Preparation, Characterization, and Salicylic Acid Release Behavior of Chitosan/Poly(vinyl alcohol) Blend Microspheres

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ABSTRACT: Blend microspheres of chitosan (CS) with poly(vinyl alcohol) (PVA) were prepared as candidates for oral delivery system. CS/PVA microspheres containing salicylic acid (SA), as a model drug, were obtained using the coacervation-phase separation method, induced by addition of a nonsolvent (sodium hydroxide solution) and then crosslinked with glutaraldehyde (GA) as a crosslinking agent. The microspheres were characterized by Fourier transform infrared spectroscopy, differential scanning calorimetry (DSC), and scanning electron microscopy. Percentage entrapment efficiency, particle size, and equilibrium swelling degree of the microsphere formulations were determined. The results indicated that these parameters were changed by preparation conditions of the microspheres. Effects of variables such as CS/PVA ratio, pH, crosslinker concentration, and drug/polymer (d/p) ratio on the release of SA were studied at three different pH values (1.2, 6.8, and 7.4) at 37°C. It was observed that SA release from the microspheres increased with decreasing CS/PVA ratio and d/p ratio whereas it decreased with the increase in the extent of crosslinking. It may also be noted that drug release was much higher at pH 1.2 than that of at pH 6.8 and 7.4. The highest SA release percentage was obtained as 100% for the microspheres prepared with PVA/CS ratio of 1/2, d/p ratio of 1/2, exposure time to GA of 5 min, and concentration of GA 1.5% at the end of 6 h. © 2008 Wiley Periodicals, Inc. J Appl Polym Sci 111: 2731–2740, 2009

Key words: controlled release; drug delivery systems; salicylic acid; hydrophilic polymers

INTRODUCTION

Controlled drug delivery technology represents one of the frontier areas of science, which involves multidisciplinary scientific approach, contributing to human health care. These delivery systems offer numerous advantages compared with conventional dosage forms, which include improved efficacy, reduced toxicity, and improved patient compliance and convenience.[1] Among different dosage forms reported, microspheres have been identified as a noble class of matrices possessing a great potential as drug carriers. Over the past 25 years much research has been focused on especially degradable polymer microspheres for drug delivery. Administration of medication via such systems is advantageous because microspheres can be ingested or injected and; they can be tailored for desired release profiles and used site-specific delivery of drugs and in some cases can even provide organ-targeted release.[2]

Although various biodegradable microspheres of natural polymers such as cellulose,[3] guar gum,[4] alginate,[5] gelatin,[6] etc., are largely in use as drug carriers in controlled drug delivery technology, chitosan (CS) is the most important polymer because of its biocompatible, nontoxic and noncarcinogenic nature.[7] Chitosan has also antacid and antiulcer activities, which can prevent or weaken drug-induced irritation in the stomach.[8]

Chitosan is a linear biopolyaminosaccharide, which is obtained by alkaline deacetylation of chitin, similar in structure to cellulose. Both are made by linear β-(1→4)-linked monosaccharides. However, an important difference to cellulose is that CS is composed of 2-amino-2-deoxy-β-D-glucan combined with glycosidic linkages.[9] The primary amine groups render special properties that make CS very useful in pharmaceutical applications. Compared with many other natural polymers, CS has a positive charge and is mucoadhesive. Therefore, it is used extensively in drug delivery application.[10–14] Chitosan microspheres are the most widely studied drug delivery systems for the controlled release of drugs viz., antibiotics,[15,16] proteins,[17,18] antihypertensive

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agents,[19,20] anticancer agents,[21,22] peptide drugs,[23,24] and anti-inflammatory drugs.[25,26] Blending of CS with other synthetic hydrophilic polymers such as polyvinyl pyrrolidone,[10,27] polyethyleneoxide[27] or natural polymers: alginate,[28] starch,[29] has been suggested as a promising approach to producing polymers for specific uses especially drug delivery systems. One of the widely used polymer for a variety of pharmaceutical applications to be blended with CS is poly(vinyl alcohol) (PVA), because of its permeability, biocompatibility, biodegradability, excellent chemical resistance and physical properties.[30] It exhibits minimal cell adhesion and protein adsorption. Simple blends of CS and PVA have good mechanical properties, and applications of these CS/PVA blends have been reported in the literature.[27,31–32] Khoo et al.,[27] studied CS blends with PVA, polyethyleneoxide, and polyvinyl pyrrolidone for oral gingival delivery systems and reported that CS blends have given superior properties in many ways compared to CS alone. These include improved comfort and reduced irritation, ease of processing, improved flexibility, and enhanced dissolution. Rao et al.[31] also investigated controlled release of cefadroxil using CS/PVA and CS/acrylamide grafted PVA microgels and indicated that blend microgels of CS with PVA have shown favorable controlled release characteristics than plain CS microgels.

In this study, it was aimed to prepare CS/PVA blend microspheres containing salicylic acid (SA) to achieve a drug release profile suitable for oral administration. SA is an active component of aspirin and regular use of aspirin by adults appears to reduce the risk of many diseases such as colon cancer, lung cancer, breast cancer, Alzheimer and heart diseases, etc.[33] However, it has the drawback of producing dyspepsia and gastrointestinal problems. One way to overcome these drawbacks is to use polymeric microspheres.

In our previous works,[34,35] we have prepared PVA/sodium alginate blend beads containing diclofenac sodium and sodium alginate/poly(vinyl pyrrolidone) blend microspheres containing diltiazem hydrochloride to achieve a controlled drug release profile suitable for oral administration. We have also studied release of SA through PVA/poly(vinyl pyrrolidone) and poly(vinyl alcohol-*g*-*N*-vinyl-2-pyrrolidone) membranes for transdermal application.[33] In the present study, CS/PVA blend microspheres were prepared in various blend ratios by the coacervation-phase separation method and then crosslinked with glutaraldehyde (GA). Particle size, microspheres yield, entrapment efficiency, equilibrium swelling degree (ESD) of the microspheres, and SA release rate were investigated at pH values of 1.2, 6.8, and 7.4. The effects of blend ratio, pH, extent of crosslinking, and drug/polymer ratio on SA release from the microspheres were researched and discussed.

EXPERIMENTAL

Materials

Chitosan was purchased from Sigma Chemical Co (St. Louis, USA). PVA was supplied by Merck (Darmstadt, Germany). The molecular weight and degree of saponification of PVA were 72,000 and greater than 98%, respectively. SA, GA (25% w/w) solution, acetic acid, NaOH, HCl, Na_2HPO_4, and NaH_2PO_4 were all supplied from Merck (Darmstadt, Germany) and were used as received.

Preparation of the CS/PVA microspheres

CS was dissolved in acetic acid solution [2%(w/v)] to prepare a 5% (w/v) CS solution; PVA solution [8% (w/v)] was prepared by dissolving PVA in hot distilled water (80°C). The mixture of CS and PVA solution in fixed blend ratios containing SA in various drug/polymer ratios was prepared and stirred for 12 h to form a homogenous solution. The blended solution containing SA was then added drop-wise manner into 1*M* NaOH solution using a peristaltic pump (Masterflex, L/S Digital Economy Drive, USA). Microspheres formed were removed from the NaOH solution after 5 min and washed with water to remove the adhered NaOH; then crosslinked with GA solution containing HCl for selected time intervals of 5, 15, and 30 min. Then the microspheres were washed with water repeatedly to remove the adhered GA and acid, and dried completely in an oven (Medcenter, Einrichtungen GmbH, Germany) at 40°C. Unloaded microspheres were prepared in a similar way without using SA to determine ESD. Preparation conditions of the microspheres were displayed in Table I. To estimate the size of the 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 given in Table I.

Equilibrium swelling study of the microspheres

Equilibrium swelling degree (ESD) of the crosslinked empty microspheres was determined by measuring gravimetrically the extent of their swelling in solutions of pH = 1.2, 6.8, and 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 microspheres were weighed using electronic balance (Precisa XB 220A, USA). The microspheres were then dried in the oven at 40°C till to constant

TABLE I
Entrapment Efficiency, Yield (%), and Microsphere Diameter for the SA Loaded Microspheres (Concentration of NaOH: 1*M*)

Code	CS/PVA ratio	Concentration of GA (%) (w/w)	Exposure time to GA (min)	Drug/ polymer ratio	Entrapment efficiency (%)	Yield (%)	Microsphere diameter (mm)
F_1	1/1	2.5	5	1/1	10.11 ± 0.55	44.44 ± 1.80	0.68 ± 0.01
F_2	1/1	2.5	5	1/1.25	5.66 ± 0.14	48.67 ± 1.28	0.53 ± 0.02
F_3	1/1	2.5	5	1/1.5	4.35 ± 0.09	54.58 ± 1.53	0.52 ± 0.02
F_4	1/1	2.5	5	1/2	4.51 ± 0.43	63.39 ± 1.07	0.49 ± 0.01
G_1	1/2	2.5	5	1/1	13.60 ± 0.11	38.62 ± 0.19	0.95 ± 0.01
G_2	1/2	2.5	5	1/1.25	4.62 ± 0.32	43.01 ± 0.41	0.82 ± 0.02
G_3	1/2	2.5	5	1/1.5	4.09 ± 0.53	47.22 ± 0.41	0.76 ± 0.02
G_4	1/2	2.5	5	1/2	3.31 ± 0.31	52.75 ± 0.33	0.63 ± 0.02
H_1	1/3	2.5	5	1/1	14.17 ± 0.09	34.25 ± 0.63	0.98 ± 0.01
H_2	1/3	2.5	5	1/1.25	10.10 ± 0.20	38.98 ± 1.06	0.89 ± 0.02
H_3	1/3	2.5	5	1/1.5	9.66 ± 0.37	44.34 ± 1.50	0.81 ± 0.01
H_4	1/3	2.5	5	1/2	9.19 ± 0.50	53.35 ± 1.09	0.71 ± 0.01
I_1	1/2	1.5	5	1/2	4.37 ± 0.55	55.85 ± 2.93	0.65 ± 0.01
I_2	1/2	3	5	1/2	5.01 ± 0.36	50.91 ± 0.52	0.64 ± 0.01
J_1	1/2	2.5	15	1/2	3.62 ± 0.14	54.44 ± 0.75	0.56 ± 0.02
J_2	1/2	2.5	30	1/2	3.34 ± 0.25	55.58 ± 1.06	0.53 ± 0.01

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 the salicylic acid content of the microspheres

The known mass of microspheres were 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 SA from the microspheres. After that, the absorbance of the methanol solution containing the extracted amount of SA was taken at a wavelength of 298 nm by a UV spectrophotometer (Unicam UV2-100, UK) using pure methanol as a blank. Practical SA loading was determined from this value. The percentage of entrapment efficiency was then calculated as:

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

Fourier transform infrared measurements

Fourier transform infrared (FTIR) spectra of the SA, CS, PVA, and CS/PVA 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 JEM-100CXII Scanning Microscope 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.

Differential scanning calorimetry

The thermal analysis was performed with differential scanning calorimeter (DSC) (General V4.1C DuPont 2000). 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).

In vitro drug release

Drug release from the microspheres was studied in 250 mL conical flasks containing HCl solution of pH = 1.2 and phosphate buffer solutions of pH = 6.8 and 7.4. The conical flasks were incubated in a shaking water-bath (Medline BS-21, Korea) at 37°C, with a speed of 50 rpm. The release medium for SA was first kept at pH: 1.2 HCl solution for 2 h. Then the medium was changed to phosphate buffer solution (pH: 6.8) and after 2 h it was replaced by pH: 7.4 phosphate buffer solution. The total release duration was 6 h. Four milliliters of the solution was withdrawn at specific time intervals and SA content was determined by UV spectrophotometer at 298 nm. Equal volume of fresh HCl or phosphate buffer

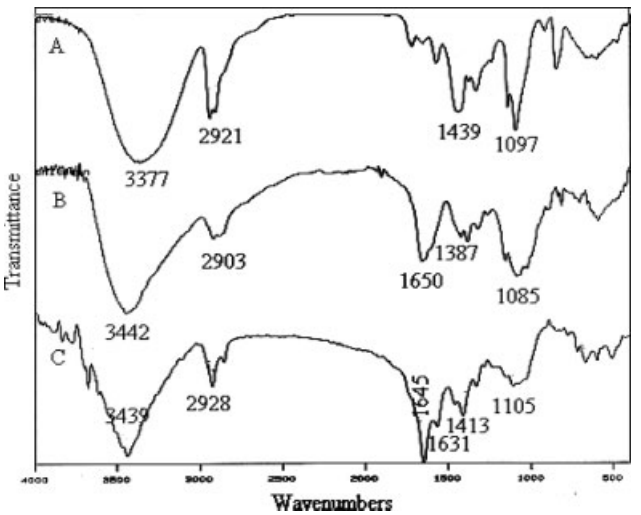

Figure 1 TIR spectra of PVA (A), CS (B), and empty CS/PVA microsphere with 1/2 ratio (C).

solution was added into the release medium to maintain constant volume. Experiments were performed in triplicate to minimize the variational error. Standard deviations from the average values were calculated.

RESULTS AND DISCUSSION

FTIR, DSC, and SEM studies

SA containing CS/PVA blend microspheres were successfully prepared using coacervation-phase separation method. FTIR spectra of PVA (A), CS (B), and the empty CS/PVA microsphere (C) were shown in Figure 1. The spectrum of PVA showed the peaks around 3377, 2921, and 1097 cm^{-1}, indicating the stretching of O—H, aliphatic C—H, and C—O, respectively. There was also a band at 1439 cm^{-1} due to C—H bending vibration. The spectrum of the CS showed peaks around 3442, 2903, 1387, and 1085 cm^{-1}, indicating the stretching of O—H, aliphatic C—H, bending of C—N, and C—O, respectively.[27] The amine group of CS has a characteristic peak in the region of 3000–3500 cm^{-1}, which has been masked by the peak due to —OH group. CS also exhibits characteristic absorption peak at 1650 cm^{-1} (amide I, C=O stretching) due to its amide group.[32] Compared with the spectrum of PVA and CS, the stretching peak at 3439 and 1105 cm^{-1} in the spectra of CS/PVA microsphere had a narrower peak and a decrease in intensity. This phenomenon suggested that CS and PVA could form

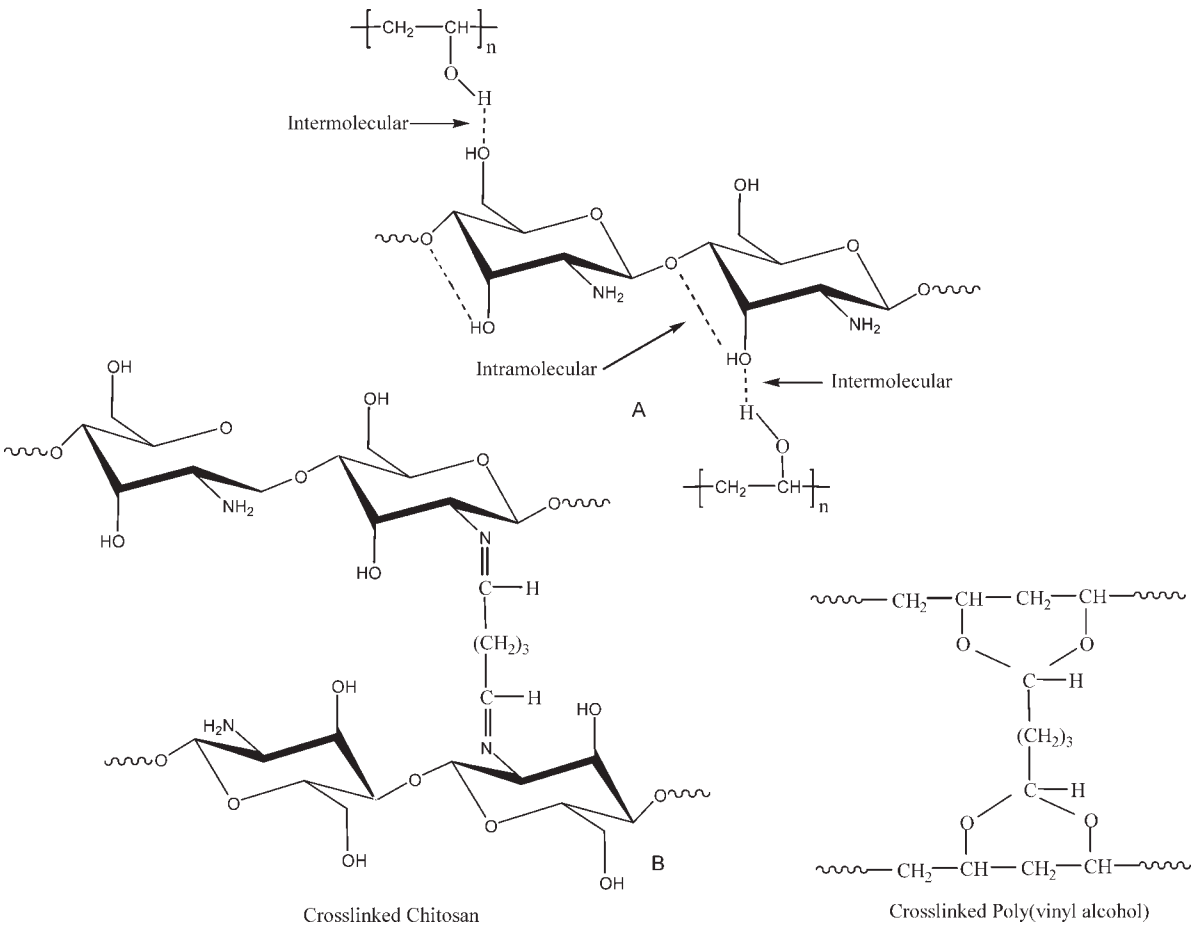

Figure 2 Interaction of CS with PVA (A) and structure of crosslinked CS and PVA (B).

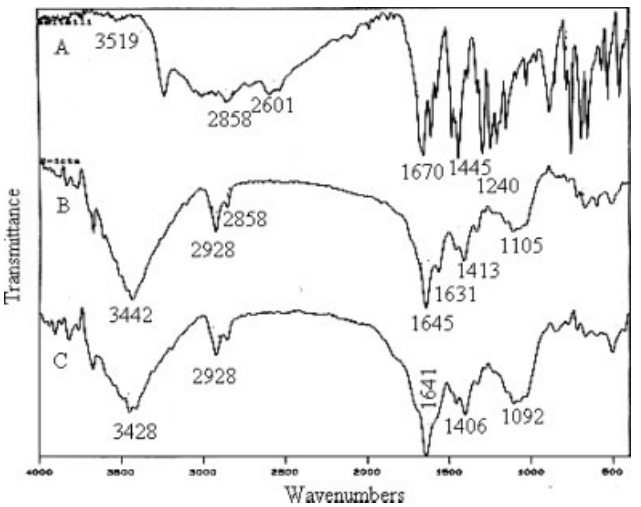

Figure 3 FTIR spectra of SA (A), empty CS/PVA microsphere (B), and SA loaded CS/PVA microsphere with 1/2 ratio (C).

intermolecular hydrogen bonding between $-NH_2$ or —OH groups of CS and —OH group of PVA as shown in Figure 2(A). Similar results were found in the previous studies.[34,36] Moreover, a new peak at 1631 cm^{-1} occurred due to the formation of C=N as a result of crosslinking reaction between amino groups of CS and aldehyde groups of GA as predicted in Figure 2(B).[37] However, band of acetal group, formed due to the reaction of glutaraldyde with hydroxyl group of PVA at around 1105 cm^{-1}, can also be seen from the spectrum.

FTIR spectra of SA (A), unloaded (B) and SA-loaded microspheres (C) were displayed in Figure 3. The characteristic bands of SA at around 3519 and 2601 cm^{-1} are due to O-H stretching bonded aromatic C atom and O-H group of carboxylic acid, respectively. The bands at 1670 and 1445 cm^{-1} are due to C=O stretching and C=C stretching of aromatic ring respectively.[38] Typical C—O carboxylic stretching vibration can also be observed in the spectrum of SA at 1240 cm^{-1}. SA-loaded microsphere showed no additional bands along with all the characteristic bands of the empty CS/PVA microsphere since the peaks due to the presence of SA were overlapped.

DSC analyses were performed to understand the thermal behavior of the blended microsphere and the results were illustrated in Figure 4. As it is reflected from the Figure 4, the end point temperature of the endotherm peak of the CS/PVA microsphere shifted to higher temperature due to the blending of CS with PVA and crosslinking of CS/PVA with GA. It is also seen that PVA has a crystalline structure and shows both T_g and T_m, while CS has an amorphous structure, and shows no T_m. T_g values of CS and PVA polymers used in this study were found to be 70 and 87°C, respectively, whereas the value for CS/PVA microsphere was found to be 97°C. The fact that higher T_g value of CS/PVA microsphere than the CS and PVA polymers can be attributed to the formation of a more rigid polymer matrix due to the crosslinking between the functional groups of polymers and glutaraldehyde. The interaction between the $-NH_2$ or —OH groups of CS and —OH groups of PVA may be another reason for the increase in T_g value of the CS/PVA blend microsphere.

SEM photographs of an empty (A) and SA loaded CS/PVA (B) microspheres taken at 50× magnifications were shown in Figure 5. As it is seen from the figure, both of the microspheres are almost spherical in shape and show roughness in the surface.

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

The results of microsphere diameter, entrapment efficiency (%) and microsphere yield (%) were shown in Table I. Microsphere size can be affected by the polymer concentration, temperature, d/p ratio, viscosity of the polymer solution, etc. As can be seen from the table, the microspheres formed have particle sizes ranging from 0.49 ± 0.01 to 0.98 ± 0.01 mm in diameter. The size of the microspheres changed with CS/PVA (m/m) ratio, drug/polymer (m/m) ratio, and crosslinking time but did not vary significantly when the crosslinking concentration was changed. Diameters of the microspheres increased significantly with increasing PVA content in all of the formulations. Moreover, an increase in crosslinking time caused a decrease in diameters of the microspheres. This is probably due to the formation of a more rigid network as a result of increased crosslinking density. Babu et al.[39] have found similar results with sodium alginate-methylcellulose blend

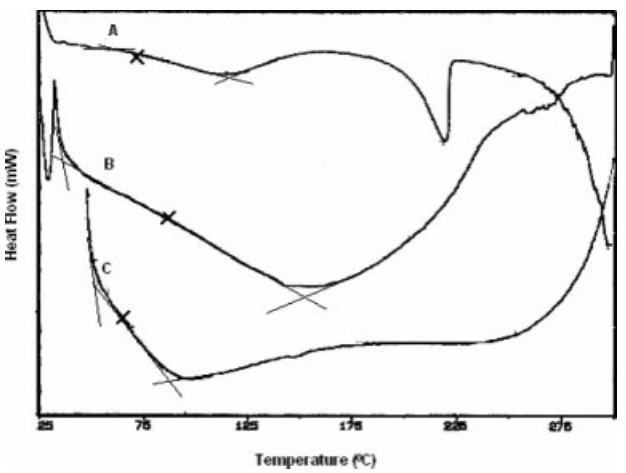

Figure 4 DSC results of PVA (A), CS/PVA microsphere (B), and CS (C).

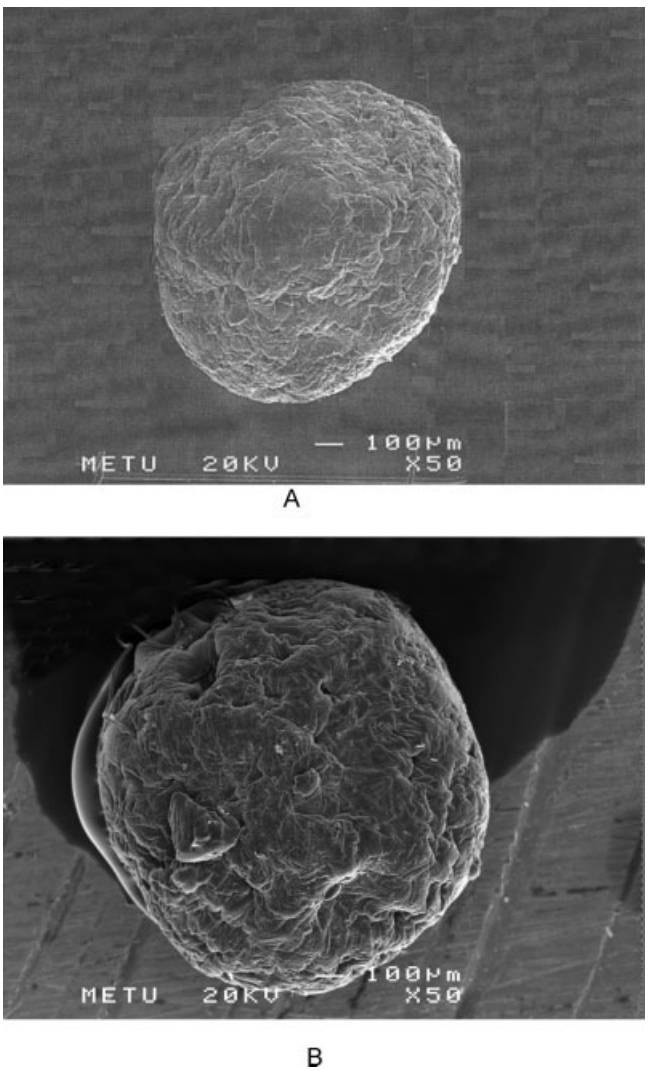

Figure 5 SEM photographs of empty CS/PVA microsphere ×50 (A), and SA loaded CS/PVA microsphere ×50 (in 1 : 2 ratio) microsphere ×50 (B).

microspheres for controlled release of nifedipine. As it is also seen from the Table I, as the d/p ratio increases, diameter of the microspheres increase due to the increase in the SA content of the CS/PVA matrix. This can be attributed to the fact that SA molecules might occupy the free volume spaces within the CS/PVA matrix, thereby hindering the inward shrinkage of the polymer matrix.

Many factors, such as nature of the drug, polymer concentration, drug polymer ratio, and the type of the matrix material of the microspheres, affect the percentage of entrapment efficiency and the microsphere yield. The results of entrapment efficiency (%) and microsphere yield (%) were also shown in Table I. The percentage of entrapment efficiency increased whereas microsphere yield decreased with the increasing of the drug/polymer ratio. As can also be seen from the table, entrapment efficiency generally increased with decreasing CS/PVA ratio.

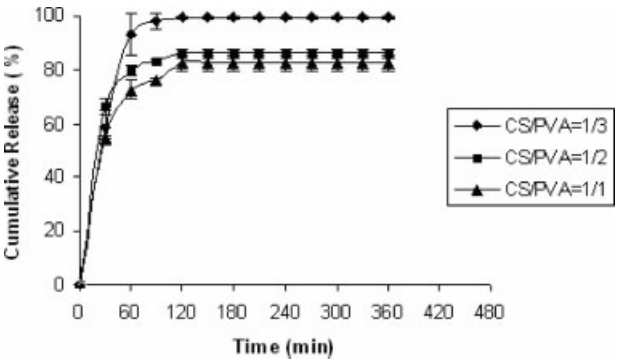

Figure 6 Effect of the CS/PVA ratio on the SA release. d/p:1/2, concentration of GA: 2.5%, exposure time to GA: 5 min.

When CS/PVA ratio was decreased, PVA content increased, and thus polymer concentration and viscosity of microsphere preparation solution increased. As a result, polymer traps more SA molecules, thus entrapment efficiency increases as obtained in our previous study.[34] Similar results were also stated by Kurkuri and Aminabhavi.[40] However, percentage of entrapment efficiency and yield value of CS/PVA microspheres did not vary significantly when the crosslinking concentration and time changed.

Effect of the CS/PVA ratio on the SA release

Controlled release is an attainable and desirable characteristic for drug delivery systems. Many parameters determine the drug release behavior from polymeric microspheres. These include concentration of polymer, physical blending of two polymers, drug crystallinity, drug/polymer ratio, concentration of crosslinking agent, crosslinking process used, etc. *In vitro* release of SA from crosslinked CS/PVA microspheres was carried out in gastric (2 h), input intestinal (2 h) and intestinal (2 h) pH conditions at 37°C. Figures 6 and 7 display the cumulative SA release of microspheres prepared with d/p ratio of

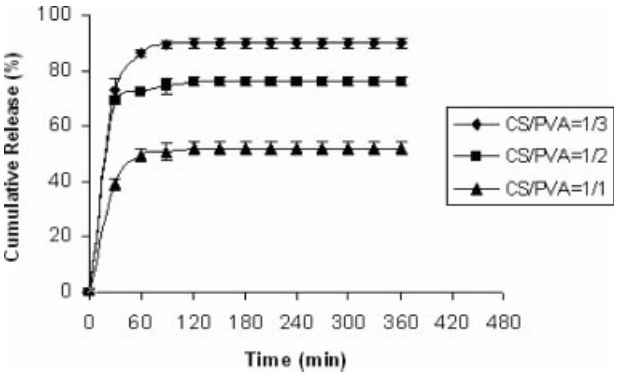

Figure 7 Effect of the CS/PVA ratio on the SA release. d/p:1/1, concentration of GA: 2.5%, exposure time to GA: 5 min.

TABLE II
Equilibrium Swelling Degree for Microspheres (Concentration of NaOH: 1*M*, Concentration of GA (%): 2.5, Exposure Time to GA: 5 min)

		Equilibrium swelling degree (%)		
		Swelling medium		
Code	CS/PVA ratio	pH = 1.2 HCl solution	pH = 6.8 buffer solution	pH = 7.4 buffer solution
F	1/1	71.50 ± 0.22	61.55 ± 0.21	60.94 ± 1.27
G	1/2	95.71 ± 0.70	76.71 ± 0.77	75.64 ± 0.61
H	1/3	101.94 ± 1.27	92.88 ± 0.26	87.02 ± 1.57

1/2 and 1/1 in different CS/PVA ratios. As it is reflected from the figures that, burst release is prevalent in the first hour for the CS/PVA blend microspheres since the conversion of glassy state to rubbery polymeric blend is very fast in acidic media. Initial drug release may be governed by the swelling of the polymeric blend (blend chain relaxation). Initial burst effect is a common phenomenon with chitosan-based delivery systems when loaded with water soluble drugs. Chitosan microparticles prepared by conventional methods have shown a porous surface due to surface-adhered free drug. These microparticles loaded with drug when brought in contact with acidic media tend to release the drug quite fast and thereby resulting in a burst effect. The burst drug release was much similar in all the other formulations. Similar trends were obtained in many studies in the literature.[7,8,10,13,41]

Moreover, the pKa of drugs and drug–polymer interactions are important factors governing drug release patterns from the polymeric matrix. SA is a weak acid (pKa = 2.9) and the percent ionization values of SA can be calculated by using Henderson-Hasselbalch equation.[42] Ionization of SA increases with the increase in the pH of the release medium. In the previous study,[43] it is stated that only the unionized species of SA determines the released percentage of SA. This could be the reason of biphasic release behavior of SA. Initially burst release occurs at pH 1.2 in which ionization of SA is very low. After that extremely slow release occurs with the increase in the pH of the release medium in which ionization of SA is high. Interactions between —OH or —COOH groups of SA and the —NH_2 or —COH groups of CS/PVA blend microsphere may also occur and effect release behavior. The drug–polymer interaction increases with the increase in ionization of SA. Therefore, SA release profile suggested a biphasic release process with an initial fast release phase followed by a slower rate. Similar drug–polymer interactions have been found in the other studies.[43,45] Puttipipatkhachorn et al.[44] studied release of SA from CS matrix and demonstrated the drug–polymer interaction between SA and chitosan, resulting salicylate formation, by ^{13}C-NMR. They have found a similar biphasic SA release profile from the CS matrix. In another study, the role of drug–polymer interaction on the sustained release from poly(DL-lactic acid) tablets was studied using propranolol HCI, diclofenac sodium, SA, sulfasalazine as model drugs by Proikakis et al.[45] They have reported that the nature of incorporated drugs and drug–polymer interaction play a significant role on the drug release behavior of the delivery system.

It can be seen from the figures that a decrease in CS/PVA ratio from 1/1 to 1/3 causes an increase in the release of SA from the microspheres. The highest cumulative SA release obtained at the end of 6 h was 100% for the 1/2 drug/p ratio and 90% for the 1/1 drug/p ratio of CS/PVA microspheres, respectively. These results are quite expected due to the increase in the hydrophilic character of microspheres with the presence of PVA. As it is seen from Table II, the ESDs of the CS/PVA microspheres increase with increasing amount of PVA in the microsphere. When the swelling degree increases, amorphous regions produce free volumes that are suitable for the penetration of liquid molecules to microsphere and the diffusion of the drug to external medium Therefore, cumulative release of SA increases with the PVA content of the microspheres. Similar observations were also found in our previous study[35] and literature.[46,47] Wang et al.[46] prepared CS/PVA films for bovine serum albumin release and reported that drug release increased with the increase in content of PVA at pH = 4.7. Also Agnihotri and Aminabhavi,[47] obtained similar results. They have found that as the gellan gum/PVA ratio in the microspheres decreased, drug release increased.

CS/PVA microspheres have also demonstrated a faster release of SA at the acidic pH as compared to medium of pH 6.8 and 7.4 due to high swelling ability of CS/PVA microsphere at acidic pH value (Table II). This can be explained by the protonation of free NH_2 groups of the CS at acidic pH. Positively charged CS at a low pH shows a high swelling ratio because the repulsive force between the same positive charges of the molecules causes long

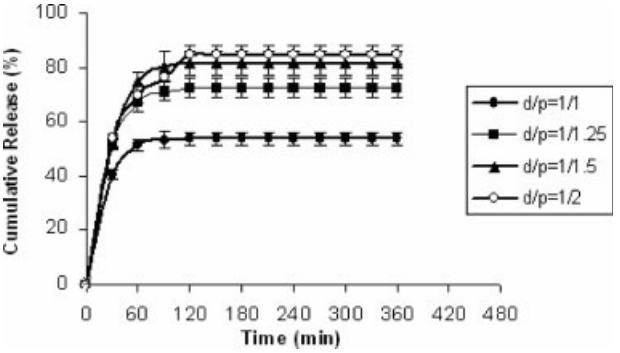

Figure 8 Effect of the drug/polymer ratio on the SA release. CS/PVA ratio: 1/1, concentration of GA: 2.5%, exposure time to GA: 5 min.

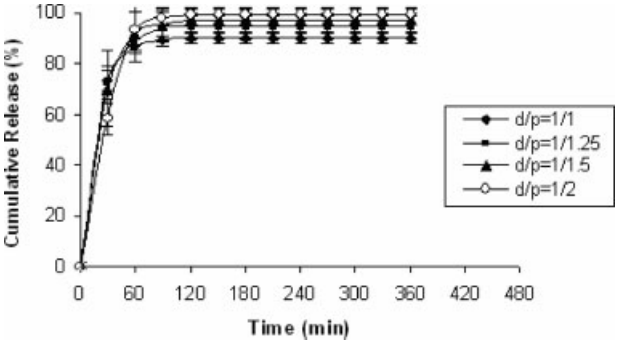

Figure 10 Effect of the drug/polymer ratio on the SA release. CS/PVA ratio: 1/3, concentration of GA: 2.5%, exposure time to GA: 5 min.

intermolecular distances and a greater hydrophilic state.[12,48] Moreover, protonation of the free amine groups causes to dissociation of the hydrogen bonds.[8] On the other hand, hydrophobicity of the CS based microsphere increases at high pH values, thus decreases the swelling degree of the microspheres as it is seen in Table II. Therefore, SA release from the CS/PVA microsphere at acidic release medium is obtained to be higher than that of pH 6.8 and 7.4.

Effect of the drug/polymer ratio on the SA release

The d/p ratio has a remarkable effect on the release of drugs from the microspheres. For this purpose d/p ratio was changed from 1/2 to 1/1 for CS/PVA (1/1, 1/2, and 1/3) microspheres prepared using 1*M* NaOH and 2.5% GA for 5 min of crosslinking time. The effect of d/p ratio on the SA release was shown in Figures 8–10. The figures illustrate that SA release from the CS/PVA microspheres increases with the decrease in d/p ratio of the CS/PVA microspheres. The cumulative release (%) of d/p ratio of 1/1 microspheres prepared with 1/1 CS/PVA ratio has shown 54% release whereas that of d/p ratio of 1/2 microspheres has shown 85% at the end of 6 h. When the d/p ratio is decreased from 1/1 to 1/2, SA content of the microspheres decreases as well. Lower SA content might lead to the easier penetrating of the liquid through the microspheres and then SA diffusion from the microspheres gains speed due to the decrease in drug–polymer interaction. In other words, while SA content of the microspheres decreases, a loose structure in the polymeric microspheres is formed and this loose structure causes the liquid to easily penetrate into the microspheres and eases the diffusion of the SA. Moreover, as the d/p ratio decreases from 1/1 to 1/2, particle size of the microspheres decreases. Release from smaller size microspheres is faster than those from the large size microspheres due to smaller diffusional path length for the drug and the larger surface area of contact of smaller particles with the dissolution media.[9,49] Similar observations were also found in the literature.[34,50]

Kumbar and Aminabhavi[50] studied controlled release of indomethacin from polyacrylamide grafted CS 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

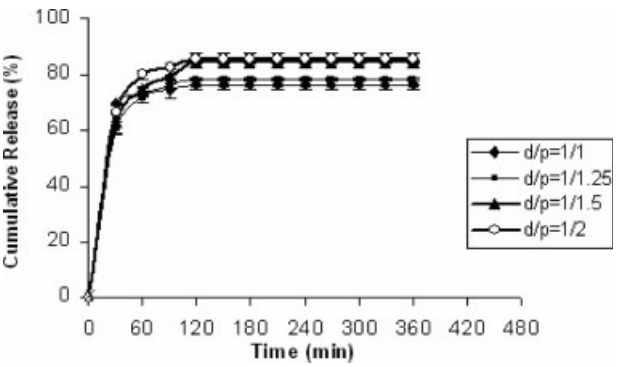

Figure 9 Effect of the drug/polymer ratio on the SA release. CS/PVA ratio: 1/2, concentration of GA: 2.5%, exposure time to GA: 5 min.

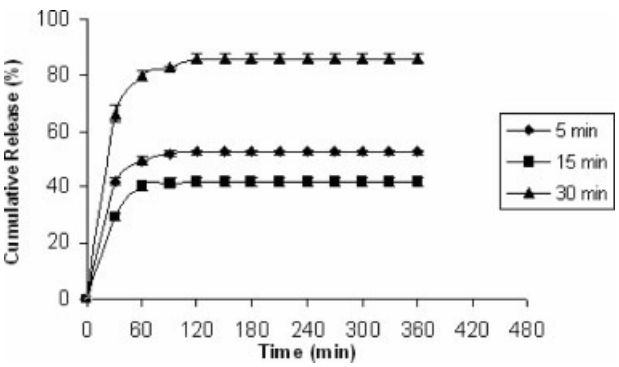

Figure 11 Effect of the exposure time to GA on the SA release. CS/PVA ratio: 1/2, d/p: 1/2, concentration of GA: 2.5%.

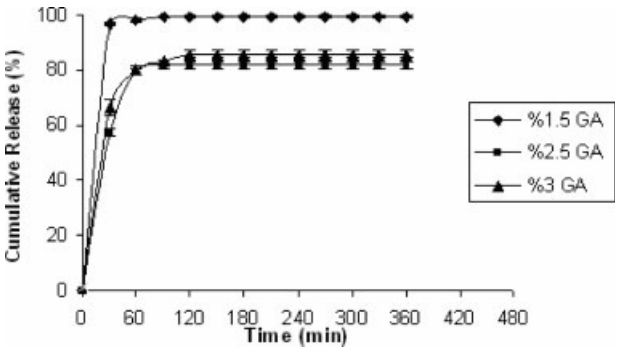

Figure 12 Effect of the GA concentration on the SA release. CS/PVA ratio: 1/2, d/p: 1/2, exposure time to GA: 5 min.

large pore volume, which might enhance the drug release.

Effect of the crosslinking time and concentration of GA on the SA release

SA release from the microspheres was subjected to a number of physical and chemical parameters including those related directly to the release medium (temperature, pH), preparation conditions, and those resulting from the change in the characteristics of the microspheres. One of the most effective ways to change the release rate of microspheres is to change crosslink density of the matrix by varying the time of exposure to crosslinking agent and change the concentrations of the crosslinking agent. The effect of crosslinking time on the release rate of SA has been investigated by varying crosslinking time from 5 to 30 min. The results were shown in Figure 11, which clearly indicates that the release rate decreases as the crosslinking time in the GA solution increases. The maximum SA release from the CS/PVA 1/2 microspheres, which were prepared with crosslinking time of 5 min, was found to be 86%.

Another way to change the crosslinking density of the microsphere is to change the concentration of GA solution. For this purpose, GA concentration was changed during the microsphere preparation from 1.5 to 3% and release results from these microspheres were presented in Figure 12. As it is seen from the figure, as the GA concentration was increased from 1.5 to 3%, SA release decreased from 100 to 82%.

The observed decreases in the cumulative release are due to the fact that increasing crosslinking time and concentration of GA solution result in an increase in crosslink density of the microspheres which give rise to a compact network of the polymer. Consequently, the free volume reduces and penetration of liquid through the microsphere and diffusion of SA molecules become difficult. Similar observations were reported in many of the studies in the literature.[4,8,34,35,40,46,47]

CONCLUSIONS

This study, which is based on the SA release from the microspheres prepared from CS/PVA blends crosslinked with GA, indicates that release from the microspheres increases with the decrease in both CS/PVA ratio and d/p ratio whereas decreases with the increase of crosslinking concentration and time in GA solution. SA from the CS/PVA microsphere is released in two steps: burst in the first hour and controlled step in later hours due to the ionization of SA and drug–polymer interaction. It is also observed that release of SA is much higher at low pH value compared with high pH values. The highest SA release percentage is obtained as 100% for the microspheres prepared with PVA/CS ratio of 1/2, d/p ratio of 1/2, exposure time to GA of 5 min and concentration of GA 1.5% at the end of 6 h. Moreover, the ESD of the formulations is in consistence with the release results.

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