Swelling Characteristics and *In Vitro* Drug Release Study with pH- and Thermally Sensitive Hydrogels Based on Modified Chitosan

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Received 26 September 2005; accepted 18 December 2005
DOI 10.1002/app.23989
Published online in Wiley InterScience (www.interscience.wiley.com).

ABSTRACT: The grafting of a poly(ethylene glycol) diacrylate macromer onto a chitosan backbone was carried out with different macromer concentrations. The grafting was achieved by $(NH_4)_2Ce(NO_3)_6$-induced free-radical polymerization. Biodegradable, pH- and thermally responsive hydrogels of poly(ethylene glycol)-*g*-chitosan crosslinked with a lower amount of glutaraldehyde were prepared for controlled drug release studies. Both the graft copolymers and the hydrogels were characterized with Fourier transform infrared, elemental analysis, and scanning electron microscopy. The obtained hydrogels were subjected to equilibrium swelling studies at different temperatures (25, 37, and 45°C) in buffer solutions of pHs 2.1 and 7.4 (similar to those of gastric and intestinal fluids, respectively). 5-Fluorouracil was entrapped in these hydrogels, and equilibrium swelling studies were carried out for the drug-entrapped gels at pHs 2.1 and 7.4 and 37°C. The *in vitro* release profile of the drug was established at 37°C and pHs 2.1 and 7.4. © 2006 Wiley Periodicals, Inc. J Appl Polym Sci 102: 977–985, 2006

Key words: biodegradable; chitosan; graft copolymers; hydrogels

INTRODUCTION

Considerable interest has been focused on the preparation and characterization of hydrogels for their use in controlled release of drugs and many other fields of life because of their high water content, softness and pliability.[1–4]

Chitosan [a (1→4)-2-amino-2-deoxy-β-D-glucan] is a cationic biopolymer obtained through alkaline N-deacetylation of natural chitin. Chitosan has many superior properties, such as biodegradability, nontoxicity, and biocompatibility.[5–7] These interesting properties make chitosan an ideal candidate for the preparation of hydrogels for controlled drug release. However, chitosan also exhibits some shortcomings, such as hydrophobicity, lower mechanical properties, and a high pH dependence of its physical properties. Therefore, it is very difficult to control drug release with chitosan itself, and this may negatively affect the human body because of drug overrelease.[8]

To overcome these shortcomings of chitosan, two main approaches have been applied. The first approach is the incorporation of chitosan into an interpolymer hydrogel (interpenetrating polymer network).[1,4] The second is chemical modification by the grafting of a suitable vinyl monomer (or monomers) onto chitosan backbone and then the crosslinking of this modified chitosan.[3,9]

Poly(ethylene glycol) (PEG) is a highly water-soluble and nontoxic polymer. Because of the high hydrophilicity and biocompatibility of PEG, grafting it onto chitosan is considered to be a convenient route to the synthesis of drug carriers.[10] PEG and some of its derivatives have been used for the modification of chitosan via grafting: by PEG alone,[11–14] by PEG aldehyde,[15–17] and by PEG ester.[18,19] However, one can find little reported work on exploiting these chitosan-*g*-PEG copolymers in the preparation of hydrogels for controlled release studies[9,10] in comparison with the number of interpenetrating polymer network systems based on chitosan and PEG used for the same purpose.[20–22] Therefore, in this study, we attempted to improve the hydrophilicity of chitosan via the grafting of a diacrylate derivative of poly(ethylene glycol) (PEGDA) onto it. The grafting was carried out with ceric ammonium nitrate (CAN) as the initiator. The hydrogels obtained from these graft copolymers crosslinked with a lower amount of glutaraldehyde were characterized, and their swelling characteristics and drug release profiles were estimated.

EXPERIMENTAL

Materials

Chitosan and 5-fluorouracil (5-FU) were purchased from Acros Organics (Morris Plains, NJ). PEGDA with

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a number-average molecular weight of approximately 575 was supplied by Aldrich (Milwaukee, WI). CAN was obtained from Ajax Chemicals (Sydney, Australia). Glutaraldehyde (25% aqueous solution), acetic acid, and all other reagents were analytical-grade and were used as received.

Methods

Characterization of chitosan

The degree of N-deacetylation of chitosan was 67%, as determined by Fourier transform infrared (FTIR) with the following relationship:[23]

$$\text{N-deacetylation } (\%) = (1 - A_{1655}/A_{3340} \times 1/1.33) \times 100 \quad (1)$$

where A is the absorbance at the given wave number. Approximately the same value of N-deacetylation was estimated from the measured elemental analysis data for chitosan (C, 44.80%; N, 7.86%; H, 7.02%).

The weight-average molecular weight of chitosan was determined to be 4.92×10^5 D with the Mark–Houwink viscometry method[24] in a solvent of 0.1*M* acetic acid/0.2*M* NaCl maintained at 25°C. The solvent was prepared by the addition of 571 μL of glacial acetic acid (17.5*M*) to a solution of 1.17 g of NaCl in 100 mL of distilled water. The efflux times of both the solvent and the chitosan solutions were measured with the aid of a Cannon-Fenske routine viscometer (Cannon Instrument Co., State College, PA). Each sample was measured three times.

Preparation of chitosan-g-PEGDA

Chitosan-*g*-PEGDA was prepared by a modified method described by Shantha and Harding.[25] In a typical experiment, a solution of 1.50 g of chitosan dissolved in 300 mL of 1*M* hydrochloric acid was placed in a flask fitted with a condenser. CAN (0.12 g), dissolved in 40 mL of 1*M* nitric acid, was added to the chitosan solution, and the flask was flushed with nitrogen for 30 min. The appropriate amount of PEGDA (see Table I) was added dropwise, and the reaction mixture was stirred for 6 h at 80°C under nitrogen. The reaction mixture was filtered through wet cheesecloth. The product was then precipitated with 5% sodium hydroxide, collected by centrifugation, and extensively washed free of alkali with distilled water. The homopolymer that formed was removed by extensive extraction with methanol. The residual graft copolymer obtained was washed with distilled water, freeze-dried, and weighed.

IR (KBr): 3415 (NH_2, OH), 2881 (ν_s CH_2), 1728 (ester C=O), 1654 (amide C=O), 1384 (δ CH_2), 1078 cm^{-1} (twisting vibration of CH_2). ANAL.: C, 42.32%; N, 7.19%; H, 6.81%.

The grafting percentage and grafting efficiency of the copolymers were calculated as follows:

$$\text{Grafting } (\%) = 100[(W_g - W_c)/W_c] \quad (2)$$

$$\text{Grafting efficiency } (\%) = 100[W_g/(W_g + W_h)] \quad (3)$$

where W_g, W_h, and W_c are the weights of the graft copolymer, homopolymer, and chitosan, respectively.

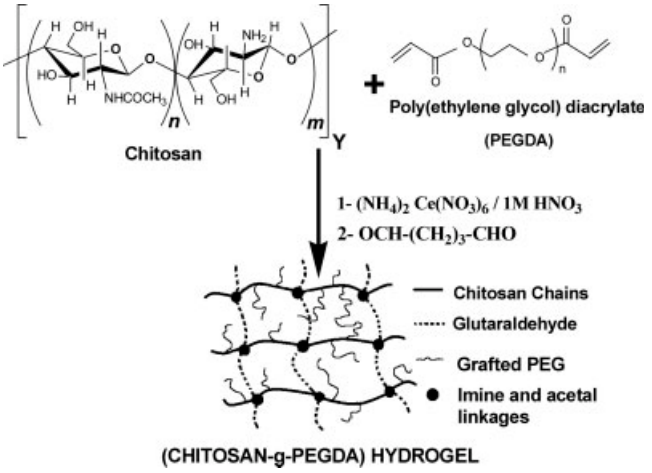
Preparation of the chitosan-g-PEGDA hydrogels

A solution of 2 g of chitosan-*g*-PEGDA in 60 mL of 2% aqueous acetic acid was prepared. To this solution was added a predetermined volume of the glutaraldehyde solution (see Table I) with stirring for 10 min. The mixture was left to undergo gelation at room temperature. The gelation time was varied, depending on the amount of glutaraldehyde and the grafting degree of the copolymer. The hydrogels produced were extensively washed with distilled water,

TABLE I
Preparation Details for the Grafted Copolymers and Their Hydrogels

Graft copolymer	Chitosan (g)	PEGDA (g)	Grafting (%)	Grafting efficiency (%)	Hydrogel	Glutaraldehyde (25% aqueous) μL	Glutaraldehyde (25% aqueous) wt %[a]
CA	1.5	1.5	26	56	CA-1	0	0
					CA-2	400	5
					CA-3	800	10
	1.5	1.8	35	59	—	—	—
CB	1.5	2.25	59	71	CB-1	0	0
					CB-2	400	5
					CB-3	800	10
	1.5	3	47	58	—	—	—
CC	1.5	4.5	44	59	CC-1	0	0
					CC-2	400	5
					CC-3	800	10

[a] Based on the weight of the graft copolymer (2 g).



Scheme 1 Preparation of the chitosan-*g*-PEGDA hydrogel.

freeze-dried, and stored until further use. Scheme 1 shows the synthesis of the hydrogel.

IR (KBr): 3363 (NH_2, OH), 2929 (ν_s CH_2), 1724 (ester C=O), 1651 (amide C=O and C=N), 1377 cm^{-1} (δ CH_2).

Characterization

IR of the prepared chitosan-*g*-PEGDA copolymer and its hydrogels was recorded with a PerkinElmer Paragon 1000 FTIR spectrometer (Wellesley, MA) in the range of 4000–400 cm^{-1} with KBr pellets. The elemental analysis was performed with a Carlo Erba EA 1108 elemental analyzer (now CE Instruments, Wigan, UK) with a flash combustion technique (Campbell Microanalytical Laboratory, Otago University, Dunedin, New Zealand). The surface morphology of the freeze-dried copolymer and its hydrogels was investigated with a scanning electron microscope (Cambridge Stereoscan S-250 mk 3 scanning electron microscope, Cambridge Instruments Ltd., Cambridge, UK). The samples were placed on an aluminum mount, sputtered with gold with a Baltec scd 050 sputter coater, and then scanned at an accelerating voltage of 20 kV.

Entrapment of the anticancer drug

Hydrogels loaded with 5-FU as a model drug were prepared in the same manner mentioned previously. Known amounts of the drug were added to the reaction mixture and stirred vigorously, and then the gelation reaction was carried out. The resulting hydrogels were washed with distilled water, freeze-dried, and stored until further use.

Determination of the amount of the drug entrapped

The quantity of the drug entrapped in the chitosan-*g*-PEGDA hydrogels was determined by an indirect method.[26] After the gel preparation, the washings were collected and filtered through a Millipore 0.45-mm filter (Bedford, MA), and the amount of 5-FU present was estimated from the absorption at 268 nm with a Varian Inc. Corg 50 scan (Palo Alto, CA) ultraviolet–visible spectrophotometer. The difference between the amount of the drug initially added to the gel and that estimated in the washings was taken as a measure of the amount of the drug entrapped.

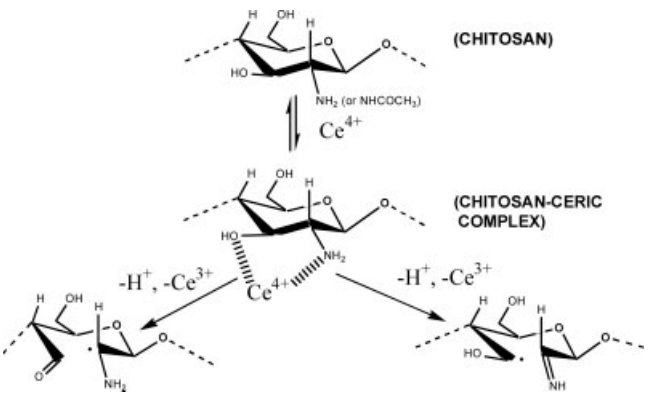
Equilibrium swelling studies

The swelling behavior of the chitosan-*g*-PEGDA hydrogels was measured at different temperatures (25, 37, and 45°C) in two buffer solutions (pHs 2.1 and 7.4) similar to gastric and intestinal fluids, respectively. The buffer solutions were prepared from a mixture of phosphoric acid (54.0 mmol), boric acid (40.0 mmol), and acetic acid (42.0 mmol), and then the pH was adjusted to the required value by the dropwise addition of a 0.2*N* NaOH solution. The pH values were monitored with a pH-meter (PHM82/Standard; accuracy = ±0.1) (Copenhagen, Denmark). The swollen weights of the gels were determined at intervals, after the removal of the surface liquid with tissue paper, until equilibrium swelling was attained. The swelling percentage was calculated with the following equation:

$$\text{Swelling } (\%) = 100[(W_t - W_0)/W_0] \qquad (4)$$

where W_0 is the initial weight and W_t is the final weight of the gel at time t. The data points represent the means plus or minus the standard deviation from three independent experiments.

For studying the effect of 5-FU entrapped (up to 5%) in the hydrogel on the gel swelling behavior, a cyclic swelling procedure was carried out. Known weights of the drug-free and drug-loaded gels were left in the swelling medium until maximum equilibrium swelling was attained. The swollen samples



Scheme 2 Role of Ce^{4+} in the initiation of graft copolymerization onto chitosan.

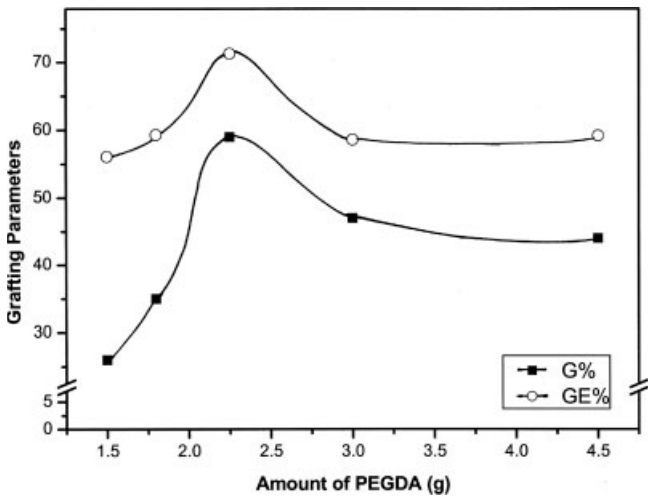


Figure 1 Effect of the amount of PEGDA on the grafting parameters (chitosan, 1.5 g; CAN, 0.12 g; time, 6 h; temperature, 80°C).

were weighed after the removal of the surface liquid, completely freeze-dried, and reweighed. This swelling–deswelling process was repeated three times for each sample.

In vitro cumulative release studies

The release of entrapped 5-FU *in vitro* was determined by the placement of the preweighed hydrogel loaded with the drug in a buffer solution (pH 2.1, simulating gastric fluid, or pH 7.4, simulating intestinal fluid) at 37°C. At intervals, an aliquot was withdrawn, and its absorbance at 268 nm was measured. The withdrawn sample was replaced with an equal volume of fresh buffer to keep the volume of the release medium constant. The data points represent the means plus or minus the standard deviation from three independent experiments.

RESULTS AND DISCUSSION

Preparation and characterization of chitosan-g-PEGDA and its hydrogels

Covalently grafting PEGDA onto a chitosan backbone with the aid of a ceric-ion-induced free-radical technique was carried out. Doba et al.[27] showed that the mechanism of graft copolymerization induced by Ce^{4+} ions onto polysaccharides involves predominantly oxidation of the anhydroglucose units through C_2—C_3 bond cleavage. Therefore, Pourjavadi et al.[28] suggested a general reaction mechanism for grafting onto chitosan that is analogous to the mechanism previously reported[27] for polysaccharides. According to this suggested mechanism, Ce^{4+} reacts reversibly with the nucleophilic groups, NH_2 and OH on C_2 and C_3, to form a complex with chitosan. Subsequently, the C—C bond cleaves to yield an aldehyde and a free radical or an imine and a free radical. Once the initiation reaction has started, the grafting of the monomer onto chitosan chains occurs immediately through traditional chain polymerization. The role of Ce^{4+} in the generation of free radicals onto the chitosan backbone is shown in Scheme 2.

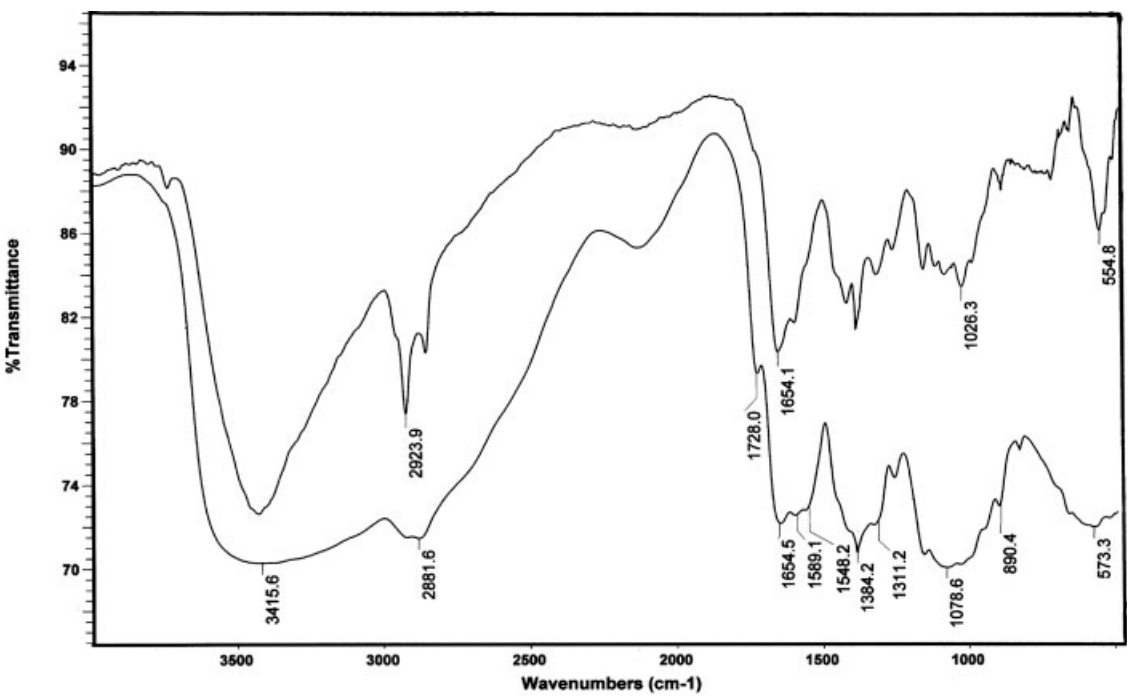


Figure 2 FTIR spectra for chitosan (upper trace) and chitosan-*g*-PEGDA (lower trace).

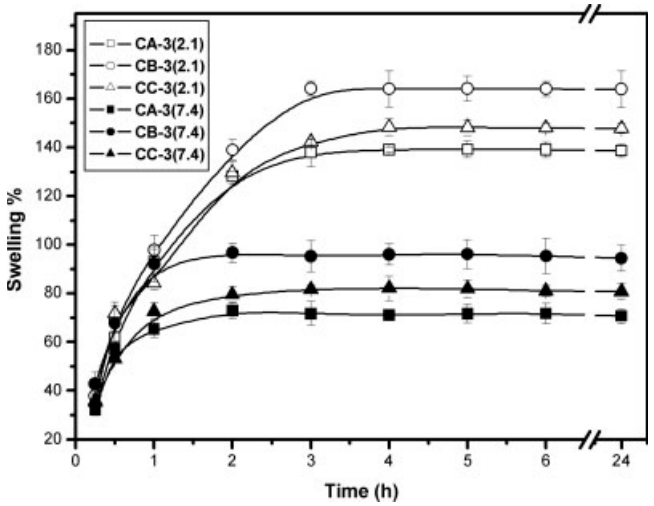


Figure 3 Swelling behavior of CA-3, CB-3, and CC-3 at 37°C and pHs 2.1 and 7.4.

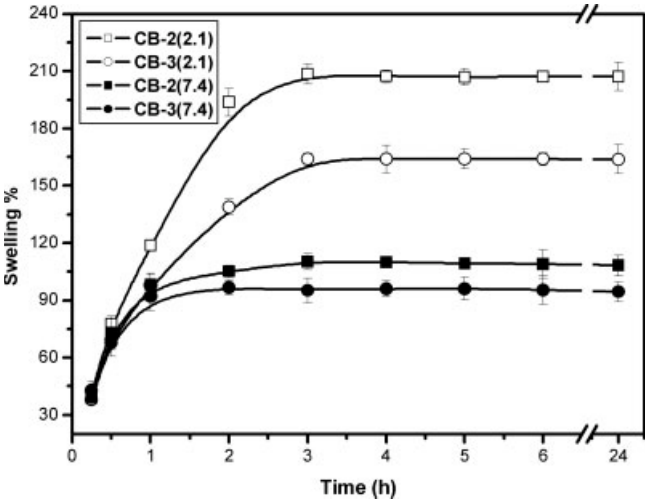


Figure 4 Swelling behavior of CB-2 and CB-3 at 37°C and pHs 2.1 and 7.4.

Figure 1 shows the influence of the amount of macromer PEGDA on the graft copolymerization. It is apparent that there is an increase in both grafting factors (grafting percentage and grafting efficiency) when the PEGDA amount increases to a certain extent, and then both decrease. A higher grafting percentage was attained when chitosan and PEGDA were reacted in a 1 : 1.5 ratio (CB graft copolymer; Table I). This phenomenon can be attributed to the limited number of active centers available for grafting onto the polymer backbone. Then, when the amount of PEGDA is increased, more competition occurs between the PEGDA units for the same sites, leading to an increase in the grafting extent until the saturation of the backbone is achieved. At higher amounts of PEGDA however, an excess of PEGDA units could induce steric hindrance to the Ce^{4+} attack. Also, increasing the amounts of PEGDA may promote many more chain-transfer and termination reactions. These two factors may lead to more homopolymerization instead of grafting.[29] Moreover, the increase in the homopolymer formation may lead to an increase in the viscosity of the reaction medium. Accordingly, the mobility of macromer PEGDA decreases, and this leads to a decrease in the grafting yield.

PEGDA has two terminal diacrylate groups, and both of them can participate in the graft copolymerization, leading to the possibility of crosslinking. Within the range shown in Table I (1 : 1 to 1 : 3 chitosan/PEGDA), no significant crosslinking was noticed, and all the graft copolymers prepared in this range were completely soluble in 2% acetic acid. First with a ratio of 1:4, an insoluble fraction was observed upon the dissolution of the graft copolymer in 2% acetic acid. The amount of the insoluble gel fraction increased with an increasing quantity of PEGDA.

Figure 2 shows the FTIR spectra of the graft copolymer and chitosan. In the copolymer spectra, the weak new peak appearing at 1728 cm^{-1} was assigned to the ester C=O stretching of PEGDA side chains. As expected, the IR charts for both the graft copolymer and its corresponding hydrogel are very similar, except for the absorption peaks at 1654 and 1651 cm^{-1}, which are assigned to amide C=O or both amide C=O and imine C=N stretching in the graft copolymer and the hydrogel, respectively.

Equilibrium swelling studies

Figure 3 shows the swelling values attained at equilibrium for hydrogels CA-3, CB-3, and CC-3 at 37°C and pHs 2.1 and 7.4. The equilibrium swelling of the CA-3 hydrogels was 138 and 73% at pHs 2.1 and 7.4,

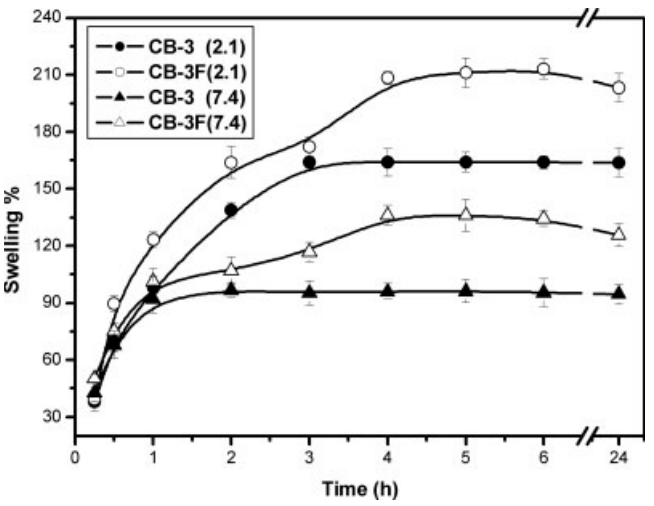


Figure 5 Swelling behavior of CB-3 and CB-3F at 37°C and pHs 2.1 and 7.4.

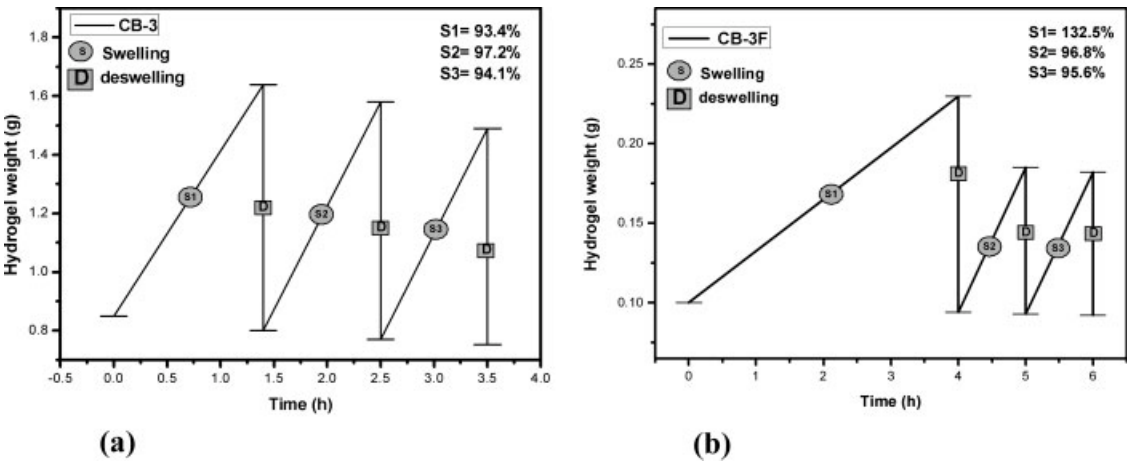


Figure 6 Cyclic swelling profile of CB-3 and CB-3F at 37°C and pH 7.4

respectively. The CB-3 gels were swollen to 164 and 96% at equilibrium, and in the case of CC-3, the equilibrium swelling values were 148 and 81% at pHs 2.1 and 7.4, respectively. The equilibrium swelling was reached after 3–4 and 2 h at pHs 2.1 and 7.4, respectively. Comparing the swelling values of CA-3, CB-3, and CC-3 at the same pH shows that as the grafting extent of PEGDA onto the chitosan backbone increases, the hydrophilicity of the gel increases, and consequently the equilibrium swelling increases. The same swelling behavior was noted upon the investigation of the uncrosslinked graft copolymers, CA-1, CB-1, and CC-1.

Figure 4 shows the difference in the swelling at equilibrium at pHs 2.1 and 7.4 and 37°C for gels prepared with various amounts of glutaraldehyde. Comparing the swelling values of CB-2 and CB-3 at the same pH confirms that as the percentage of glutaraldehyde increases, the extent of crosslinking increases, and consequently the equilibrium swelling decreases.

The equilibrium swelling values were higher at pH 2.1 than at pH 7.4. These results reflect a situation contrary to that found by Vazquez et al.[30] upon the investigation of gel matrices based on gelatin. This contrary pH sensitivity can be attributed to the chemical structure of chitosan, in which, in an acidic medium, protonation can occur at the unreacted NH_2 groups of chitosan, leading to the dissociation of the hydrogen bonding involving amino groups.[31] Moreover, an acidic medium can hydrolyze the imine bond, and consequently higher values of swelling can be obtained. Thus, the swelling values at pH 7.4 will be lower than the values at pH 2.1 because of the increased hydrophobicity of the chitosan-based hydrogels dominating at higher pH values, thus preventing faster swelling in neutral and alkaline media.[26]

The equilibrium swelling values of CB-3 and CB-3 loaded with 5-FU (i.e., CB-3F; 50 mg of drug/g of hydrogel) at pHs 2.1 and 7.4 are shown in Figure 5. At pH 2.1, CB-3 attained about 164% swelling at equilibrium after 3 h, whereas under the same conditions, CB-3F reached equilibrium at 208% after approximately 4.5 h. Similar behavior was observed at pH 7.4, at which CB-3 and CB-3F attained 95 and 136% after 1.5 and 4 h, respectively. This increase in the swelling upon the loading of 5-FU may be attributed to the expected higher hydrophilicity of the 5-FU molecules, which facilitated the diffusion of the swelling fluids into the partially swollen hydrogels.

The difference in the swelling behavior of both drug-loaded (CB-3F) and drug-free (CB-3) gels was also confirmed by the study of their cyclic swelling. Figure 6 illustrates that the CB-3 gel [Fig. 6(a)] attained about 93% equilibrium swelling in the first cycle. Only small changes were noted for the other two cycles plus a slight decrease in the weight of the dried gel. In the case of the drug-loaded gel [Fig.

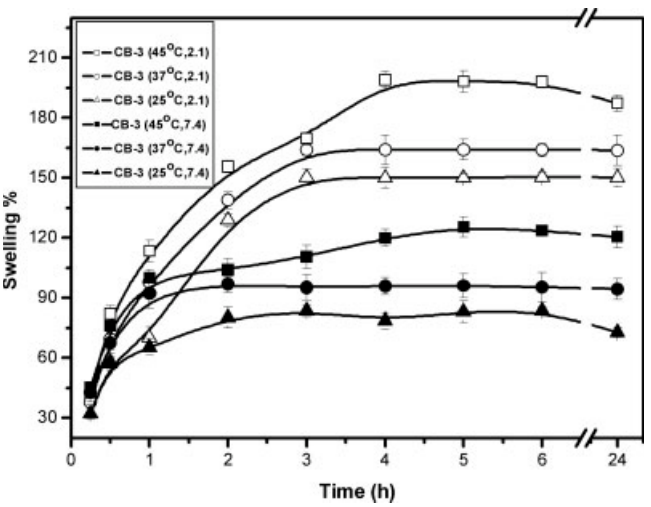


Figure 7 Swelling behavior of CB-3 at 25, 37, and 45°C and pHs 2.1 and 7.4.

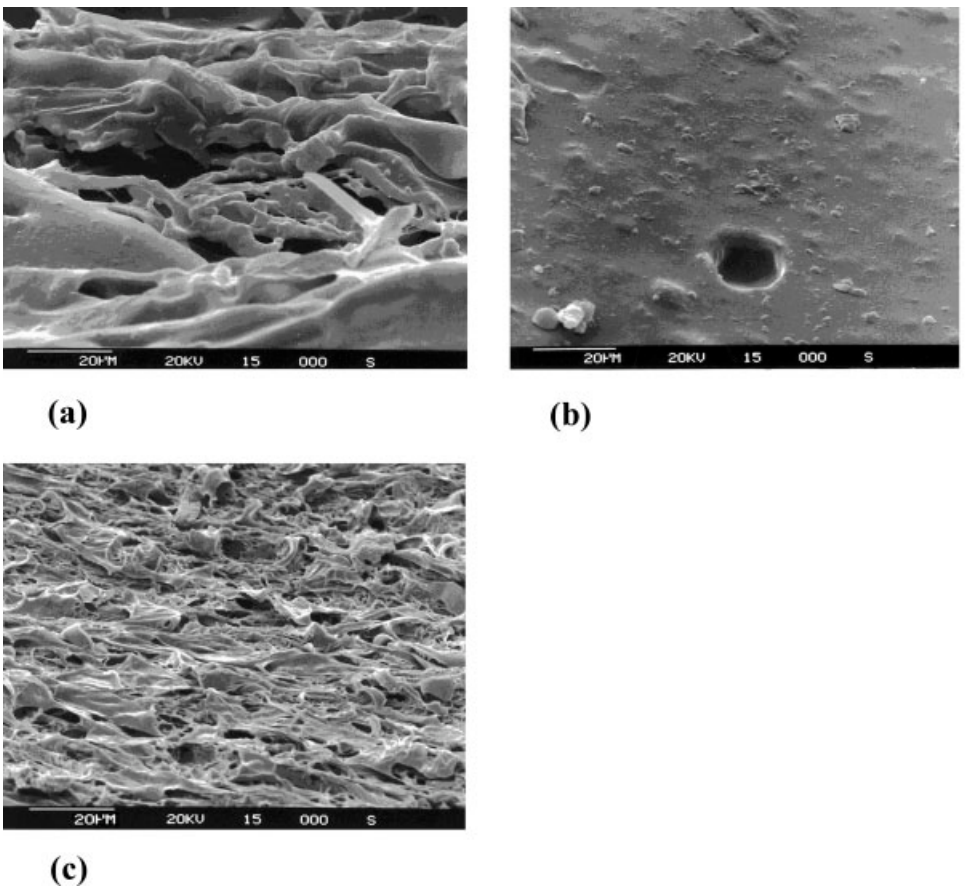


Figure 8 Scanning electron micrographs of (a) the freeze-dried chitosan-*g*-PEGDA copolymer, (b) the freeze-dried hydrogel before the drug release, and (c) the freeze-dried hydrogel after 24 h of drug release at 37°C and pH 2.1.

6(b)], the equilibrium swelling for the first cycle attained about 133%. Deswelling of the sample and repetition of the experiment showed that the equilibrium swelling decreased and achieved its maximum value after a shorter time. The third cycle showed little change in both the maximum equilibrium swelling and the time for achieving this equilibrium. These results confirm that 5-FU is responsible for the increase in the equilibrium swelling value because of its hydrophilic nature. Figure 6(b) shows also that all the accessible 5-FU was released from the matrix in the first cycle. The lack of change seen in the other two cycles implies the role played by 5-FU and tends to indicate that little or no soluble fraction remains in the matrix after 4 h of initial swelling.

Figure 7 shows the temperature-responsive swelling of CB-3, as an example for all the other prepared hydrogels, at pHs 2.1 and 7.4. The equilibrium swelling increased with the increasing temperature of the swelling medium. This temperature-responsive swelling behavior is due to the dissociation of the hydrogen bonding in chitosan within the hydrogel matrices.[31]

The surface morphology of the freeze-dried (chitosan-*g*-PEGDA) copolymer [Fig. 8(a)] shows the grafted PEGDA on the chitosan backbone making the surface rougher. The fine distribution of 5-FU introduced into the hydrogel [Fig. 8(b)] makes the surface smoother. After the release of 5-FU for 24 h at 37°C and

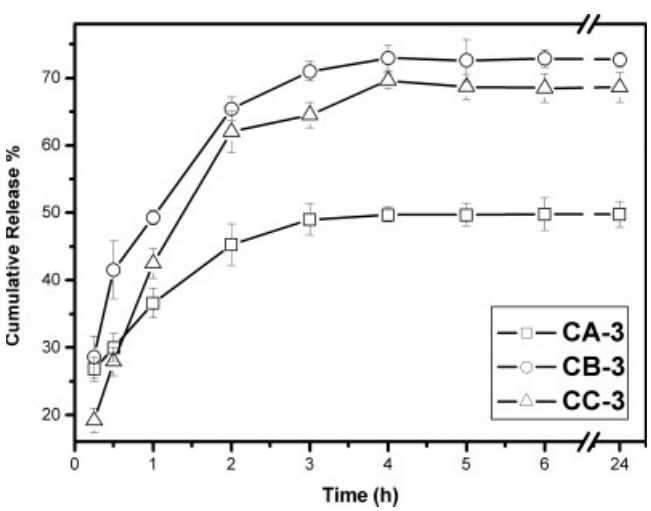


Figure 9 *In vitro* cumulative release measurements for 5-FU-loaded CA-3, CB-3, and CC-3 hydrogels at 37°C and pH 7.4.

TABLE II
***In Vitro* Cumulative Release Measurements of 5-FU-Loaded CB1–CB3 Hydrogels at 37°C and pHs 2.1 and 7.4**

	Cumulative release (%)									
	Simulated gastric fluid (pH 2.1)				Simulated intestinal fluid (pH 7.4)					
Time (h)	CB-2	SD	CB-3	SD	CB-1	SD	CB-2	SD	CB-3	SD
0.25	40.6	1.8	23.1	1.8	44	3.1	28.3	1.8	23.0	1.1
0.5	54.2	2.1	31.9	2.1	66.1	1.9	40.8	2.1	32.2	1.8
1	69.7	2.2	42.6	2.2	76.7	1.1	57.1	2.2	40.0	2.1
2	82.9	3.1	68.1	3.1	93.8	1.8	86.0	1.8	65.4	2.2
3	96.3	1.9	85.8	1.9	98.5	2.1	86.2	2.1	71.2	3.1
4	96.1	1.1	93.4	1.1	98.5	2.2	86.3	2.2	73.9	1.9
5	97.3	1.8	93.4	1.8	98.6	3.1	86.1	3.1	71.2	1.1
6	96.1	2.1	93.4	2.1	98.5	1.9	86.2	1.9	71.2	1.1
24	96.3	2.2	93.2	2.2	98.6	1.1	86.2	1.1	71.2	1.8

pH 2.1 [Fig. 8(c)], very fine holes appeared, indicating the release process.

In vitro cumulative release studies

Figure 9 shows the cumulative release profiles from the gels CA-3, CB-3, and CC-3 in pH 7.4. These release values demonstrate the variation in release at equilibrium for hydrogels prepared from chitosan with different grafting extents of PEGDA. Comparing these release values showed that the release percentage at equilibrium was directly proportional to the grafting percentage of PEGDA onto the chitosan backbone.

The cumulative release values from the CB-1–CB-3 hydrogels at 37°C for pHs 2.1 and 7.4 are shown in Table II. These release measurements estimate the difference in release at equilibrium for gels prepared with various amounts of glutaraldehyde. Comparing the amounts of drug released from CB-1–CB-3 at pH 7.4 clearly confirmed that the extent of release at equilibrium was inversely related to the degree of crosslinking. Similar results were obtained from a comparison of CB-2 and CB-3 at pH 2.1 (CB-1 was completely dissolved at pH 2.1 within 10 min).

The percentage of drug released was much higher in an acidic buffer (pH 2.1) than in a weakly basic buffer (pH 7.4). This is due to the fact that the release depends on the swelling rate of the hydrogel, in which the drug release may be due to the diffusion–dissolution mechanism through swollen gels. As discussed previously, the swelling of the prepared gels in an acidic medium is greater than in a weakly basic medium.

Most of the hydrogels reached equilibrium after about 3–4.5 h. This time of release may seem short for some applications, but it can be controlled by the variation of both the extent of crosslinking and the degree of grafting onto the chitosan backbone. Besides, this preliminary study was carried out with a single model drug (small and highly hydrophilic), and applying the results of this study directly to the entrapment of other drugs may be more useful. It was noticed also from the release data that the drug was not quantitatively released from the gels. Some drug molecules may be deeply buried in the gel matrix and are more slowly released or indeed may never be released into the surrounding media as long as the hydrogel has not been practically dissolved.

CONCLUSIONS

Biodegradable, pH- and thermally responsive hydrogels based on chitosan-*g*-PEGDA were prepared for controlled drug release studies. The equilibrium swelling measurements of the hydrogels carried out at different temperatures in simulated body fluids (pHs 2.1 and 7.4) clearly showed their pH- and thermally responsive nature. The *in vitro* release profiles of 5-FU from the gels were also estimated at pHs 2.1 and 7.4. The results illustrated that the grafting of PEGDA in the matrix assembly was beneficial. With an increase in the PEGDA grafting extent, higher percentages of the drug were released over longer release times with a reduced use of the crosslinker glutaraldehyde. This preliminary investigation of chitosan-based hydrogels has shown that they may be used to expand the utilization of these systems in controlled release applications.

We wish to thank Dr. D. Hopcroft for his assistance with obtaining the scanning electron micrographs shown in Figure 8.

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