In Vitro Release Study of Diltiazem Hydrochloride from Poly(vinyl pyrrolidone)/Sodium Alginate Blend Microspheres

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ABSTRACT: Polymeric blend microspheres of poly(vinyl pyrrolidone) (PVP) with sodium alginate (NaAlg) were prepared by cross-linking with calcium ions and used to deliver a calcium channel blocker drug, diltiazem hydrochloride (DT). The prepared microspheres were characterized by Fourier transform infrared spectroscopy and scanning electron microscopy. Scanning electron microscopy confirmed the spherical nature of the particles. Preparation conditions for the microspheres were optimized by considering the percentage entrapment efficiency, particle size, and swelling capacity. Effects of variables such as PVP/NaAlg ratio, molecular weight of PVP, cross-linker concentration, and drug/polymer ratio on the release of DT were discussed at two different pH values (1.2, 6.8) at 37°C. It was observed that DT release from the microspheres decreased with increasing molecular weight of PVP and extent of cross-linking. However, DT release increased with increasing PVP content and drug/polymer ratio (d/p) of the blend microspheres. The highest DT release percentage was obtained as 99% for PVP/NaAlg ratio of 1/2 with d/p ratio of 1/2 at the end of 4 h. It was also observed from release results that DT delivery from the microspheres through the external medium are much higher at low pH (1.2) value than that of high pH (6.8) value. The drug release from the microspheres mostly followed Fickian transport. J Appl Polym Sci 107: 1973–1980, 2008

Key words: controlled release; drug delivery systems-diltiazem hydrochloride; hydrophilic polymers; blend systems

INTRODUCTION

Polymeric controlled delivery systems have been used in a wide range of the drug industry. The main objective in drug delivery applications is to achieve an effective therapeutic administration over an extended period of time. These delivery systems often use macromolecules as carriers for the drugs. During the past decade, polymeric microspheres, beads, polymer micelles, and hydrogel-type materials have been shown to be effective in enhancing drug targeting specificity, lowering systemic drug toxicity, improving treatment absorption rates, and providing protection for pharmaceuticals against biochemical degradation.[1–3]

The parameters that affect the properties of controlled delivery systems such as beads, microspheres, or nanoparticles depend upon the nature and type of the polymer used. Several research work have contributed to development of formulations for the controlled release of drugs in pharmaceutics.[4–10] Despite several polymers used in these works, natural polymers are often preferred to synthetic polymers due to their nontoxic, low cost, free availability, and biodegradability.[11,12] However, several natural biopolymers, especially the class of polysaccharides, have some inherent disadvantages such as poor mechanical strength, uncontrolled water uptake, and microbial contamination.[11] To overcome these problems, efforts have been made to develop chemically modified matrices with improved or new properties by grafting[13–17] or blending[18–20] with other polymer. Chemical grafting is an unlimited method to get new substances with well defined properties but it is often time consuming and not seldom costly. On the other hand blending is an important well-known method for modification or improvement of the physical properties of polymeric materials.

Alginate is a naturally occurring polysaccharide obtained mainly from brown algae's belonging to the *Phaeophyceae* and composed of two monomeric units, β-D-mannuronic acid (M) and α-L-guluronic acid (G).[4] It has been used not only in controlled release applications of drugs[21–23] or pesticides[8,19,24] but also used in the biotechnology industry as a

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thickening agent, a gelling agent, and a colloidal stabilizer.[25] 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.[4,5]

As a polymer being soluble in both water and organic solvents, poly(*N*-vinyl-2-pyrrolidone) has been the focus of numerous applications including additives, cosmetics, coating, and biomedicines.[26] The principal reason for successful poly(vinyl pyrrolidone) (PVP) applications is its excellent biocompatibility with living tissues and extremely low cytotoxicity.

The polymer blending technique can be considered as a useful tool for the preparation of a new alginate microspheres with PVP. Sodium alginate (NaAlg) can be cross-linked using calcium chloride solution due to the ionotropic bonding between carboxyl groups of NaAlg and calcium ions according to the well-known ''egg-box model''.[25]

In this study it was aimed to prepare PVP/NaAlg blend microspheres containing diltiazem hydrochloride (DT) to achieve a controlled drug release profile suitable for oral administration. DT is an orally active calcium channel blocking agent effective in angina pectoris and the management of hypertension.[27] It has been reported to be rapidly absorbed from the gastrointestinal tract, and to be extensively metabolized in the liver, mainly by deacetylation.[28] Because of its low bioavailability and short half-life, many attempts have been made to develop slow release formulations for DT with an extended clinical effect.[29–31]

In our previous work,[32] we have prepared PVA-*g*-PAAm/NaAlg and PVA/NaAlg blend beads containing diclofenac sodium to achieve a controlled drug release profile suitable for oral administration. We have also studied release of salicylic acid through poly(vinyl alcohol)/PVP and poly(vinyl alcohol-*g*-*N*-vinyl-2-pyrrolidone) membranes for transdermal application.[33] In the present study, PVP/NaAlg blend microspheres were prepared in various blend ratios using calcium chloride as a cross-linking agent. Particle size, microspheres yield, entrapment efficiency, equilibrium swelling degree (ESD) of the microspheres, and DT release rate were investigated at 1.2 and 6.8 pH values. The effects of blend ratio, molecular weight of the PVP, extent of cross-linking, and drug/polymer ratio on DT release from the beads were researched and discussed.

EXPERIMENTAL

Materials

NaAlg with a viscosity 3500 cps (2% solution, 25°C) was purchased from Sigma Chemical (Louis, USA). PVP (MW: 40,000, 360,000, and 1,300,0000) was supplied by Fluka (Buchs, Switzerland). DT was kindly provided by Mustafa Nevzat A.Ş. (Turkey). Calcium chloride, Na_2HPO_4, and NaH_2PO_4 were all supplied from Merck (Darmstadt, Germany) and were used as received.

Preparation of the PVP/NaAlg microspheres

The mixture of NaAlg with PVP containing DT in various drug/polymer ratios were prepared and stirred to form homogenous solution for 12 h. The polymer solution containing DT was then added drop wise into calcium chloride solution using peristaltic pump (Masterflex, L/S Digital Economy Drive, USA), which has pump tubing with 0.8 mm of inside diameter. The formed microspheres were then removed from the cross-linking solution at selected time intervals of 1, 2.5, 5, 30 min and were washed with water repeatedly to remove the adhered calcium chloride solution; the microspheres were then dried completely in oven (Medcenter, Einrichtungen GmbH, Germany) at 40°C. Unloaded microsphes were prepared in a similar way without DT to determine ESD. Microspheres preparation conditions were displayed in Table I. To estimate the size of microspheres, 10 samples of the completely dried microspheres from different formulations were selected and their sizes were measured by using a micrometer screw gauge (Aldrich, Germany) and their standard deviations from the average values were also given in Table I.

Equilibrium swelling study of the microspheres

ESD of the cross-linked empty microspheres was determined by measuring gravimetrically the extent of their swelling should be in solution of pH = 1.2, and distilled water 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 microspheres were weighed using electronic balance (Precisa XB 220A, USA). The microspheres were then dried in an oven at 40°C till to constant weight. The percent ESD was calculated as follows:

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

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

Determination of DT content of the microspheres

The known mass of microspheres were crushed in an agate mortar with a pestle and then polymeric

TABLE I
Preparation Conditions and Microsphere Diameter for the DT Loaded Microspheres

Code	Polymer	Molecular weight of PVP	$CaCl_2$ concentration (*M*)	Crosslinking time in $CaCl_2$ (min)	Drug/polymer ratio	Microsphere diameter (mm)
K_1	PVP/NaAlg 1/1	40,000	0.1	30	1/2	0.27 ± 0.05
K_2	PVP/NaAlg 1/2	40,000	0.1	30	1/2	0.53 ± 0.01
K_3	PVP/NaAlg 1/4	40,000	0.1	30	1/2	0.64 ± 0.06
L_1	PVP/NaAlg 1/1	40,000	0.1	5	1/2	0.32 ± 0.01
L_2	PVP/NaAlg 1/2	40,000	0.1	5	1/2	0.63 ± 0.02
L_3	PVP/NaAlg 1/4	40,000	0.1	5	1/2	0.84 ± 0.02
L_4	PVP/NaAlg 1/2	40,000	0.1	1	1/2	0.65 ± 0.04
L_5	PVP/NaAlg 1/2	40,000	0.1	2.5	1/2	0.61 ± 0.02
N	NaAlg		0.025	1	1/2	0.90 ± 0.02
N_1	PVP/NaAlg 1/2	40,000	0.025	1	1/2	0.62 ± 0.01
N_3	PVP/NaAlg 1/2	40,000	0.025	5	1/2	0.52 ± 0.01
N_4	PVP/NaAlg 1/2	40,000	0.025	1	1/4	0.70 ± 0.02
N_5	PVP/NaAlg 1/2	40,000	0.025	1	1/8	0.80 ± 0.01
N_6	PVP/NaAlg 1/2	40,000	0.025	1	1/16	0.83 ± 0.02
N_7	PVP/NaAlg 1/2	40,000	0.025	1	1/32	0.87 ± 0.02
N_8	PVP/NaAlg 1/2	360,000	0.025	1	1/2	0.61 ± 0.03
N_9	PVP/NaAlg 1/2	1,300,000	0.025	1	1/2	0.64 ± 0.01
M_3	PVP/NaAlg 1/2	40,000	0.05	5	1/2	0.49 ± 0.09

powder were refluxed with 250 mL of buffer solution at pH = 6.8, for 2 h to ensure the complete extraction of DT from the microspheres. After that, the absorbance of the buffer solution containing the extracted amount of DT was taken at a wavelength of 237 nm in a UV spectrophotometer (Unicam UV2-100, UK) using pure buffer solution as a blank. Practical DT loading was determined from this value. The percentage of entrapment efficiency was then calculated as:

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

Fourier transform infrared measurements

Fourier transform infrared (FTIR) spectra of the DT and PVP/NaAlg microspheres were taken with a Mattson 1000 FTIR spectrometer (UK). FTIR spectra were taken in the wavelength region 400–4000 cm^{-1} at ambient temperature.

Scanning electron microscope

Scanning electron microscope (SEM) photographs were taken with JSM 5600 Scanning Microscope (Japan) to examine the morphology and surface structure of the microspheres at the required magnification at room temperature. The microspheres were deposited on brass hold and sputtered with a thin coat of gold under vacuum.

In vitro drug release

The *in vitro* drug release from the microspheres was studied in 250-mL conical flasks containing pH = 1.2 HCl solution, pH = 6.8 phosphate buffer solution and incubated in a shaking water-bath (Medline BS-21, Korea) at 37°C, with a speed of 50 rpm. At 2 h intervals DT release medium was changed to be pH: 1.2 and 6.8, respectively. Four milliliter solution was withdrawn at specific time intervals and DT content was determined by UV spectrophotometer at 237 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.

RESULTS AND DISCUSSION

FTIR and SEM studies

DT containing PVP/NaAlg blend microspheres were successfully prepared using calcium chloride solution. In the present research, PVP was found to be compatible for forming blends with NaAlg.

FTIR spectra of PVP/NaAlg empty microsphere, NaAlg, and PVP are shown in Figure 1. The spectra of NaAlg showed the peaks around 3416, 2935, 1618, 1421, and 1034 cm^{-1}, indicating the stretching of O—H, aliphatic C—H, COO^-(asymmetric), COO^-(symmetric), and C—O—C, respectively [Fig. 1(b)]. The spectra of the PVP showed peaks around 3423, 2954, 1650, 1423, and 1297 cm^{-1} indi-

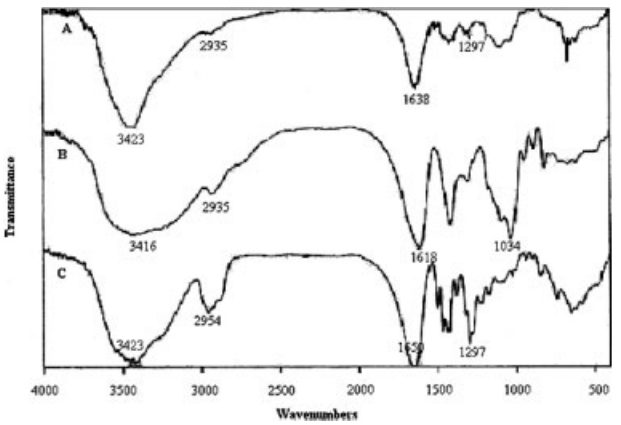

Figure 1 IR spectra of empty PVP/NaAlg microsphere with 1/2 ratio (A), NaAlg (B), and PVP (C).

cating the stretching of O—H, aliphatic C—H, COO^-(asymmetric) bonded to N atom, C—N, and bending of C—N, respectively [Fig. 1(c)]. The cross-linking process with calcium ion and blending of PVP with the NaAlg obviously provided a shift of lower intensity of COO^- stretching peak at 1618 cm^{-1} to a higher wavenumber (1638 cm^{-1}) [Fig. 1(a,b)]. Moreover, compared with the spectrum of NaAlg and PVP, the stretching peak at 3423 cm^{-1} in the PVP/NaAlg microsphere spectra had narrower peak. These phenomena suggested that PVP and NaAlg could form intermolecular hydrogen bonding between carbonyl group of PVP and hydroxyl group of NaAlg. Similar results were found in the previous studies.[32,33,34]

SEM photographs of a single NaAlg and PVP/NaAlg microsphere taken at ×50 and ×60 magnifications were shown in Figure 2. As it is seen from the figure, NaAlg and PVP/NaAlg microsphere are almost spherical in shape and shows smooth surface.

Particle size, entrapment efficiency, and yield value evaluation of microspheres

The values of microsphere diameter are shown in Table I. As can be seen from the table, the microspheres formed have particle sizes ranging from 0.27 ± 0.05 to 0.90 ± 0.02 mm in diameter. The size of the microspheres changed with PVP/NaAlg (m/m) ratio, drug/polymer (m/m) ratio, cross-linking concentration, and time, whereas did not vary significantly with molecular weight of PVP. Diameter of the NaAlg microspheres is much larger than that of PVP/NaAlg microspheres. In all of the formulations, with increasing PVP content, diameters of the microspheres significantly decrease, which could be attributed to the formation of smaller droplets due to decrease in the viscosity of microsphere preparation solution. Moreover, increase in cross-linking concentration and time cause decrease in diameters of the microspheres. With an increase in cross-link concentration, the microspheres with smaller size were produced, probably due to the formation of a more rigid network as a result of increased cross-link density. Agnihotri and Aminabhavi[35] have found similar results with gellan gum and poly(vinyl alcohol) hydrogel microspheres. As it is also seen from the Table I that as the d/p ratio decreases, diameter of microsphere increases. As the d/p ratio decreases the DT content in the blend microsphere decreases. Hence, decrease in the DT content cause the microsphere shape change from spherical to irregular form. Therefore, diameter of microsphere increased with decreasing d/p ratio. Similar observation was also found in the earlier study.[34]

The percentage of entrapment efficiency and microsphere yield may change depending on the preparation conditions and the type of matrix material of the microspheres. The results of entrapment efficiency (%) and microsphere yield (%) were

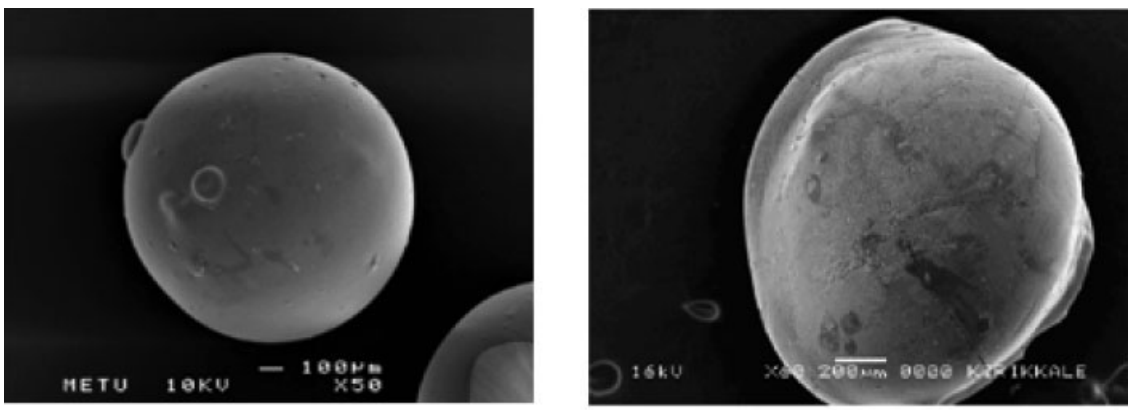

Figure 2 SEM photographs of empty NaAlg microsphere ×50 (A), PVP/NaAlg (in 1 : 2 ratio) microsphere ×60 (B).

TABLE II
The Results of Entrapment Efficiency (%) and Microsphere Yield (%) for the DT Loaded Microspheres

Code	Entrapment efficiency (%)	Microsphere yield (%)
K_1	7.78 ± 1.38	42.9 ± 0.09
K_2	5.04 ± 0.54	40.38 ± 1.32
K_3	3.46 ± 0.75	38.82 ± 0.77
L_1	21.17 ± 4.22	51.82 ± 2.41
L_2	19.63 ± 3.95	48.13 ± 1.02
L_3	15.89 ± 2.97	47.74 ± 1.22
L_4	22.37 ± 1.04	48.82 ± 1.45
L_5	21.25 ± 0.14	47.52 ± 1.04
N	35.21 ± 1.76	53.52 ± 0.83
N_1	27.44 ± 0.10	40.93 ± 0.25
N_3	22.61 ± 1.97	40.95 ± 0.82
N_4	28.25 ± 0.20	46.07 ± 0.67
N_5	34.77 ± 1.76	49.42 ± 1.09
N_6	43.82 ± 1.51	55.41 ± 1.35
N_7	54.39 ± 2.25	57.26 ± 1.14
N_8	30.01 ± 2.79	45.89 ± 1.56
N_9	32.59 ± 1.01	48.27 ± 0.55
M_3	22.38 ± 0.88	42.00 ± 0.35

shown in Table II. These values decreased with increasing the drug/polymer ratio whereas they increased with increasing the PVP/NaAlg ratio. By increasing the amount of PVP loose network may occur that allows the leaching out of more of drug particles during the production stage of the microspheres. Similar results were stated by Rokhade and coworkers.[36] In the PVP/NaAlg microsphere, d/p ratio increases from 1/32 to 1/2, the entrapment efficiency decreases from 54.39% ± 2.25% to 27.44% ± 0.10%, respectively. This phenomenon is explained as follows: when the d/p ratio increases PVP/NaAlg blend solution is bound to trap less DT and thus decrease the entrapment efficiency. As can be also seen from the table, cross-linking concentration and time decrease entrapment efficiency. Such a decreasing trend could be attributed to increased cross-linking density of the microspheres, which might have become more rigid structure as a result of reduction in free volume within the polymer matrix; thereby reducing their entrapment efficiencies. On the other hand, percentage of entrapment efficiency and yield value of PVP/NaAlg microspheres increased with increase in molecular weight of PVP from 40,000 to 1,300,000. When the molecular weight of PVP is increased, viscosity of microsphere preparation solution increases. As a result, polymer traps more DT molecules and entrapment efficiency and yield value increases. The highest entrapment efficiency was found to be 54.39 ± 2.25 for the microsphere prepared with d/p ratio of 1/32.

Effect of PVP/NaAlg ratio on the DT release

In vitro release of DT from cross-linked PVP/NaAlg microspheres was carried out in gastric (2 h), input intestinal (2 h) pH conditions at 37°C. Figure 3 displays the cumulative DT release of microspheres prepared using 40,000 molecular weight PVP in different PVP/NaAlg ratios. As it is reflected from the figure that increase in PVP/NaAlg ratio from 1/4 to 1/1 increases the release of DT from the microspheres. The highest cumulative DT release obtained at the end of 4 h was 96% for the 1/1 PVP/NaAlg microspheres. These results are quite expected since presence of PVP increases hydrophilic character of microspheres. As it is seen in Table III, increase in the amount of PVP in the microsphere increases the ESDs of the PVP/NaAlg microspheres. When the swelling degree increases, amorphous regions produce free volumes that are suitable for penetration of liquid molecules to microsphere and then diffusion of drug to external medium. Therefore, cumulative release of DT increases with the PVP content of the microspheres. Similar observations were found in the previous studies.[33,34] PVP/NaAlg microspheres have also demonstrated a faster release of DT in the acidic pH as compared to medium of pH 6.8 due to high solubility of DT in low pH.

Effect of drug/polymer ratio on the DT release

Another parameter that affects the DT release from the microspheres is drug/polymer ratio. For this purpose d/p ratio was changed from 1/32 to 1/2 for PVP/NaAlg (1/2) microspheres prepared with molecular weight of 40,000 PVP. The effect of d/p ratio on DT release is shown in Figure 4. The figure illustrates that DT release from the PVP/NaAlg microspheres increases with the increase in d/p ratio of PVP/NaAlg microspheres. The cumulative release (%) of d/p ratio of 1/2 microspheres have shown 100% release whereas that of d/p ratio of 1/32 microspheres have shown 70% at the end of 4 h. When the d/p ratio increases from 1/32 to 1/2, DT content of the microspheres increases. Larger initial load of microsphere cause the faster movement of the water penetrating the surface of the loaded

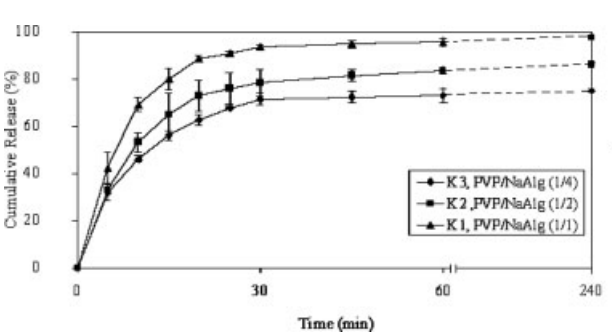

Figure 3 Effect of PVP/NaAlg ratio on DT release. Molecular weight of PVP: 40,000, d/p: 1/2, concentration of $CaCl_2$: 0.1*M*, cross-linking time: 30 min.

TABLE III
Equilibrium Swelling Degree for the Microspheres

Code	Polymer ratio (PVP/NaAlg) (w/w)	$CaCl_2$ concentration (*M*)	Cross-linking time in $CaCl_2$ (min)	Equilibrium swelling degree (%)	
				Swelling medium	
				Distilled water	pH = 1.2 HCl solution
K_1	1/1	0.1	30	192.6 ± 2.3	156.1 ± 0.8
K_2	1/2	0.1	30	150.2 ± 0.4	133.1 ± 1.3
K_3	1/4	0.1	30	108.2 ± 0.9	61.3 ± 1.4
L_2	1/2	0.1	5	290.8 ± 1.6	142.5 ± 0.9
L_5	1/2	0.1	2.5	3122.9 ± 5.1	146.4 ± 2.1
L_4	1/2	0.1	1	3181.3 ± 1.3	158.2 ± 2.7
M_3	1/2	0.05	1	9282.0 ± 2.3	160.1 ± 0.6
N_1	1/2	0.025	1	12111.3 ± 3.1	165.7 ± 2.7

microsphere. Larger loading of the microsphere may also facilate the relaxation of polymer chains. Similar finding was reported for ketorolac tromethamine loaded gelatin/sodium carboxymethyl cellulose microspheres by Rokhade et al.[36]

Ramesh Babu et al.[37] studied pH sensitive interpenetrating network microgels of sodium alginate-acrylic acid for the controlled release of ibuprofen and reported that ibuprofen release increases with the amount of drug in the matrix.

Effect of molecular weight of PVP in the PVP/NaAlg microsphere on the DT release

Molecular weight of PVP was altered for the purpose of slowing down DT release from the PVP/NaAlg microspheres with keeping all the other parameters constant. Figure 5 displays the effect of molecular weight of PVP in the PVP/NaAlg microsphere on the DT release. As it is seen from the figure, DT release is less for the PVP/NaAlg microsphere prepared with molecular weight of 1,300,000 than that of other microspheres. As the molecular weight of PVP increases, release percentage of DT decreases. However, release rate of DT was not affected from the molecular weight of PVP especially for 1 h. This result is attributed to increase in length of polymer chain with the molecular weight. Hence viscosity of PVP/NaAlg microsphere preparation solution increased and more dense structure formed. Therefore, penetration of liquid to microsphere and diffusion of drug to external medium become slower. Moreover, it is thought that increase in intermolecular interactions between PVP and NaAlg with increasing molecular weight of PVP may cause the decrease in DT release. Kim et al.[38] studied effect of low and high molecular weight of chitosan on release of albumin from the chitosan-coated pectin beads and obtained similar findings.

Effect of cross-linking time and concentration of $CaCl_2$ on the DT release

DT release from the microspheres were 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 microspheres. One of the most effective ways to change release rate of microspheres is to change cross-link density of the matrix by employing varying time of exposure to cross-linking agent and concentrations of the cross-linking agent. The effect of cross-linking time

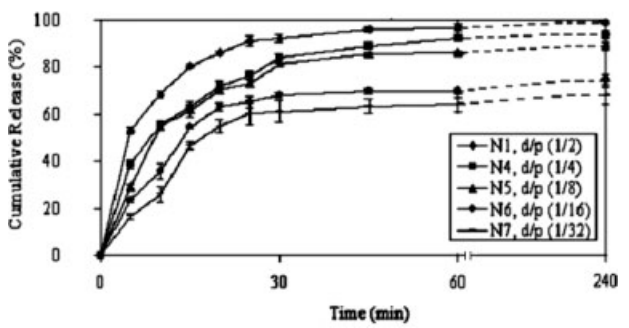

Figure 4 Effect of drug/polymer ratio on DT release. PVP/NaAlg: 1/2, molecular weight of PVP: 40,000, concentration of $CaCl_2$: 0.025*M*, cross-linking time: 1 min.

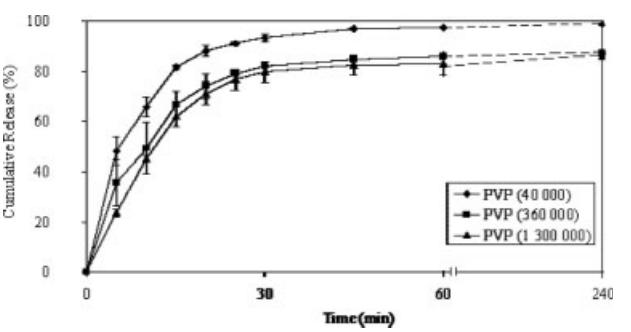

Figure 5 Effect of molecular weight of PVP on DT release. *d*/*p*: 1/2, concentration of $CaCl_2$: 0.025*M*, cross-linking time: 1 min.

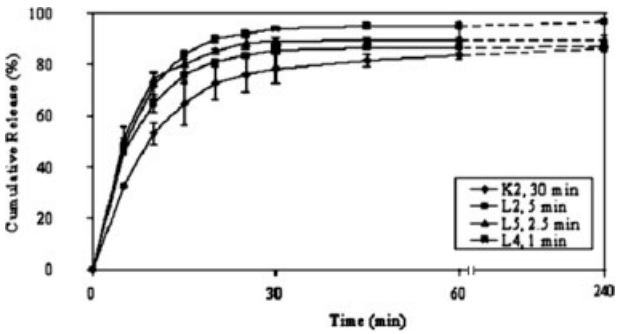

Figure 6 Effect of cross-linking time on DT release. PVP/NaAlg: 1/2, *d*/*p*: 1/2, molecular weight of PVP: 40,000, concentration of $CaCl_2$: 0.1*M*.

on the release rate of DT has been investigated at cross-linking time from 1 to 30 min. The results were shown in Figure 6, which clearly indicates that with increasing cross-linking time in the $CaCl_2$ solution, the release rate decreases. The maximum DT release from the PVP/NaAlg 1/2 microspheres, which were prepared with cross-linking time of 1 min, was found to be 96%.

Another way to change the cross-link density of the microsphere is to change the concentration of $CaCl_2$ solution. For this purpose, $CaCl_2$ concentration was changed during the microsphere preparation from 0.025*M* to 0.1*M* and release results from these microspheres are presented in Figure 7. As it is seen from the figure as the $CaCl_2$ concentration increased from 0.025*M* to 0.1*M*, DT release slightly decreased.

The observed decreases in the cumulative release are due to the fact that increasing cross-linking time and concentration of $CaCl_2$ solution result in an increase in cross-link density of the microspheres which give rise to a compact network of the polymer. Consequently, the free volume reduces, and penetration of water molecules and diffusion of DT molecules become difficult.

DT release results were also supported by swelling measurements. As it is seen from the Table III, increase in cross-linking concentration from 0.025*M* to 0.1*M*, ESD decreases from 165.7% ± 2.7% to 158.2% ± 2.7% in pH 1.2 HCl solution. Also it is observed from the Table III that increase in time in $CaCl_2$ solution from 1 to 30 min decreases swelling percentage from 158.2 ± 2.7 to 133.1 ± 1.3 in pH 1.2 HCl solution because of increasing cross-link density of the PVP/NaAlg blend microspheres. Similar results were reported by many other workers.[4,5,25,39]

Analysis of kinetic results

The phenomenon of solvent sorption by a polymeric microsphere depends mechanistically on the diffusion of water molecules into the gel matrix and subsequent relaxation of macromolecular chains of the microsphere.[39] 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[40]

$$\frac{M_t}{M_\infty} = kt^n \tag{3}$$

where M_t is the amount of DT 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.[41] A value of $n = 0.5$ indicates the Fickian transport (mechanism), while $n = 1$ is of Case II or non-Fickian transport (swelling-controlled).[37] The intermediary values ranging between 0.5 and 1.0 are indicative of the anomalous transport.[32,37] The least-squares estimations of the fractional release data along with the estimated correlation coefficient values, r, are presented in Table IV. From these data, the n value ranged between 0.292–0.842, with correlation coefficient values of 0.95, indicating DT release from the microspheres slightly deviates from the Fickian transport.

The values of k and n have shown a dependence on the d/p ratio as well as the molecular weight of PVP in the matrix. Values of n for the microspheres prepared by varying the d/p ratio in the microsphere from 1/2 to 1/32 by keeping other parameters constant, has shifted drug transport from Fickian type, in which drug release is governed by drug diffusion, to anomalous type, in which drug release is governed by coupling of drug diffusion and polymer relaxation processes.[42] On the other hand, k values have decreased with decrease in the d/p ratio

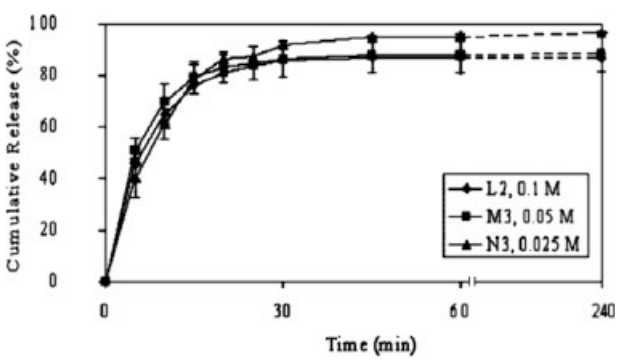

Figure 7 Effect of $CaCl_2$ concentration on DT release. PVP/NaAlg: 1/2, *d*/*p*: 1/2, molecular weight of PVP: 40,000, cross-linking time: 5 min.

TABLE IV
The Results of *k*, *n*, and *r* Calculated from Eq. (3)

Code	k (min^{-n})	n	r	Diffusion mechanism
K_1	0.190	0.403	0.994	Fickian transport
K_2	0.219	0.362	0.950	Fickian transport
K_3	0.230	0.436	0.965	Fickian transport
L_1	0.190	0.486	0.965	Fickian transport
L_2	0.276	0.350	0.948	Fickian transport
L_3	0.230	0.404	0.956	Fickian transport
L_4	0.262	0.411	0.975	Fickian transport
L_5	0.336	0.306	0.952	Fickian transport
N	0.090	0.609	0.957	Anomalous transport
N_1	0.289	0.362	0.986	Fickian transport
N_3	0.225	0.412	0.948	Fickian transport
N_4	0.221	0.384	0.989	Fickian transport
N_5	0.160	0.473	0.955	Fickian transport
N_6	0.088	0.630	0.980	Anomalous transport
N_7	0.041	0.842	0.985	Anomalous transport
N_8	0.165	0.489	0.989	Fickian transport
N_9	0.084	0.696	0.981	Anomalous transport
M_3	0.338	0.292	0.965	Fickian transport

because of decreasing interaction between the DT and the PVP/NaAlg matrix with reducing content of the drug. Moreover, increase in the molecular weight of the PVP from 40,000 to 1,300,000 cause to increase of the n value from 0.362 to 0.696, whereas it cause to decrease of the k value from 0.289 to 0.084, respectively. As increasing molecular weight of PVP, transport mechanism shift to anamolous transport. This is attributed to the physical changes induced in the blend microsphere with varying of the molecular weight of the PVP.

CONCLUSIONS

DT release studies from the microspheres prepared from PVP/NaAlg blends and cross-linked with $CaCl_2$ indicate that DT release from the microspheres increases with the increase in both PVP/NaAlg ratio and d/p ratio whereas it decreases with the increase of cross-linking concentration and time in $CaCl_2$ solution, and molecular weight of PVP. It is also observed that release of DT is much higher at low pH value compared to high pH value showing that the release system is interesting as a release system for stomach-specific drug delivery. ESD of all the formulations is in consistence with the release results. From the release data, most of the microsphere formulations display Fickian diffusion transport, while few of them display anamolous transport.

References

1. Kydonieus, A. F. Controlled Release Tecnologies: Methods, Theory, and Applications; CRC Press: Boca Raton, Florida, 1980; Vol. 1, pp 3–4.
2. Bajpai, A. K.; Choubey, J. J Macromol Sci Pure Appl Chem 2005, 42, 253.
3. Duarte, A. R. C.; Costa, M. S.; Simplicio, A. L.; Cardoso, M. M.; Duarte, C. M. M. Int J Pharm 2006, 308, 168.
4. Almeida, P. F.; Almeida, A. J. J Control Release 2004, 97, 431.
5. Gombotz, W. R.; Wee, S. F. Adv Drug Delivery Rev 1998, 31, 267.
6. Horiike, S.; Matsuzawa, S.; Yamaura, K. J Appl Polym Sci 2002, 84, 1178.
7. Sreenivasan, K. J Appl Polym Sci 1997, 65, 1829.
8. Orienti, I.; Trere, R.; Luppi, B.; Bigucci, F.; Cerchiara, T.; Zuccari, G.; Zecchi, V. Arch Pharm 2002, 335, 89.
9. Kim, S. Y.; Lee, Y. M. J Appl Polym Sci 1999, 74, 1752.
10. Kweon, D. K.; Kang, D. W. J Appl Polym Sci 1999, 74, 458.
11. Kumbar, S. G.; Soppimath, K. S.; Aminabhavi, T. M. J Appl Polym Sci 2003, 87, 1525.
12. Feng, X.; Huang, R. Y. M. J Membr Sci 1996, 109, 165.
13. Lee, K. H.; Kim, H. K.; Rhim, J. W. J Appl Polym Sci 1995, 58, 1707.
14. Huang, R. Y. M.; Yeom, C. K. J Membr Sci 1991, 62, 59.
15. Işiklan, N.; Şanlı, O. J Appl Polym Sci 2004, 93, 2322.
16. Işiklan, N.; Şanlı, O. Chem Eng Process 2005, 44, 1019.
17. Şanlı, O.; Asman, G. J Appl Polym Sci 2004, 91, 72.
18. Kulkarni, A. R.; Soppimath, K. S.; Aminabhavi, T. M. J Control Release 2000, 63, 97.
19. Gohel, M. C.; Amin, A. F. J Control Release 1998, 51, 115.
20. Todd, P. A.; Sorkin, E. M. Drugs 1988, 35, 244.
21. Fernandez-Hervas, M. J.; Holgado, M. A.; Fini, A.; Fell, J. T. Int J Pharm 1998, 163, 23.
22. Tuncay, M.; Çaliş, S.; Kaş, H. S.; Ercan, M. T.; Peksoy, İ.; Hincal, A. A. Int J Pharm 2000, 195, 179.
23. Basan, H.; Gümüşderelioğlu, M.; Orbey, T. Int J Pharm 2002, 245, 191.
24. Aminabhavi, T. M.; Naik, H. G. J Appl Polym Sci 2002, 83, 244.
25. Rousseau, I.; Le Cerf, D.; Picton, L.; Argillier, J. F.; Muller, G. Eur Polym J 2004, 40, 2709.
26. Liu, Z.-M.; Xu, Z.-K.; Wan, L.-S.; Ulbricht, M. J Membr Sci 2005, 249, 21.
27. Bayomi, M. A.; Al-Suwayeh, S. A.; El-Helw, A. M.; Mesnad, A. F. Pharm Acta Helv 1998, 73, 187.
28. Miyazaki, S.; Nakayama, A.; Oda, M.; Takada, M.; Attwood, D. Int J Pharm 1995, 118, 257.
29. Follonier, N.; Doelker, E.; Cole, E. T. J Control Release 1995, 36, 243.
30. Kakish, H. F.; Tashtoush, B.; Ibrahim, H. G.; Najib, N. M. Eur J Pharm Biopharm 2002, 54, 75.
31. Vergote, G. J.; Kiekens, F.; Vervaet, C.; Remon, J. P. Eur J Pharm Biopharm 2002, 17, 145.
32. Şanlı, O.; Ay, N.; Işıklan, N. Eur J Pharm Biopharm 2007, 65, 2004.
33. Şanlı, O.; Orhan, E.; Asman, G. J Appl Polym Sci 2006, 102, 1244.
34. Işıklan, N. J Appl Polym Sci 2006, 99, 1310.
35. Agnihotri, S. A.; Aminabhavi, T. M. Drug Dev Ind Pharm 2005, 31, 491.
36. Rokhade, A. P.; Agnihotri, S. A.; Patil, S. A.; Mallikarjuna, N. N.; Kulkarni, P. V.; Aminabhavi, T. M. Carbohydr Polym 2006, 65, 243.
37. Ramesh Babu, V.; Krishna Rao, K. S. V., Sairam, M.; Vijaya Kumar Naidu, B.; Hosamani, K. M.; Aminabhavi, T. M. J Appl Polym Sci 2006, 99, 2671.
38. Kim, T. H.; Park, Y. H.; Kim, K. J.; Cho, C. S. Int J Pharm 2003, 250, 371.
39. Bajpai, A. K.; Sharma, M. J Macromol Sci Pure Appl Chem 2005, 42, 663.
40. Peppas, N. A. Pharm Acta Helv 1985, 60, 110.
41. Ritger, P. L.; Peppas, N. A. J Control Release 1987, 5, 37.
42. Mundargi, R. C.; Patil, S. A.; Aminabhavi, T. M. Carbohydr Polym 2007, 69, 130.