlg polymers.

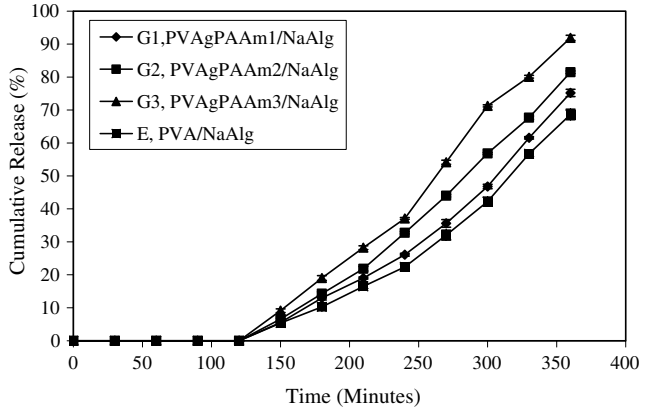

Fig. 13. Effect of grafting pecentage on DS release. PVA-g-PAAm/NaAlg:1/1, d/p: 1/1.5, exposure time to GA: 5 min, concentration of GA: 1%.

The results are quite expected and may be attributed to the fact that grafting of acrylamide onto PVA and increasing its content lead to increase in swelling of the beads as seen in Table 3 because of hydrophilic free amide groups in the grafted PVA. Thus, DS release from the swelled beads is easier than from the other beads and release rate increases with acrylamide content. Similar findings were obtained in the studies of Kulkuri et al. [30] They have reported that with increasing poly(acrylic acid) (PAA) content in the PVA and PAA microspheres, cumulative release of DS increases.

The results of all the release studies from the PVA/NaAlg beads are in good agreement with the results of studies reported in the literature based upon exposure time or concentration of GA, i/p ratio and PVA/NaAlg ratio [19,27–29,31,35]. As the increase of AAm grafting onto PVA increases the DS release rate, it is also in good accordance with the study of Kumbar and Aminabhavi [31]. They found the same results with the grafting of AAm onto guar gum.

3.8. Analysis of kinetic results

The phenomenon of solvent sorption by a polymeric bead depends mechanistically on the diffusion of water molecules into the gel matrix and subsequent relaxation of macromolecular chains of the bead [33]. The release data of all the systems have been further substantiated by fitting the fraction release data M_t/M_∞ to an empirical equation proposed by Peppas [39]

$$\frac{M_t}{M_\infty} = kt^n \tag{5}$$

where M_t is the amount of DS released at time t and M_∞ is the drug released at equilibrium time; k, a constant characteristic of the drug-polymer system; and n, 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 [40]. A value of $n = 0.5$ indicates the Fickian transport (mechanism), while $n = 1$ is of Case II or non-Fickian transport (swelling-controlled) [41]. The intermediary values ranging between 0.5 and 1.0 are indicative of the anomalous transport [28,29,35]. The least-squares estimations of the fractional release data along with the estimated correlation coefficient values, r, are presented in Table 4. From these data, the n value ranged between 0.68 and 1.27, with correlation coefficient values of 0.99, indicating DS release from the beads deviates from the Fickian transport.

To calculate the values of the apparent diffusion coefficients, the D of DS from the beads the initial portions of the release profiles (i.e.) $0 < M_t/M_\infty < 0.4$ as shown in Figs. 5–13 were analyzed by the Fickian theory [42]. This equa-

Table 4
The results of D, k, n and r calculated from Eqs. (5) and (6)

Code	$D \times 10^7$ (cm^2/s)	k (min^{-n}) $\times 10^2$	n	r	Diffusion mechanism
A_1	7.37	0.20	0.81	0.993	Case II
A_2	8.83	0.08	0.93	0.992	Case II
A_3	10.22	0.08	0.91	0.991	Case II
B_1	6.28	0.38	0.80	0.993	Non-Fickian
B_2	7.00	0.05	1.12	0.996	Case II
B_3	7.65	0.07	1.03	0.997	Case II
C_1	4.32	0.04	1.27	0.993	Case II
C_2	3.99	0.07	1.12	0.996	Case II
C_3	4.15	0.02	1.37	0.998	Case II
D_1	3.86	1.80	0.68	0.988	Non-Fickian
D_2	3.79	1.20	0.73	0.969	Non-Fickian
D_3	3.44	0.73	0.81	0.966	Non-Fickian
E	4.59	0.07	1.23	0.992	Case II
F	5.43	0.45	0.96	0.998	Case II
G_1	2.26	0.08	1.23	0.996	Case II
G_2	2.58	0.09	1.24	0.999	Case II
G_3	2.16	0.19	1.12	0.998	Case II

tion, given in the most simplified form, calculates the diffusion coefficients from the initial time approximation [39]:

$$\frac{M_t}{M_\infty} = \left(\frac{36Dt}{\pi r^2}\right)^{1/2} - \left(\frac{3Dt}{r^2}\right) \quad (6)$$

where r is the average radius of the beads. The data reported in Table 4 show a relationship between the exposure time and concentration of GA, d/p ratio and PVA/NaAlg ratio. The D value decreases from 5.43×10^{-7} cm^2/s to 4.59×10^{-7} cm^2/s with increasing exposure time to GA from 2.5 to 5 min, respectively. An increase in concentration of GA decreases diffusion coefficient which is also in agreement with release results (C_1, E). The D values also increase with increasing i/p (for example A_1, A_2, A_3) and PVA/NaAlg ratio (for example A_1, B_1, C_1).

4. Conclusions

DS release studies from the beads prepared from PVA/NaAlg and PVA-g-PAAm/NaAlg blends cross-linked with GA indicate that blending of PVA with NaAlg polymers leads to decrease in the release rate of DS whereas it increases the entrapment efficiency. It is also observed that release of DS is much higher at high pH values compared to low pH values showing that the release system is interesting as a controlled release system for colon-specific drug delivery. Further DS release from the beads increases with the increase in acrylamide grafting onto PVA whereas it decreases with the increase of exposure time to GA, concentration of GA, PVA/NaAlg ratio and drug/polymer ratio.

Acknowledgement

The authors are grateful to the Gazi University Scientific Research Foundation for support of this study.

References

[1] K.E. Uhrich, S.M. Cannizzaro, R.S. Langer, K.M. Shakesheff, Polymeric systems for controlled drug release, Chem. Rev. 99 (1999) 3181–3198.
[2] S. Haznedar, B. Dortunç, Preparation and in vitro evaluation of eudragit microspheres containing acetazolamide, Int. J. Pharm. 269 (2004) 131–140.
[3] M.H. Ottøy, O. Smidsrød, Swelling of poly-L-lysine and chitosan-coated superswelling sodium-alginate gel beads, Polym. Gels Netw. 5 (1997) 307–314.
[4] R.T. Thimma, S. Tammishetti, Barium chloride crosslinked carboxymethyl guar gum beads for gastrointestinal drug delivery, J. Appl. Polym. Sci. 82 (2001) 3084–3090.
[5] Y.-H. Lin, H.-F. Liang, C.-K. Chung, M.-C. Chen, H.-W. Sung, Physically crosslinked alginate/N,O-carboxymethyl chitosan hydrogels with calcium for oral delivery of protein drugs, Biomaterials 26 (2005) 2105–2113.
[6] P.F. Almeida, A.J. Almeida, Cross-linked alginate-gelatine beads: a new matrix for controlled release of pindolol, J. Control. Release 97 (2004) 431–439.
[7] W.R. Gombotz, S.F. Wee, Protein release from alginate matrices, Adv. Drug Deliv. Rev. 31 (1998) 267–285.
[8] S. Horiike, S. Matsuzawa, K. Yamaura, Preparation of chemically crosslinked gels with maleate-denatured poly(vinyl alcohol) and its application to drug release, J. Appl. Polym. Sci. 84 (2002) 1178–1184.
[9] K. Sreenivasan, On the restriction of the release of water-soluble component from polyvinyl alcohol film by blending β-cyclodextrin, J. Appl. Polym. Sci. 65 (9) (1997) 1829–1832.
[10] I. Orienti, R. Trere, B. Luppi, F. Bigucci, T. Cerchiara, G. Zuccari, V. Zecchi, Hydrogels formed by crosslinked poly(vinyl alcohol) as sustained drug delivery systems, Arch. Pharm. 335 (2002) 89–93.
[11] S.Y. Kim, Y.M. Lee, Drug release behavior of electrical responsive poly(vinyl alcohol)/poly(acrylic acid) IPN hydrogels under an electric stimulus, J. Appl. Polym. Sci. 74 (1999) 1752–1761.
[12] D.K. Kweon, D.W. Kang, Drug-release behavior of chitosan-g-poly(vinyl alcohol) copolymer matrix, J. Appl. Polym. Sci. 74 (1999) 458–464.
[13] X. Feng, R.Y.M. Huang, Preparation and performance of asymmetric polyetherimide membranes for isopropanol dehydration by pervaporation, J. Membr. Sci. 109 (1996) 165–172.
[14] K.H. Lee, H.K. Kim, J.W. Rhim, Pervaporation separation of binary organic-aqueous liquid mixtures using crosslinked PVA membranes III. Ethanol–water mixtures, J. Appl. Polym. Sci. 58 (1995) 1707–1712.
[15] R.Y.M. Huang, C.K. Yeom, Development of cross-linked poly(vinyl alcohol) (type II) and permeation of acetic acid–water mixtures, J. Membr. Sci. 62 (1991) 59–73.
[16] N. Işıklan, O. Şanlı, Permeation and separation characteristics of acetic acid/water mixtures through poly(vinyl alcohol-g-itaconic acid) membranes by pervaporation, evapomeation and temperature-difference evapomeation, J. Appl. Polym. Sci. 93 (2004) 2322–2333.
[17] N. Işıklan, O. Şanlı, Separation characteristics of acetic acid-water mixtures by pervaporation using poly(vinyl alcohol) membranes modified with malic acid, Chem. Eng. Process. 44 (2005) 1019–1027.
[18] O. Şanlı, G. Asman, Release of diclofenac through glutaraldehyde crosslinked poly(vinyl alcohol)/poly(acrylic acid), J. Appl. Polym. Sci. 91 (2004) 72–77.
[19] A.R. Kulkarni, K.S. Soppimath, T.M. Aminabhavi, Glutaraldehyde crosslinked sodium alginate beads containing liquid pesticide for soil application, J. Control. Release 63 (2000) 97–105.
[20] M.C. Gohel, A.F. Amin, Formulation optimization of controlled release diclofenac sodium microspheres using factorial design, J. Control. Release 51 (1998) 115–122.
[21] P.A. Todd, E.M. Sorkin, Diclofenac sodium, a reappraisal of its pharmacodynamic and phamacokinetic properties, and therapeutic efficacy, Drugs 35 (1988) 244–285.

[22] B. Arıca, M.Y. Arıca, H.S. Kaş, A.A. Hıncal, V. Hasırcı, In vitro studies of enteric coated Diclofenac sodium-carboxymethylcellulose microspheres, J. Microencapsul. 13 (1996) 689–699.
[23] M.J. Fernandez-Hervas, M.A. Holgado, A. Fini, J.T. Fell, In vitro evaluation of alginate beads of a diclofenac salt, Int. J. Pharm. 163 (1998) 23–34.
[24] M. Tuncay, S. Çaliş, H.S. Kaş, M.T. Ercan, İ. Peksoy, A.A. Hincal, Diclofenac sodium incorporated PLGA (50:50) microspheres: formulation considerations and in vitro/in vivo evaluation, Int. J. Pharm. 195 (2000) 179–188.
[25] H. Basan, M. Gümüşderelioğlu, T. Orbey, Diclofenac sodium releasing pH-sensitive monolithic devices, Int. J. Pharm. 245 (2002) 191–198.
[26] J. Brandrup, E.H. Immergut, Polymer Handbook, second ed., John Wiley and Sons, USA, 1975.
[27] T.M. Aminabhavi, H.G. Naik, Synthesis of graft copolymeric membranes of poly(vinyl alcohol) and polyacrylamide for pervaporation separation of water/acetic acid mixtures, J. Appl. Polym. Sci. 83 (2002) 244–258.
[28] S.G. Kumbar, K.S. Soppimath, T.M. Aminabhavi, Synthesis and characterization of polyacrylamide-grafted chitosan hydrogel microspheres for the controlled release of indomethacin, J. Appl. Polym. Sci. 87 (2003) 1525–1536.
[29] K.S. Soppimath, T.M. Aminabhavi, Water transport and drug release study from cross-linked polyacrylamide grafted guar gum hydrogel microspheres for the controlled release application, Eur. J. Pharm. Biopharm. 53 (2002) 87–98.
[30] M.D. Kurkuri, T.M. Aminabhavi, Poly(vinyl alcohol) and poly(acrylic acid) sequential interpenetrating network pH-sensitive microspheres for the delivery of diclofenac sodium to the intestine, J. Control. Release 96 (2004) 9–20.
[31] S.G. Kumbar, T.M. Aminabhavi, Synthesis and characterization of modified chitosan microspheres: effect of the grafting ratio on the controlled release of nifedipine through microspheres, J. Appl. Polym. Sci. 89 (2003) 2940–2949.
[32] A.K. Bajpai, A. Giri, Swelling dynamics of a macromolecular hydrophilic network and evaluation of its potential for controlled release of agrochemicals, React. Funct. Polym. 53 (2002) 125–141.
[33] A.K. Bajpai, M. Sharma, Preparation and characterization of binary grafted polymeric blends of polyvinyl alcohol and gelatin and evaluation of their water uptake potential, J. Macromol. Sci.-Pure Appl. Chem. 42 (2005) 663–682.
[34] C.K. Yeom, K.H. Lee, Characterization of sodium alginate and poly(vinyl alcohol) blend membranes in pervaporation separation, J. Appl. Polym. Sci. 67 (1998) 949–959.
[35] A.R. Kulkarni, K.S. Soppimath, T.M. Aminabhavi, Controlled release of diclofenac sodium from sodium alginate beads crosslinked with glutaraldehyde, Pharm. Acta Helv. 74 (1999) 29–36.
[36] A.K. Bajpai, M. Rajpoot, Release and diffusion of sulfamethoxazole through acrylamide-based hydrogel, J. Appl. Polym. Sci. 81 (2001) 1238–1247.
[37] O. Şanlı, N. Işıklan, Controlled release formulations of carbaryl based on copper alginate, barium alginate and alginic acid beads, J. Appl. Polym. Sci., in press.
[38] N. Işıklan, Controlled release of insecticide carbaryl from crosslinked carboxymethyl cellulose beads, Fresen. Environ. Bull. 13 (6) (2004) 537–544.
[39] N.A. Peppas, Analysis of Fickian and non-Fickian drug release from polymer, Pharm. Acta Helv. 60 (1985) 110–111.
[40] P.L. Ritger, N.A. Peppas, A simple equation for description of solute release II Fickian and anomalous release from swellable devices, J. Control. Release 5 (1987) 37–42.
[41] V. Ramesh Babu, K.S.V. Krishna Rao, M. Sairam, B. Vijaya Kumar Naidu, K.M. Hosamani, T.M. Aminabhavi, pH-Sensitive interpenetrating network microgels of sodium alginate-acrylic acid for the controlled release of ibuprofen, J. Appl. Polym. Sci. 99 (2006) 2671–2678.
[42] J. Crank, The Mathematics of Diffusion, second ed., Oxford, Clarendon, 1974.