Effect of Oppositely Charged Polymer and Dissolution Medium on Swelling, Erosion, and Drug Release From Chitosan Matrices

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Kiran S. Bhise,[1] Ravindra S. Dhumal,[1] Bhaskar Chauhan,[1] Anant Paradkar,[1] and Shivajirao S. Kadam[1]

[1]Department of Pharmaceutics, Bharati Vidyapeeth Deemed University, Poona College of Pharmacy, Erandwane, Pune, Maharashtra, India

ABSTRACT

The purpose of this research was to investigate the potential use of anionic κ-carrageenan and nonionic hydroxypropylmethylcellulose (HPMC, K4) to improve the matrix integrity of directly compressed chitosan tablets containing naproxen sodium, an anionic drug. The influence of buffer pH and drug:polymer ratio on the water uptake, matrix erosion, and drug release were studied. The rapid release of naproxen sodium was seen from matrices containing 100% chitosan due to loss in the matrix cohesiveness; whereas, it was relatively slow for matrices containing optimum concentration of κ-carrageenan. In-situ interaction between oppositely charged moieties resulted in the formation of polyelectrolyte complexes with stoichiometric charge ratios of unity. Fourier transform infrared (FTIR) spectroscopy and powder x-ray diffraction (PXRD) data confirmed the importance of ionic bonds in polyelectrolyte complexation. The ionic interactions between polymers were absent in matrices containing HPMC and the integrity of tablets was improved owing to the presence of viscous gel barrier.

The reasons for retarded release of naproxen sodium from the chitosan matrices at different pH include poor aqueous solubility of drug, the formation of a rate-limiting polymer gel barrier along the periphery of matrices, the interaction of naproxen sodium with protonated amino groups of chitosan, and the interaction of ionized amino groups of chitosan with ionized sulfate groups of κ-carrageenan.

KEYWORDS: Charged polymers, naproxen sodium, in-situ complexation, sustained release matrices, chitosan, κ-carrageenan.

INTRODUCTION

Natural polymers are widely used in the design of controlled release drug formulations. Apart from widely used neutral polymers (eg, hydroxypropylmethylcellulose [HPMC]), cationic polymer (eg, chitosan) and anionic polymers (eg, κ-carrageenan, sodium alginate) have been used in the form of polyelectrolyte complexes for control of drug release. As excipients, ionic polymers have shown to affect release of oppositely charged drugs. Ionic drugs form complexes with the polyelectrolytes, and the bound drug is released in exchange of ions present in the dissolution medium. Factors such as pH, viscosity of the polymer solution, ionic nature of dispersed drug, and ionic strength of the dissolution medium affect drug-polymer interactions. Complexes between oppositely charged polyelectrolytes such as sodium alginate-chitosan,[1-5] polyacrylic acid-chitosan,[6] and chitosan-carrageenan[7] have been used in the design of controlled release formulations.

Chitosan, (1–4)-2-amino-2-deoxy-B-D-glucan, is a linear cationic polysaccharide comprising copolymers of glucosamine and N-acetylglucosamine and can be derived by partial deacetylation of chitin from crustacean shells. The term chitosan is used to describe a series of chitosan polymers with different molecular weights (50-2000 kd), viscosity (1% chitosan in 1% acetic acid, <2000 mPa), and degree of deacetylation (40%-98%). Chitosan salts are soluble in water, with the solubility being dependent on the degree of deacetylation and thereby on the pH of the buffer. Chitosans with a relatively low degree of deacetylation (40%) have been found to be soluble up to pH 9, whereas chitosans with a degree of deacetylation of ~85% have been found to be soluble up to pH 6.5. At acidic pH, the amine groups of chitosan are protonated, acquire positive charge, and coagulate upon addition of negatively charged molecules.[8] With increasing degree of deacetylation, the viscosity of chitosan increases because of the different confirmations of the molecule. At a high degree it is highly charged and has an extended confirmation with more flexible chains, whereas at a lower degree of deacetylation the chitosan molecule adopts a rod- or coil-like shape because of low charges.[3-10] Chitosan drug complexes, chitosan beads, and polymers have been reported in the literature.[9-17] Carrageenans are naturally occurring high molecular weight polysaccharides extracted from seaweeds and are made up of the repeating units of galactose and 3,6 anhydrogalactose.[10] They consist of the sulfate esters of galactose and 3,6 anhydrogalactose joined by alternating α-1,3 and β-1,4 glycosidic linkages.[11] There are 3 main

Corresponding Author: Anant Paradkar, Department of Pharmaceutics, Bharati Vidyapeeth Deemed University, Poona College of Pharmacy, Erandwane, Pune-411038, Maharashtra State, India. Tel: +91 20 2543 7237; Fax: +91 20 2543 9383; E-mail: arparadkar@rediffmail.com

types of carrageenans available: iota (ι), kappa (κ), and lambda (λ), with 1, 2, or 3 ester sulfate groups, respectively.

The highly sulphated λ-carrageenan does not gel, but both other types, ι- and κ-carrageenan, are able to generate gels with different characteristics that can influence release behavior of mixtures. The κ-carrageenan shows controlled release for 8 hours tending to zero-order kinetics.[10,11] Because of the presence of strongly acidic sulfate groups that allow a certain degree of ionization at low pH, κ-carrageenan-basic drug complexes have been tried.[1,9,18-22] Polyelectrolyte complex of κ-carrageenan and chitosan has been reported; the disappearance of the electrostatic linkage between the amino group of chitosan and the sulphonate group of κ-carrageenan in the prepared complex was found to contribute to the swelling of the complex gel.[17] Complexation with chitosan, though, retards drug release to some extent, but further control may not be achieved owing to the lack of integrity of the matrices.[9] In such cases, other polymers are added to strengthen the matrices. One of the major factors responsible for dissolution of an organic compound is its ability to dissociate into ionic species, which in turn depends on the pH of the medium. Naproxen sodium is a nonsteroidal anti-inflammatory weakly acidic drug that contains ionizable groups. The drug solubility increases with an increase in pH. Naproxen sodium exhibits gastric toxicities, mucosal ulcerations, and hemorrhage due to inhibition of prostaglandin production. The severity of these side effects can be reduced by altering the conventional dosage forms so that the peak plasma concentrations will be lowered and will be delayed.[19,20] In the present study, an attempt has been made to compare the effect of neutral polymer HPMC and anionic polyelectrolyte κ-carrageenan on water uptake, matrix erosion, and drug release from chitosan matrices. Naproxen sodium was chosen as a model drug because of its anionic nature.

Materials and Methods

Materials

The κ-carrageenan, Gelcarin GP 911 NF (FMC Corp, Philadelphia, PA [through Signet Chem, Mumbai, India]); chitosan, 87% deacetylation, molecular weight 80 000 as reported by the manufacturer (Marine Chemicals, Chennai, India); HPMC, Methocel K4 (Colorcon Asia Pvt Ltd, Mumbai, India); and naproxen sodium (Divis Laboratories Ltd, Hyderabad, India) were generous gift samples. All other chemicals were purchased and were of analytical grade.

Methods

Analytical Method and pH - Solubility Profile for Naproxen Sodium

The partition coefficient (pK_a) of naproxen sodium is 4.2 (Newton and Kluza 1978), and its solubility depends upon the pH of the dissolution medium. Ethanol was incorporated into the various dissolution media to compensate for the low solubility of naproxen sodium at acidic Ph.[9] Standard solutions of naproxen sodium were prepared in the following dissolution media: (1) 30% vol/vol ethanol and 70% vol/vol hydrochloric acid buffer pH 1.2 (medium A), (2) 30% vol/vol ethanol and 70% vol/vol phosphate buffer pH 6.8 (medium B), and (3) phosphate buffer pH 6.8 (medium C), respectively. Spectrophotometric analysis was performed at wavelengths (λ_{max}) of 229.4 nm, 327.5, and 329 nm, respectively. Jasco double-beam UV-visible (UV-VIS) spectrophotometer, (model V-530, Jasco International Co Ltd, Tokyo, Japan) was used for drug analysis.

The pH solubility profile of naproxen sodium was obtained in the pH range 1.2 to 7.4 by determining the solubility of the drug in media A, B, and C. The pH of the saturated drug solution, measured on a pH meter, was taken as the final pH in each case. For determination of saturation solubility, excess drug was placed in contact with 10 mL of solvent media A, B, and C in sealed glass vials. The vials were shaken continuously for 24 hours on linear motion shaker (model RM -8, Spectralab, Mumbai, India). The saturated solutions were centrifuged, and the supernatant solutions were filtered through Whatman filter paper 41 (Whatman International Ltd, Maidstone, UK), and drug concentrations were determined by UV absorption spectroscopy after appropriate dilutions with the selected solvents.[21] Table 1 presents naproxen sodium solubility in different dissolution media.

In Situ Polyelectrolyte Interaction

In situ polyelectrolyte interaction was studied using various methods found in literature;[21-31] in particular using an experiment reported by Hugerth et al.[32] Solutions of chitosan (1 mg/mL) were prepared in 1% vol/vol acetic acid solution by continuous stirring at 25°C for 24 hours. Care was taken to ensure total solubility of the chitosan. Series of dilutions were prepared in the concentration range of 5 μg/mL to 60 μg/mL. To 5 mL of the diluted solutions, was added 5 mL of acetic acid/acetate buffer (pH 5.5). Ninhydrin reagent was added to each solution and the samples were agitated vigorously. The tubes were placed in a boiling water bath for 20 minutes. After the solutions had cooled down,

Table 1. Solubility of Naproxen Sodium in Different Dissolution Media

Serial Number	Dissolution Media	pH of Media	pH of Drug Dispersion	Saturation Solubility*
01	Media A	1.65	2.48	10 mg/mL
02	Media B	7.3	7.78	30 mg/mL
03	Media C	6.9	6.65	200 mg/mL

*All values represent mean (n = 3).

their absorbances were taken at 555 nm in a UV-VIS spectrophotometer. Carrageenan solution (1 mg/mL) was prepared in 100 mL warm distilled water. The polyelectrolyte complex formation between chitosan and κ-carrageenan was studied by mixing stock solutions (1 mg/mL) of chitosan-carrageenan in ratio 1:0.25, 0.75:0.5, 1:1, 0.5:0.75, and 0.25:1 to make up the final volume to 5 mL and then vigorously shaking in a Whirlmatic motorless magnetic stirrer (WS-MEGA, Spectra lab, Mumbai, India) for 3 hours. The resulting solutions were thereafter centrifuged for further 24 hours. The supernatants obtained were analyzed quantitatively for chitosan by means of ninhydrin reagent.

Preparation of Matrices

Naproxen sodium and chitosan were mixed separately with κ-carrageenan or HPMC in the various ratios in a laboratory mixer (Seema Enterprises, Pune, India) and were passed through 40-mesh screen. The formulations prepared are presented in Table 2. The mixtures were then compressed using a 10-station minipress II "D" tooling, tableting machine (Rimek, Karnavati Engineering Ltd, Gujarat, India) fitted with 13-mm diameter flat-faced punches. Powder admixtures were manually filled into the die, and 1 compaction cycle was performed. For each batch, 50 tablets were produced. Tablet diameter, thickness, and crushing strength of 5 tablets from each batch were determined using Pharma Test (INCORP Ltd, Mumbai, India). Tablets with $(\text{diameter})_{\text{average}}$ 12.71 ± 0.57 mm, $(\text{thickness})_{\text{average}}$ 3.000 ± 0.001 mm, $(\text{hardness})_{\text{average}}$ 5 ± 0.5 kg/cm^2 and $(\text{weight})_{\text{average}}$ 500 ± 10 mg, were held constant for all batches.

Particle size. A particle size analysis was performed in triplicate with a Stereo Image Microscope at original magnification ×1.25 and total count of 300 particles. Table 3 describes average diameters of naproxen sodium, chitosan, κ-carrageenan, and HPMC (K4).

Table 2. Compositions of Sustained Release Matrices Containing 250 mg of Drug*

Batch Code	Chitosan	κ-Carrageenan	HPMC
K1	50 mg	200 mg	—
K2	100 mg	150 mg	—
K3	125 mg	125 mg	—
K4	150 mg	100 mg	—
K5	200 mg	50 mg	—
K6	250 mg	—	—
M1	50 mg	—	200 mg
M2	100 mg	—	150 mg
M3	125 mg	—	125 mg
M4	150 mg	—	100 mg
M5	200 mg	—	50 mg
M6	250 mg	—	—

*HPMC indicates hydroxypropylmethylcellulose. Tablet weight was 500 mg.

Table 3. Characterization of Naproxen Sodium and Polymers*

Samples	Average Diameter (μm)	Average Density† (g/cm^3)	
		Bulk	Tap
Naproxen sodium	23.30	0.22	0.19
Chitosan (Ch)	42.82	0.542	0.460
k-Carrageenan (Ca)	31.59	0.330	0.300
HPMC (K4)	20.00	0.360	0.391

*HPMC indicates hydroxypropylmethylcellulose.

†All values represent mean (n = 3).

Density. Bulk and tap density for 10-g samples of naproxen sodium, chitosan, κ-carrageenan, and HPMC (K4) was determined in triplicate in a 100-mL measuring cylinder. The results are presented in Table 3.

Viscosity. The viscosities of 2% wt/vol polymer solutions in 1% vol/vol acetic acid, and in all 3 dissolution media used in the present study were measured at 25°C with Brookfield viscometer (CAP viscometer, model CAP 2000 +L, P01 spindle, Brookfield Engineering Laboratories, Middleboro, MA), at 10 rpm for 30-second run time. Readings were taken in triplicate. Table 4 describes average viscosities of chitosan, κ-carrageenan, and HPMC (K4) in different media.

Fourier Transform Infrared Spectrometry

Fourier transform infrared (FTIR) spectra of naproxen sodium, chitosan, κ-carrageenan, HPMC (K4), physical mixtures, and dried samples of pretreated K3 and M3 matrices were recorded on FTIR spectrometer (model FTIR-4100 Plus, Jasco).

X-ray Powder Diffractometry

X-ray powder diffractograms of naproxen sodium, chitosan, κ-carrageenan, HPMC (K4), physical mixtures, and dried samples of presoaked K3 and M3 matrices were recorded on powder X-ray diffractometer (PW 1729, Philips, Eindhoven, The Netherlands). The samples were irradiated with monochromatized Cu Kα radiation (1.54060 °A) and analyzed between 10 and 40 °2θ. The voltage and current used were 30 kV and 30 mA, respectively. The range and chart speed were 2 × 10^3 cps and 10 mm /2θ, respectively.

Evaluation of Matrices

Water-uptake study. Water uptake studies were performed by equilibrium weight method.[24] The preweighed matrices were subjected to dissolution in 900 mL of 3 media, A, B, and C, separately maintained at 37°C ± 0.5°C. United States Pharmacopeia (USP) XXIV Type II dissolution test apparatus (dissolution tester model TDT-08 L, Electrolab, Mumbai,

Table 4. Absolute Viscosity of Polymers (2% wt/vol) in Different Dissolution Media*

Serial Number	Polymer	Absolute Viscosity (Pa) at 20°C†				
		1% AA	DW	Medium A	Medium B	Medium C
01	Chitosan	1.400	Insoluble	1.20	Insoluble	Insoluble
02	k-Carrageenan	0.980	1.7	0.944	1.300	1.875
03	HPMC	1.210	2.8	1.94	2.39	3.38

*AA indicates acetic acid; DW, distilled water.

†All values represent mean (n = 3).

India) was used for this purpose. The speed of basket rotation was maintained at 100 rpm. The basket matrix systems were removed from the dissolution vessels at regular intervals, blotted with tissue papers to remove excess water, and reweighed. In order to simulate in situ conditions, K3 and M3 matrices were pretreated with medium A for the first 2 hours, followed by 4 hours with medium B in 1 run and C in a second run. The percentage water uptake was calculated using Equation 1:

$$\text{Percentage Water Uptake} = [W_s - W_i - W_e/(W_p - W_{pe})] \times 100 \quad (1)$$

where W_i and W_s represent weight of initial matrix and swollen matrix at time t (minutes) respectively; W_p and W_{pe} denote initial weight of the polymer added to matrix and weight of polymer eroded up to time t, respectively; and W_e represents the total weight loss due to dissolution of drug and polymer from matrix up to time t (minutes). Studies were performed using 5 matrices for each batch code in each dissolution fluid.

Erosion studies. Erosion studies of drug-loaded matrices were performed as reported by Paradkar et al.[24] The preweighed matrices were placed in dissolution basket of USP XXIV Type I dissolution test apparatus (dissolution tester model TDT-08 L, Electrolab) and were subjected to dissolution in 900 mL of dissolution fluids maintained at 37°C ± 0.5°C, the speed of basket rotation was 100 rpm. The dissolution fluids used were medium A, medium B, and medium C. The matrix systems were removed at regular intervals from the dissolution vessels and dried to constant weight in hot air oven at 50°C. Erosion studies were also performed by pretreating K3 and M3 matrices with medium A for first 2 hours followed by 4 hours in medium B and medium C in separate runs. The percentage matrix erosion at time t minutes was calculated using Equation 2:

$$\text{Percentage Matrix Erosion} = (W_{pe}/W_i) \times 100 \quad (2)$$

where W_i and W_{pe} represent weight of initial matrix and weight of polymers eroded at time t (minutes). Studies were performed using 5 matrices for each batch.

Drug Release Studies. Release of naproxen sodium was performed in triplicate for each batch using USP XXIV Type II, dissolution test apparatus (dissolution tester model TDT-08 L, Electrolab). The preweighed matrices were subjected to dissolution in 900 mL of dissolution fluids maintained at 37°C ± 0.5°C, speed of paddle rotation was 100 rpm. The dissolution fluids used were medium A, medium B, and medium C. Five-milliliter samples were collected at a time interval of 1 hour and were replaced by the fresh dissolution medium. Solutions were filtered through Whatman filter paper 41 and drug concentration was determined spectrophotometrically at 327.5 nm for medium A, 329 nm for medium B, and 229.4 nm for medium C. Dissolution studies were also performed by pretreatment of K3 and M3 matrices with medium A for first 2 hours followed by the next 4 hours in medium B and medium C in separate runs.

Results and Discussion

In Situ Polyelectrolyte Interaction

Results from experiments on the interaction between chitosan with deacetylation degree of 87% and κ-carrageenan are presented in Figure 1. The chitosan concentration (micrograms) in the supernatant after mixing and centrifugation is plotted against the total amount of chitosan in micrograms per milligram of the polyelectrolyte mixture. The results indicate that all added chitosan binds to κ-carrageenan until a point is reached where the entire amount of chitosan present has reacted with κ-carrageenan. Minima can be seen at this point. Beyond this point, further addition results in an increasing amount of unreacted chitosan in the supernatant. The data presented in Figure 1 indicate minimum concentration (69.49 μg) of chitosan in the supernatant at equimolar concentration (500 μg/mg) of chitosan-carrageenan in the polyelectrolyte mixture. Thus, the experimental data support the hypothesis of polyelectrolyte complexation between chitosan and κ-carrageenan at concentration of 1:1.

Water-uptake Study

Water uptake profiles of some batches are shown in Figure 2. Matrices containing 80% and 100% chitosan disintegrated within 60 minutes and 5 minutes, respectively. Profiles of

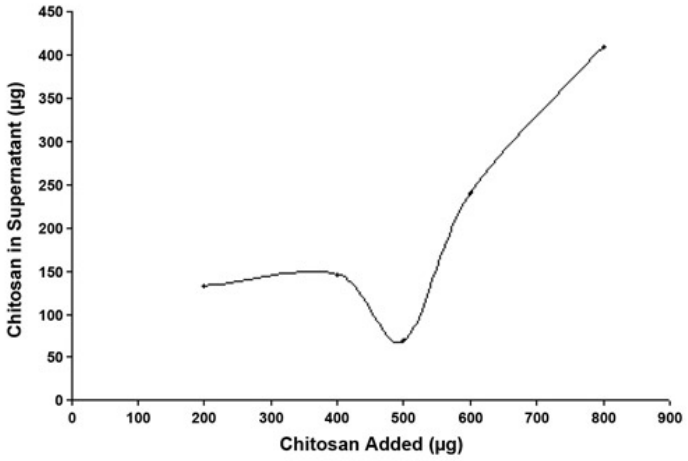

Figure 1. Complex formation between chitosan 87% DD and κ-carrageenan.

other batches are not included as they followed a pattern similar to those shown in Figure 2.

Fast swelling and expansion of K matrices were observed in all 3 buffers, whereas M matrices showed a lag time in swelling and expansion. It has been reported that κ-carrageenan bind more water than HPMC in the same ratio, therefore the water content for κ-carrageenan matrices was found to be 2 or 3 times that of HPMC.[25] This behavior is probably because of the high mobility of the water molecules between polymer chains wherein sulfate groups get hydrated.[25] Both κ-carrageenan and chitosan owe their solubility in water-based solvents to their charged groups, because except for these groups, the polymer backbones are quite hydrophobic.[32-37] Table 5 depicts that the swelling behavior depends upon the percentage of polymers used and pH of the dissolution medium. At pH 1.2, free amino groups of chitosan were protonated, resulting in the electronic repulsions and solvation of ionic groups thus contributing to the maximum swelling. At this pH, the sulfate groups of κ-carrageenan were ionized and acquired negative charge. Because of the ionization of polymers at pH 1.2, the electrostatic flux produced by the mixture of chitosan and κ-carrageenan favored the formation of polyelectrolyte complex. Figures 3 and 4 demonstrate that K3 matrices pretreated with medium A formed in-situ polyelectrolyte complexes; probably after pretreatment with acidic buffer, the charge densities in polyelectrolytes improved, favoring more interactions between the oppositely charged polyelectrolytes. Water uptake of K matrices in media B and C was greater as compared with medium A. Probably the potassium, sodium, and hydrogen ions, present in the phosphate buffer, were entrapped by double-helix structures of κ-carrageenan, thus contributing to the increased water uptake. Presence of alcohol reduced hydration of K and M matrices and thus reduced the water uptake in media A and B. Swelling of M batches was slow and steady and was due to solvation followed by gelation in the cellulose chains. Consistent with the data presented in Table 6, no significant difference was seen in the water uptake of M3 matrices after pretreating them with medium A.

Erosion Study

Figure 5 illustrates matrix erosion profiles of some batches and indicates their inverse relationship with water uptake. Matrices containing 80% and 100% chitosan disintegrated within 60 minutes and 5 minutes, respectively. Profiles of other batches are not included as they followed a pattern similar to those shown in Figure 5. The erosion data of all matrices are shown in Table 5. The rate of κ-carrageenan erosion was affected by the pH of the dissolution medium. Rate of erosion was too high at acidic pH values. High κ-carrageenan content (K1) exhibited more erosion in all 3 dissolution fluids. Table 6 demonstrates a comparative account of pretreated K3 and M3 matrices. K3 matrices pretreated with medium A showed reduced tendency of matrix erosion in media B and C. Possible explanation of the results could be in-situ complexation between chitosan and κ-carrageenan in medium A that might affect matrix integrity. However, no improvement in the erosion behavior was noticed after pretreatment in M3 matrices as can be interpreted from Table 6. Absence of electrostatic interaction between polymers at acidic pH might be responsible for continuous erosion of pretreated M3 matrices.

Drug Release Studies

Naproxen sodium being poorly soluble at acidic pH results in poor drug dissolution. Therefore, ethanol was added in acidic medium to compensate for poor solubility of drug. For comparison purpose, the same amount of ethanol was added to alkaline buffer medium B. Drug release profiles of some batches are shown in Figure 6. Matrices containing

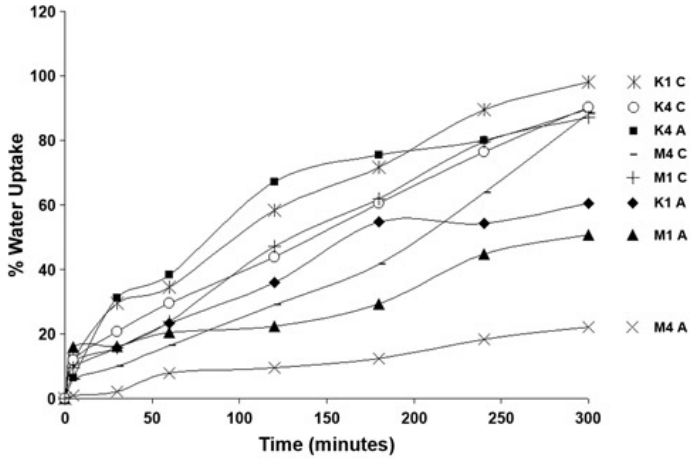

Figure 2. Percentage water uptake in dissolution media A and C.

Table 5. Percentage Drug Release, Water Uptake, and Matrix Erosion of Matrices in the 3 Media, A, B, and C, After 300 Minutes

		Drug Release* (%)			Water Uptake† (%)			Matrix Erosion† (%)		
Code	Chitosan (%)	A	B	C	A	B	C	A	B	C
K1	20	19.52	21.50	57.84	60.45	96.59	98.17	8.22	6.96	6.63
K2	40	7.78	19.32	43.36	89.88	94.84	98.15	8.06	5.73	5.08
K3	50	8.40	20.33	22.38	90.57	93.13	97.99	7.08	5.71	3.73
K4	60	8.76	30.50	36.48	91.42	90.99	90.12	6.39	4.09	4.28
M1	20	20.08	45.30	56.69	50.78	82.68	87.15	2.99	3.46	5.69
M2	40	22.53	49.54	62.92	79.35	83.61	93.00	3.36	3.72	3.06
M3	50	23.95	54.66	65.00	80.98	90.53	91.68	3.22	3.17	3.95
M4	60	37.92	66.25	69.00	75.00	92.17	88.23	6.39	7.78	7.10

*All values represent mean (n = 3).

†All values represent mean (n = 5).

80% and 100% chitosan disintegrated within 60 minutes and 5 minutes, respectively. Profiles of other batches are not included as they followed pattern similar to those shown in Figure 6.

Table 5 summarizes dissolution data of naproxen sodium from K and M matrices in the 3 media. The drug release was slowed from chitosan matrices containing κ-carrageenan or HPMC in different proportions. Release of naproxen sodium was almost 100% from K6 and M6 matrices. Overall release of naproxen sodium in the acidic pH was less being

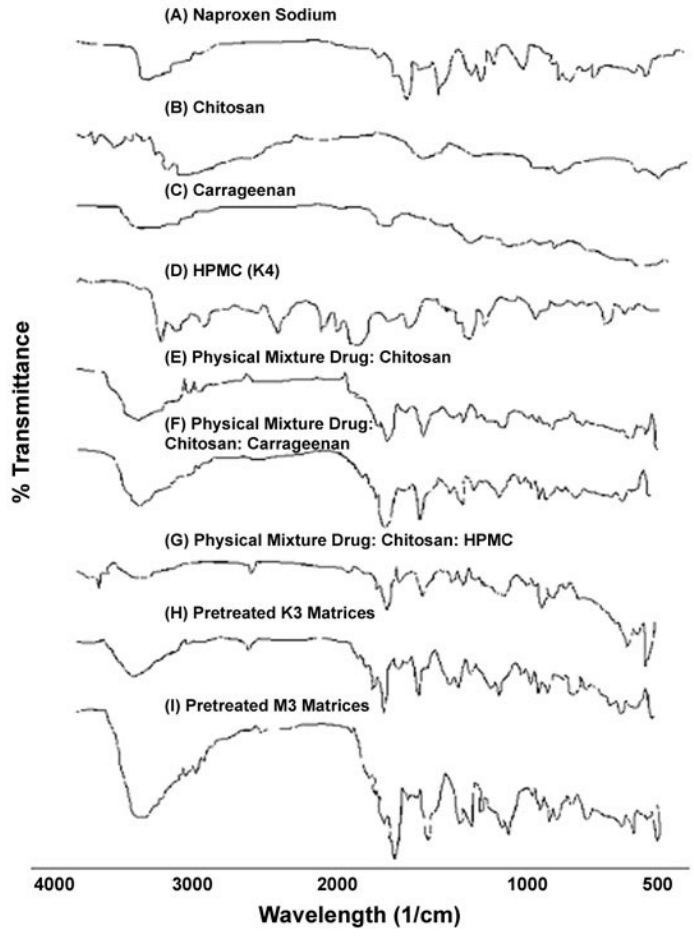

Figure 3. Fourier transform infrared spectroscopy patterns: (A) naproxen sodium; (B) chitosan; (C) κ-carrageenan; (D) hydroxypropylmethylcellulose (HPMC K4); (E) physical mixture drug:chitosan; (F) physical mixture drug:chitosan:κ-carrageenan; (G) physical mixture drug:chitosan:HPMC; (H) pretreated K3 matrices; and (I) pretreated M3 matrices.

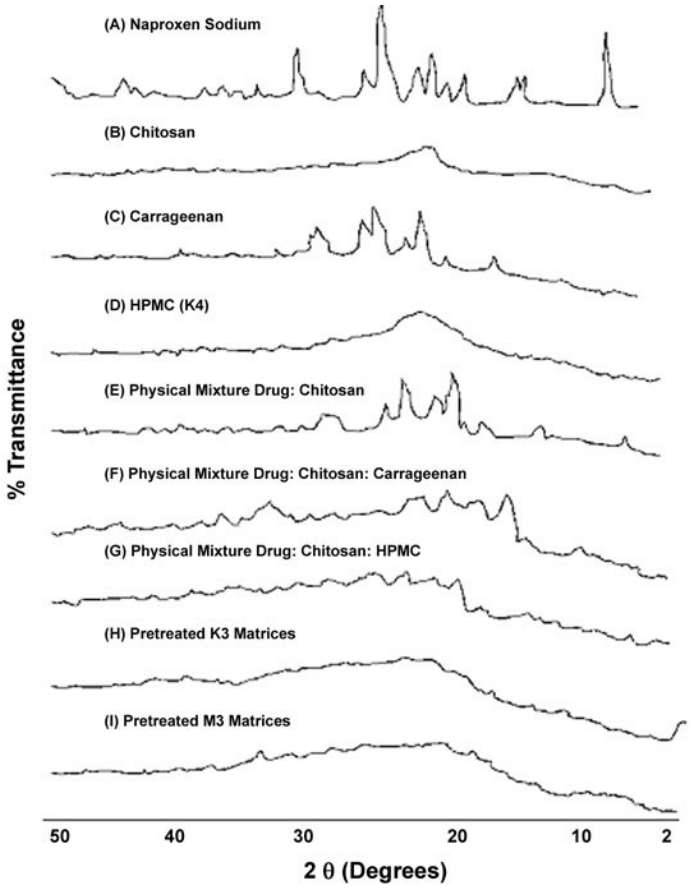

Figure 4. Powder x-ray diffraction patterns: (A) naproxen sodium; (B) chitosan; (C) κ-carrageenan; (D) hydroxypropylmethylcellulose (HPMC K4); (E) physical mixture drug:chitosan; (F) physical mixture drug:chitosan:κ-carrageenan; (G) physical mixture drug:chitosan:HPMC; (H) pretreated K3 matrices; (I) pretreated M3 matrices.

Table 6. Percentage Drug Release, Water Uptake, and Matrix Erosion After 300 Minutes for K3 and M3 Matrices With and Without Soaking in Medium A Followed by Dissolution in Media B and Media C

	Drug Release				Water Uptake				Matrix Erosion			
	Without Soaking		With Soaking		Without Soaking		With Soaking		Without Soaking		With Soaking	
Batch Codes	B	C	B	C	B	C	B	C	B	C	B	C
K3	20.33	22.38	13.62	32.06	93.13	97.99	93.23	96.50	5.70	3.73	5.36	3.66
M3	54.66	65.00	19.51	40.52	80.98	91.68	73.46	75.80	3.17	3.95	4.35	4.96

*All values represent mean (n = 3).

†All values represent mean (n = 5).

a weak acid, with a $pK_a = 4.2$. Naproxen sodium is soluble in water at alkaline pH. Similarly, at acidic pH, chitosan and κ-carrageenan are ionized to a substantial extent and may form polyelectrolyte complex resulting in retarded drug release. At intermediate pH naproxen sodium and chitosan are ionized resulting in better ionic interaction.[9]

Because of the high solubility of naproxen sodium and suppressed ionization of polyelectrolytes at alkaline pH, the drug release from K matrices was found to increase in both medium B and medium C. Saturation solubility of naproxen sodium was determined in all 3 media. From the pH solubility profile, it is clear that the solubility of naproxen sodium was improved due to addition of ethanol in acidic dissolution media. As evident from Table 1, a pH shift was observed as a result of the addition of ethanol in acidic and alkaline dissolution media A and B. However, maximum drug solubility occurred in medium C buffer pH 6.8, and hence maximum drug release from all the matrices occurred at this pH. This finding is supported by the data presented in Table 5. Potassium ions present in the alkaline buffers might have influenced the swelling and release behavior of K matrices. It has been reported previously that potassium and calcium ions are able to change the gelling properties of κ-carrageenan matrices.[27] Minimum drug release was observed for K3 matrices at alkaline pH because of the formation of in-situ polyelectrolyte complexes. After comparing drug release data of M matrices with K matrices in all 3 buffers, the following observations were noted:

1. Drug release from M matrices was retarded possibly due to formation of highly viscous gel barrier of HPMC that might have influenced the drug release.
2. For the initial 60 minutes, a lag time for swelling was observed in M matrices, and therefore drug release was faster as compared with K matrices. But after 180 minutes, drug release was retarded from M matrices almost in all the buffers, indicating pH-independent drug release from matrices containing HPMC.
3. Ionic interaction was absent between HPMC and chitosan due to the neutral nature of the former polymer. The interaction between anionic naproxen and cationic chitosan at optimum pH cannot be neglected as a potential cause of retarded drug release from the in-situ complex. The viscous gel barrier of HPMC might have prevented fast disintegration of in-situ drug-chitosan complexes and retained the cohesiveness of M matrices.

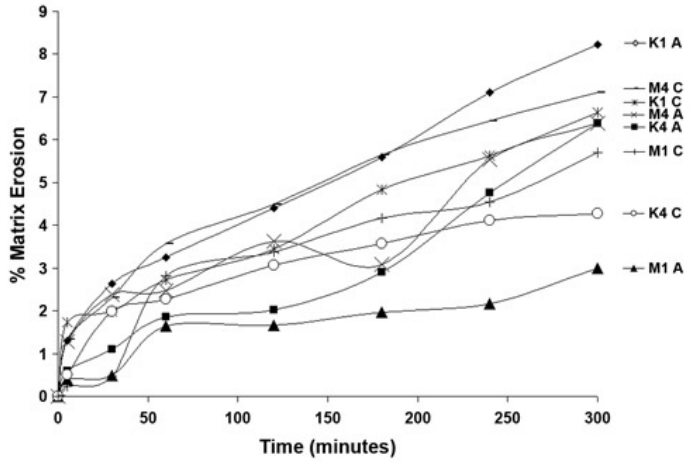

Figure 5. Percentage matrix erosion in dissolution media A and C.

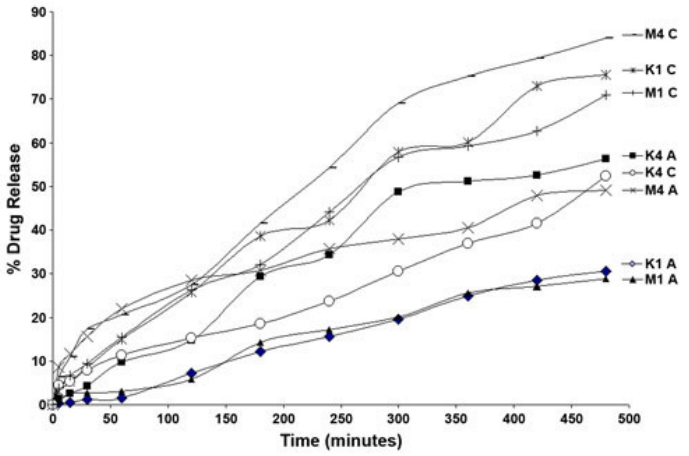

Figure 6. Percentage drug release in dissolution media A and C.

4. The fast disintegration of M5 and M6 matrices was due to high percentage of chitosan, where HPMC was not effective in maintaining matrix cohesiveness.
5. The pretreated K3 matrices showed retarded drug release in alkaline buffers. The release of drug from M3 matrices was not significantly affected after the pretreatment. It is unlikely that the delay in drug release resulted from slow ionization of naproxen-free acid formed in the acidic environment, because no delay was observed for matrices containing 100% chitosan. Accordingly, the delay in drug release could be attributed to the complex formation between the 2 oppositely charged polyelectrolytes in medium A before exposure to the alkaline buffers. FTIR and PXRD patterns (Figures 3 and 4) support the above observations. Figure 3 indicates that naproxen sodium exhibits sharp bands at 1726.2 cm^{-1} due to carboxylic stretching (–C=O); 3180 cm^{-1}, due to –OH stretching; 1604.7 cm^{-1}, due to aromatic stretch; 3000 cm^{-1}, due to aromatic C-C stretch; and 2940 cm^{-1} and 2930 cm^{-1}, due to aliphatic stretch.

A broad absorption band at 1357.8 cm^{-1} assigned to sulphonic acid (SO_4^-) groups was observed for κ-carrageenan, and an intense and broad absorption band at 1643.2 cm^{-1} assigned to $–NH_2$ groups was observed for chitosan. The spectra of physical mixtures as well as pure drug and polymers appeared almost unchanged in the carbonyl stretching region, indicating the absence of any hydrogen bonding interaction between drug and polymers. However, the spectra of the dried samples of pretreated K3 matrices showed a new absorption band at 1560.3 cm^{-1} due to $–NH^+_3$ groups and strong reduction in the intensity of the absorption band of (SO_4^-) groups. This evidenced the formation of strong in-situ polyelectrolyte complex between chitosan and κ-carrageenan. The disappearance of sharp carbonyl peak of naproxen sodium in the dried pretreated K3 and M3 matrices indicates conversion of crystalline to amorphous form of drug and could be attributed to the in-situ complex formation between chitosan-naproxen sodium at intermediate pH.

The sharp peaks were seen in the X-ray powder diffractogram of K3 and M3 physical mixtures, whereas, a more evident loss of drug crystallinity was observed in the dried samples of pretreated K3 and M3 matrices that confirmed in-situ complex formation between chitosan, κ-carrageenan, and naproxen sodium-chitosan at acidic pH (Figure 4).

Figure 7 demonstrates the possible electrostatic interactions between oppositely charged polymers chitosan and κ-carrageenan. It can be interpreted that the protonated amine group of chitosan interacts with the sulphonate group of κ-carrageenan and forms the polyelectrolyte complex. Naproxen anion can interact with protonated amine group of chitosan to form naproxen-chitosan complex.

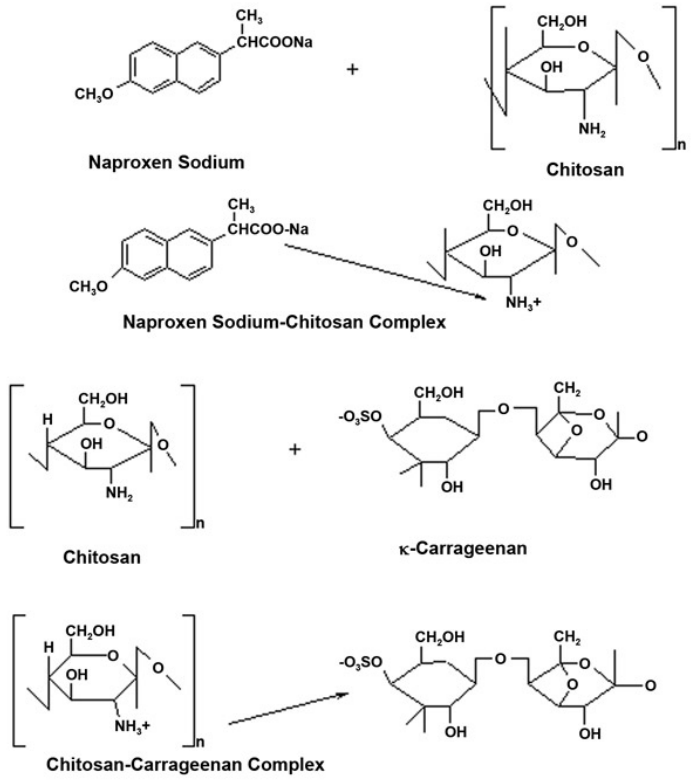

Figure 7. Schemes of probable interactions between naproxen sodium and chitosan; chitosan and κ-carrageenan.

CONCLUSION

The results obtained confirm the importance of in-situ ionic interactions between oppositely charged polyelectrolytes. Water uptake, matrix erosion, and drug release behavior of chitosan matrices containing HPMC and κ-carrageenan in different dissolution media were compared. These findings could thus be of importance in developing a suitable model for sustained release technology.

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REFERENCES

1. Bonferoni MC, Rossi S, Ferrari F, Bettinetti GP, Caramella C. Characterization of diltiazem lambda carrageenan complex. *Int J Pharm.* 2000;200:207–216.

2. Graham H, Baker Y, Nojoku-obi A. Complex formation between hydrocolloids and tranquilizers and hypotensive agents. *J Pharm Sci.* 1963;52:192–198.

3. Miyazaki S, Nakayama A, Oda M, Takada M, Attwood D. Drug release from oral mucosal adhesive tablets of chitosan and sodium alginate. *Int J Pharm.* 1995;118:257–263.

4. Tapia C, Costa E, Sapag-Hagar J, Valenzuela F, Basualto C. Study of the influence of the pH media dissolution, degree of polymerization, and degree of swelling of the polymers on the mechanism of release of diltiazem from matrices based on the mixtures of chitosan/alginate. *Drug Dev Ind Pharm.* 2002;28:217–224.

5. Tapia C, Escobar Z, Costa E, et al. Comparative studies polyelectrolyte complexes and mixtures of chitosan-alginate and chitosan-carrageenan as prolonged diltiazem clorhydrate release systems. *Eur J Pharm Biopharm.* 2004;57:65–75.

6. de la Torre PM, Enobakhare Y, Torrado S, Torrado S. Interpolymer complexes of poly(acrylic acid) and chitosan, influence of the ionic hydrogel forming medium. *Biomaterials.* 2003;24:1499–1506.

7. Tomida H, Nakamura C, Kiryu S. A novel method for the preparation of controlled release theophylline capsules coated with a polyelectrolyte complex of κ-carrageenan and chitosan. *Chem Pharm Bull (Tokyo).* 1994;42:979–981.

8. Winterowd J, Sanford P eds. Chitin and chitosan. *Food Polysaccharides and Their Applications.* 2nd ed. New York, NY: Marcel Dekker Inc; 1995:441–462.

9. Rege PR, Shukla DJ, Block LH. Chitinosan-drug complexes: effect of electrolyte on naproxen release in vitro. *Int J Pharm.* 2003;250:259–272.

10. Errington N, Harding S, Varum KM, Illum L. Hydrodynamic characterization of chitosan varying in molecular weight and degree of deacetylation. *Int J Biol Macromol.* 1993;15:112–117.

11. Bartkowiak A, Hunkeler D. Carrageenan-oligochitosan microcapsules: optimization of the formation process. *Colloids Surf B Biointerfaces.* 2001;21:285–298.

12. Sezer AD, Akbuga J. Controlled release of piroxicam from chitosan beads. *Int J Pharm.* 1995;121:113–116.

13. Genta I, Perugini P, Pavanetto F. Different molecular weight chitosan microspheres: influence on drug loading and drug release. *Drug Dev Ind Pharm.* 1998;24:779–784.

14. Akbuga J, Durmaz G. Preparation and evaluation of cross-linked chitosan microspheres containing furosemide. *Int J Pharm.* 1994;111:217–222.

15. Thacharodi D, Rao KP. Release of nifedipine through cross-linked chitosan membranes. *Int J Pharm.* 1993;96:33–39.

16. Filipovic-Grcic J, Becirevic-Lacan M, Skalko N, Jalsenjak I. Chitosan microspheres of nifedipine and nifedipine-cyclodextrin complexes. *Int J Pharm.* 1996;135:183–190.

17. Thanoo BC, Sunny MC, Jayakrishnan A. Cross-linked chitosan microspheres: preparation and evaluation as a matrix for the controlled release of pharmaceuticals. *J Pharm Pharmacol.* 1992;44:283–286.

18. Jameela SR, Jayakrishnan A. Glutaraldehyde cross-linked chitosan microspheres as a long acting biodegradable drug delivery vehicle: studies on the in vitro release of mitoxantrone and in vivo degradation of microspheres in rat muscle. *Biomaterials.* 1995;16:769–775.

19. Amaral HM, Sousa Lobo JM, Ferreira DC. Effect of hydroxypropyl methylcellulose and hydrogenated castor oil from sustained release naproxen tablets. *AAPS PharmSciTech.* 2001;2:E6.

20. Iqbal Z, Babar A, Ashraf M. Controlled release naproxen using micronized ethylcellulose by wet granulation and solid dispersion method. *Drug Dev Ind Pharm.* 2002;28:129–134.

21. Seedher N, Bhatia S. Solubility enhancement of Cox-2 inhibitor using various solvent systems. *AAPS PharmSciTech.* 2003;4:E33.

22. Curotto E, Aros F. Quantitative determination of chitosan and percentage of free amino groups. *Anal Biochem.* 1993;211:240–241.

23. Caram-Lelham N, Cleland RL, Lars-Olof S. Temperature and salt optimization of kappa carrageenan fractionation by DEAE-cellulose. *Int J Biol Macromol.* 1994;16:71–75.

24. Paradkar A, Chauhan B, Naim S, Samuel B. Effect of potassium chloride and cationic drug on swelling, erosion, and release from κ-carrageenan matrices. *AAPS PharmSciTech.* 2004;5:E25.

25. Picker KM. Matrix tablets of carrageenans. II. Release behavior and effect of added cations. *Drug Dev Ind Pharm.* 1999;25:339–346.

26. Sakiyama T, Chia-Hong C, Fujii T, Yano T. Preparation of a polyelectrolyte complex gel from chitosan and kappa-carrageenan and its pH sensitive swelling. *J Appl Polym Sci.* 1993;50:2021–2025.

27. Gupta VK, Madhusudan H, Wheatley TA, Price JC. Controlled release tablets from carrageen: effect of formulation storage and dissolution factors. *Eur J Pharm Biopharm.* 2001;51:242–248.

28. Felt O, Buri P, Gurny R. Chitosan: a unique polysaccharide for drug delivery. *Drug Dev Ind Pharm.* 1998;24:979–993.

29. Picker KM. Carrageenans used for tabletting and controlled release. Proceedings of 2nd World Meeting; May 25-28, 1998; Paris, France.

30. Bonferoni MC, Rossi S, Ferrari F, Bettinetti GP, Caramella C. Factorial analysis of the influence of dissolution medium on drug release from carrageenan diltiazem complexes. *AAPS PharmSciTech.* 2000;1:E15.

31. Huang RG, Schwartz JB, Ofner CM. Microencapsulation of chlorpheniramine maleate-resin particles with crosslinked chitosan for sustained release. *Pharm Dev Technol.* 1999;4:107–115.

32. Hugerth A, Lelham NC, Sundelof LO. The effect of charge density and conformation the polyelectrolyte complex formation between carrageenan and chitosan. *Carbohydr Polym.* 1997; 34:149–156.

33. Bonferoni MC, Rossi S, Ferrari F, Bertoni M, Bolhuis GK, Caramella C. The employment of lambda carrageenan in a matrix system. III. Optimization of a lambda carrageenan-HPMC hydrophilic matrix. *J Control Release.* 1998;51:231–239.

34. Sipahigil O, Dortune B. Preparation and in vitro evaluation of verapamil HCL and ibuprofen containing carrageen beads. *Int J Pharm.* 2001;228:119–128.

35. Liu LS, Liu SQ, Sy NG, Froix M, Ohno T, Heller J. Controlled release of interleukin-2 for tumour immunotherapy using alginate/ chitosan porous microspheres. *J Control Release.* 1997;43:65–74.

36. Zerrouk N, Mennini N, Maestrelli F, Chemtob C, Mura P. Comparison of the effect of chitosan and polyvinylpyrrolidone on dissolution properties and analgesic effect of naproxen. *Eur J Pharm Biopharm.* 2004;57:93–99.

37. Paula HCB, Gomes FJS, de Paula RCM. Swelling studies of chitosan/cashew nut gum physical gels. *Carbohydr Polym.* 2002;48:313–318.