Chitosan-Based Interpolymeric pH-Responsive Hydrogels for *In Vitro* Drug Release

M. Y. Abdelaal, E. A. Abdel-Razik, E. M. Abdel-Bary, I. M. El-Sherbiny

Chemistry Department, Faculty of Science, Mansoura University, 35516-Mansoura, Egypt

Received 22 November 2005; accepted 19 April 2006
DOI 10.1002/app.25154
Published online in Wiley InterScience (www.interscience.wiley.com).

ABSTRACT: Two series of pH-responsive biodegradable interpolymeric (IPN) hydrogels based on chitosan (Ch) and poly(vinyl alcohol) (PVA) were prepared for controlled drug release investigations. The first series was chemically crosslinked with different concentrations of glutaraldehyde and the second was crosslinked upon γ-irradiation by different doses. The equilibrium swelling characteristics were investigated for the gels at 37°C in buffer solutions of pH 2.1 and 7.4 as simulated gastric and intestinal fluids, respectively. 5-Fluorouracil (FU) was entrapped in the hydrogels, as a model therapeutic agent, and the *in vitro* release profiles of the drug were established at 37°C in pH 2.1 and 7.4. FTIR, SEM, and X-ray diffraction analyses were used to characterize and investigate the structural changes of the gels with the variation of the blend composition and crosslinker content before and after the drug loading. © 2006 Wiley Periodicals, Inc. J Appl Polym Sci 103: 2864–2874, 2007

Key words: hydrogel; drug delivery systems; gelation; interpenetrating network; irradiation

INTRODUCTION

Characteristics of interpenetrating polymeric networks (IPNs) — such as degree of swelling (DS), soluble fraction percent, cumulative release profile of an entrapped bioactive material, and so forth — depend mainly on the type and composition of monomers, the type and degree of crosslinking, and the swelling medium.[1] Different hydrogel matrices of precisely defined structure have been prepared[2] and have served as drug delivery systems.[3,4]

Chitosan is a cellulose-like polymer produced by alkaline deacetylation of natural chitin[5–9] and usually refers to a large number of polymers with different degrees of *N*-deacetylation (40–98%) and molecular weight ($5 \times 10^4 - 2 \times 10^6$ Da). These two characteristics are very important and strongly affect the physico-chemical properties and, consequently, the biological properties of chitosan.[10] Chitosan exhibits many favorable biological properties such as biocompatibility, biodegradability, and nontoxicity.[9] Moreover, it has good film-forming ability via the casting technique from dilute acetic acid solutions. It exhibits, however, limitations in reactivity and processing ability. Hence, many attempts have been reported to overcome such limitations by chemical or physical alteration through incorporation in IPNs with poly(vinyl alcohol) (PVA), which has superior properties such as water solubility, high hydrophilicity, and good film-forming ability by solution casting as well.[11]

Glutaraldehyde is a common crosslinker used in the crosslinking of polypeptide, protein, chitin, chitosan, and some polysaccharides such as heparin and hyaluronic acid.[12] In spite of the good properties of both chitosan and PVA, little work has been reported regarding the interpolymeric hydrogel films based on chitosan and PVA combinations as drug delivery carriers.[13]

Irradiation, especially if combined with simultaneous sterilization of the product, is a very convenient tool for the synthesis of hydrogels. Radiation processing has many advantages over other conventional methods.[14] In radiation processing, no catalysts or additives are needed to initiate the reaction. The advantages of radiation methods are that they are relatively simple, and the degree of crosslinking, which strongly determines the extent of swelling of hydrogels, can be controlled easily by varying the radiation dose.[15,16] Therefore, these methods are found to be very useful in preparing hydrogels for medical applications, where even the slightest contamination is undesirable.[17] Several articles have been published regarding the γ-irradiation of wide spectrum of polymers, and among them is polyvinyl alcohol (PVA).[18]

In the present work, different interpolymeric network (IPN) gel films based on chitosan and PVA were prepared and crosslinked either chemically with glutaraldehyde or by γ-irradiation. The obtained IPNs were characterized, and equilibrium swelling and the *in vitro* cumulated release of 5-fluorouracil (FU), as a model drug, in different buffer solutions were studied.

Correspondence to: M. Y. Abdelaal (magdyabdelaal@ yahoo.com).

©2006 Wiley Periodicals, Inc.
WILEY InterScience® DISCOVER SOMETHING GREAT

TABLE I
Composition of Ch and Ch/PVA Blend Films

Type	Sample	Chitosan g (%)	PVA g (%)	Glutaraldehyde ml (%)	γ-irradiation dose KGy
Chemically crosslinked Ch films	CCh1	2.0 (100)	—	0.4 (5)	—
	CCh2	2.0 (100)	—	0.8 (10)	—
	CCh3	2.0 (100)	—	2.0 (25)	—
	CCh4	2.0 (100)	—	2.8 (35)	—
Ch/PVA blend films	Ch	2.0 (100)	—	—	—
	ChVA1	1.0 (50)	1.0 (50)	—	—
	ChVA2	0.8 (40)	1.2 (60)	—	—
	ChVA3	0.5 (25)	1.5 (75)	—	—
Chemically crosslinked Ch/PVA blend films	CVA1	1.0 (50)	1.0 (50)	0.4 (5)	—
	CVA2	1.0 (50)	1.0 (50)	0.8 (10)	—
	CVA3	1.0 (50)	1.0 (50)	2.0 (25)	—
	CVA4	1.0 (50)	1.0 (50)	2.8 (35)	—
	CVA5	0.8 (40)	1.2 (60)	2.0 (25)	—
	CVA6	0.5 (25)	1.5 (75)	2.0 (25)	—
Irradiation crosslinked Ch/PVA blend films	GCV1	1.0 (50)	1.0 (50)	—	10
	GCV2	0.8 (40)	1.2 (60)	—	10
	GCV3	0.5 (25)	1.5 (75)	—	10
	RCV1	1.0 (50)	1.0 (50)	—	20
	RCV2	0.8 (40)	1.2 (60)	—	20
	RCV3	0.5 (25)	1.5 (75)	—	20

EXPERIMENTAL

Materials

Chitosan of medium molecular weight, 98% hydrolyzed PVA, aqueous solution of 25% glutaraldehyde, 5-fluorouracil (FU), acetic acid, and all other reagents were of pure grade were purchased from Aldrich (Milwaukee, WI). Chitosan was purified through dissolution/precipitation technique using 2% aq. acetic acid and 1 M NaOH solutions as dissolving and precipitating agents, respectively. Solution of chitosan was filtered under suction after dissolution and the precipitated chitosan was washed repeatedly with hot distilled water and then dried under vacuum at 25°C for two days. The other chemicals were used as received without further purification.

Instruments and tools

A Cannon–Fenske Routine Viscometer was supplied by Cannon Instrument Company (State College, PA). FTIR was recorded on a Perkin Elmer Paragon 1000 FTIR spectrometer. UV/Vis spectrophotometric analysis of the FU samples was performed by using HP UV/Vis 8452A Spectrophotometer at λ_{max} of 268 nm. Elemental analysis was performed with Carlo Erba Elemental Analyser EA 1108. Data were the mean of three replicates. Surface morphology of films was investigated using a Cambridge Stereoscan S-250 mk 3 SEM from Hort Research (Palmerston North, New Zealand) while 2D-XRD investigations were carried out at the Institute of Bioscience, Massey University, New Zealand. The film specimens were mounted in a way that X-ray beam directed to their flat surface.

γ-Irradiation has been performed in a ^{60}Co gamma cell at the National Centre for Radiation Research and Technology (NCRRT), Cairo, Egypt. The dried cast strips were irradiated under air atmosphere at a dose rate of 6.92 KGy/h and placed in the γ-irradiation chamber in such a way that each one was exposed to the same dose.

Film preparation

Chitosan (Ch) was dissolved in 40 ml of 2% aqueous acetic acid, stirred for 5 min before casting at room temperature. In case of Ch/PVA blends the appropriate amounts of 5 wt % solution of Ch was added to a solution of the predetermined amounts of PVA and the mixtures were stirred for 20 min before casting at room temperature. The obtained films after drying in vacuum at 20°C were of ~0.2 mm thickness.

For the chemically crosslinked chitosan and its PVA blends the appropriate amount of glutaraldehyde (25% aqueous solution) was added and stirred for 25 min before casting while for samples to be crosslinked by γ-irradiation, certain Ch/PVA blend films were irradiated to the desired dose (10 or 20 KGy). The composition of all samples is listed in Table I

Entrapment of FU as a model drug

Known amounts of FU (24 mg/g matrix) were added to the solution of Ch or Ch/PVA blend and stirred vigorously, and then the whole mixture was casted. However, some samples were also loaded with FU in 14 and

40 mg/g matrices in order to study the effect of initial concentration (Ei) of FU on the release behavior. The desired amounts of glutaraldehyde were incorporated during film preparation while films were irradiated to the required dose for the materials to be crosslinked by γ-irradiation. All samples were washed with distilled water, dried under vacuum at 20°C, and then stored ready for further use.

Characterization

Degree of *N*-deacetylation and molecular weight of chitosan

Degree of *N*-deacetylation of chitosan was determined with the aid of FTIR spectroscopic analysis. The absorption peaks at 1655 cm^{-1} and 3340 cm^{-1} corresponding to the amide and primary amino groups of chitosan were considered for estimation of the degree of *N*-deacetylation of chitosan.[19] Elemental analysis was also used to determine the degree of *N*-deacetylation of chitosan based on the mole fraction concept.[20]

For determination of the average molecular weight ($\overline{M}_w$) of Ch, 100 mg Ch was dissolved in 100 ml of a mixture of 0.1 M acetic acid and 0.2 M NaCl to give a final concentration of 0.1% wt/v. The solution was left overnight at room temperature and filtered off to remove insoluble residuals. After that, five diluted Ch concentrations, 0.02%, 0.04%, 0.06%, 0.08%, and 0.10% (wt/v), were prepared and the efflux time t for 3 ml of these solutions and for solvent t_o were measured, from which the viscosity of the investigated samples could be calculated.[21]

Gel fraction percent of the irradiated Ch/PVA films

A weighed sample of the irradiated film was soaked for 48 h in 2% aqueous solution of acetic acid at room temperature and rinsed with flow water for 10 min. After that, the sample was kept in distilled water for 24 h at 50°C and the remaining gel portion was dried at 40°C under vacuum to constant weight. Gel fraction percent was then determined using the following equation:

$$\text{Gel Fraction}(\%) = 100(W_g/W_o) \quad (1)$$

where W_o and W_g are the weights of the initial sample and of the dried gel, respectively.

The entrapped amount of drug

The washings after loading of film or gel with FU were collected, filtered, and then investigated with the aid of UV spectroscopic analysis at λ_{max} of 268 nm, corresponding to FU.[22] Both entrapped and free FU exhibited the same λ_{max}, indicating that the entrapped drug did not suffer chemical reactions during gel formation. The difference between the initial amount of drug (24 mg/g matrix) and the drug content in the washings was taken as a measure of the entrapped amount of FU.

Equilibrium swelling characteristics

The degree-of-swelling (DS) percent of Ch film and its blends with PVA was determined at 37°C in two buffer solutions of pH 2.1 and 7.4, corresponding to those of stomach and intestine, respectively. The weight of swollen samples was determined after removal of the surface liquid with lint-free tissue paper at certain time intervals until equilibrium swelling was attained. The DS was then calculated according to the following equation:

$$\text{DS} = [(W_t - W_o)/W_o] \times 100 \quad (2)$$

where W_o and W_t are the initial and final weights of the swelled gel, respectively, at time t.

In vitro cumulative release studies

In vitro release of the entrapped FU was carried out by immersion of the loaded film in a buffer solution of pH 2.1 and 7.4 at 37°C in a shaking water bath incubator. Concentration of FU in the samples withdrawn at certain intervals was determined at λ_{max} 268 nm. The withdrawn aliquots were compensated with equal volumes of fresh buffer solution.

RESULTS AND DISCUSSION

Structure investigation

Degree of *N*-deacetylation of chitosan

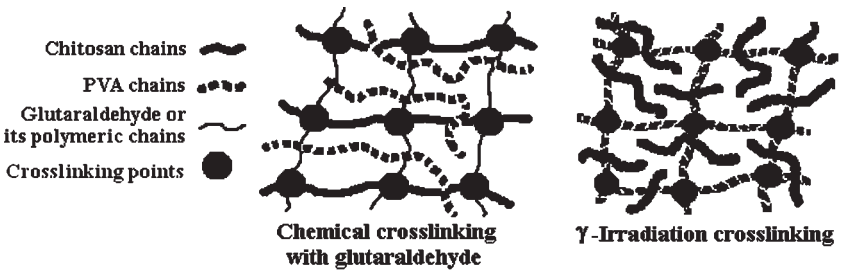
As the *N*-deacetylation percent increases, the solubility in acidic solutions, the metal ion uptake capacity and the overall reactivity of Ch increase. This is due to the high reactivity of the primary amino groups regenerated by deacetylation. The degree of *N*-deacetylation of Ch was determined by two methods, namely, elemental and FTIR spectroscopic analyses. The degree of *N*-deacetylation of Ch was estimated as follows:

$$\text{Degree of } N - \text{Deacetylation} = (1 - I/I_o) \times 100 \quad (3)$$

where $I = (A_{1655}/A_{3340})$ is the amide index which is the relative area under absorption peak of the amide group at 1655 cm^{-1} to that of the primary amino group of chitosan at 3340 cm^{-1}. $I_o = 1.33$ and refers to the amide index of the fully *N*-acetylated Ch.[19] Degree of *N*-deacetylation of chitosan was 67.2% which is nearly similar to that determined by using the elemental analysis data of chitosan (C, 44.80; N, 7.86; H, 7.02) based on the mole fraction concept.[20]

Average molecular weight of chitosan

The average molecular weight ($\overline{M}_w$) of Ch was estimated by viscosity measurements, from which the intrinsic viscosity [η] can be determined. Conse-



Scheme 1 Schematic representation of Ch/PVA interpolymeric hydrogels resulting from chemical crosslinking with glutaraldehyde and upon γ-irradiation.

quently, $\overline{M}_w$ of Ch can be calculated by using Eq. 4 according to the Mark–Houwink equation:[23,24]

$$[\eta] = k\overline{M}_W^a \quad (4)$$

where k and a are constants independent of $\overline{M}_W$ over a wide range. In our case, k and a are 1.81×10^{-3} and 0.93, respectively, at 25°C[21,24] and $[\eta] = 355.8$ ml/g. Therefore, $\overline{M}_w$ was found to be 492 KDalton.

FTIR investigations

FTIR spectroscopic analysis of Ch showed the characteristic absorptions related to the saccharide structure and to amide C=O, N—H, and O—H stretching vibrations.[25] Glutaraldehyde-crosslinked chitosan (CCh1—CCh4) showed a new peak at about 1642 cm^{-1} due to the formation of imine bonding (C=N) upon condensation with glutaraldehyde, and the

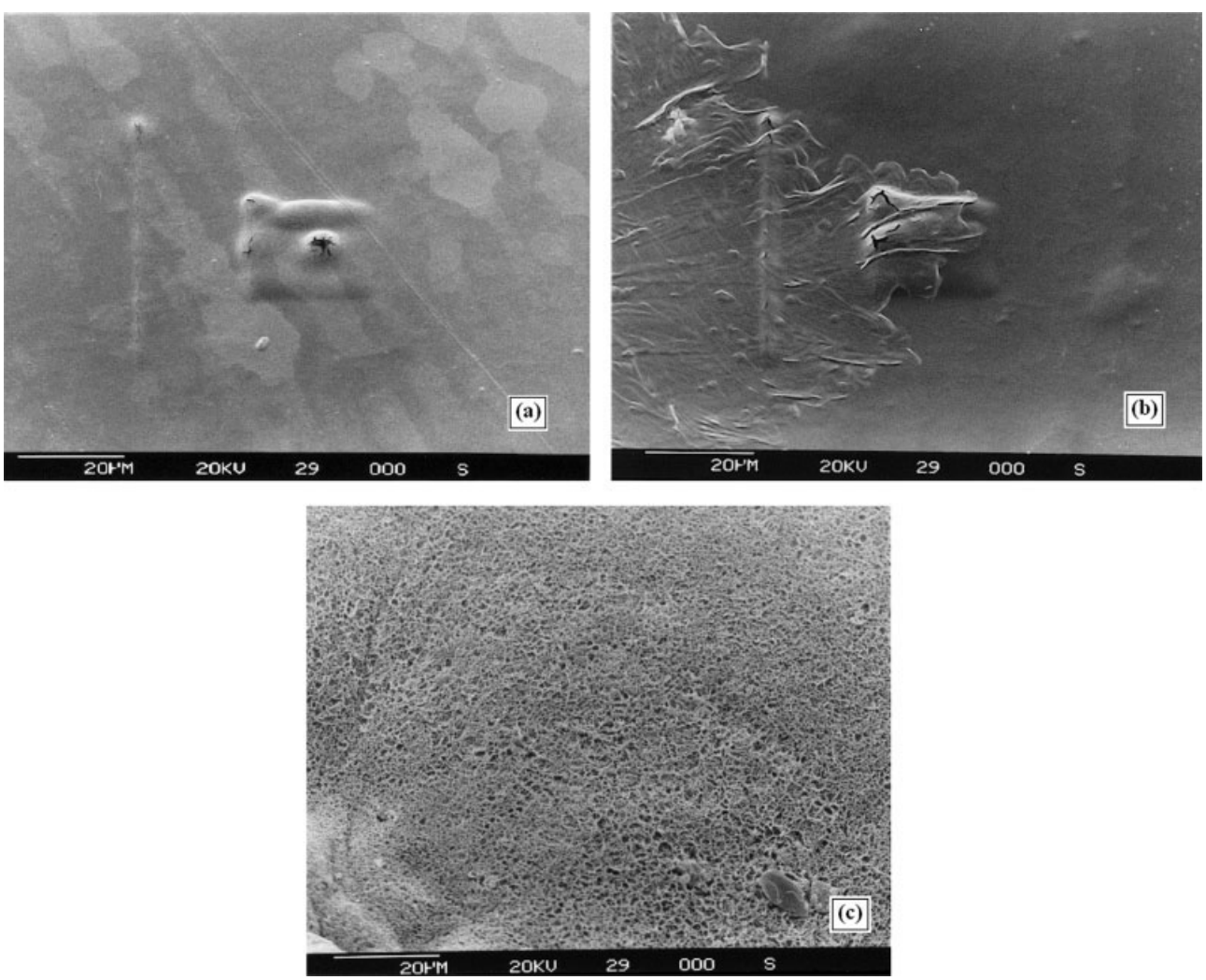


Figure 1 SEM micrograph of the surface of (a) ChVA1 film, (b) loaded ChVA1 film with FU (24 mg/g), and (c) ChVA1 after 24 h of FU release in pH 7.4 at 37°C.

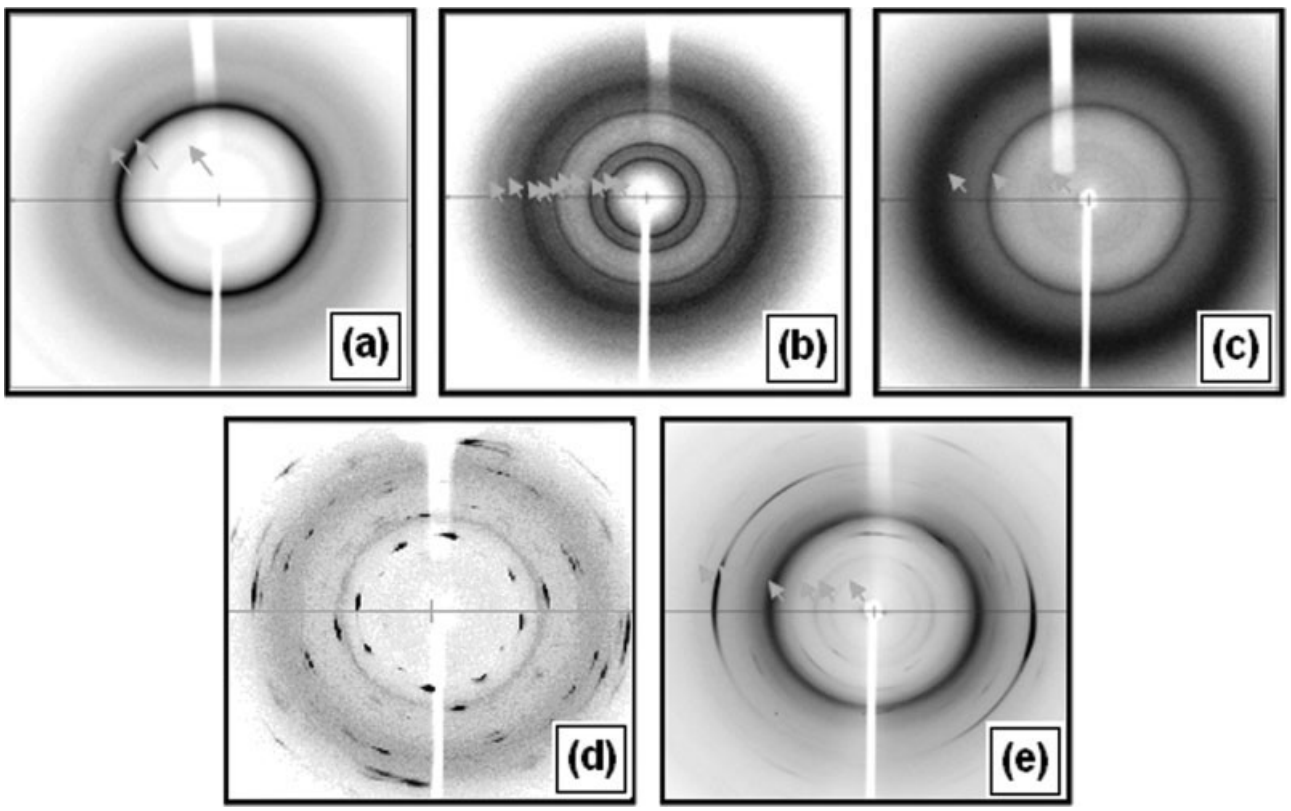


Figure 2 2D-XRD patterns of (a) Ch, (b) PVA, (c) ChVA1, (d) the feathery part of ChVA1 loaded with 5% FU, and (e) non-feathery part of ChVA1 loaded with 5% FU.

signal becomes sharper as the glutaraldehyde content increases.

This also holds true for Ch/PVA blends as a new significant signal at 1646 cm^{-1} appeared, which strengthened as glutaraldehyde content increases. Possible crosslinking through acetal or hemiacetal formation between PVA and glutaraldehyde can be excluded, as the characteristic absorptions at 1140–1190 cm^{-1} and at 1035–1060 cm^{-1} are approximately absent.[25]

FTIR spectra of chitosan, PVA, and ChVA1 blend showed absorption at 1548–1560 cm^{-1} assigned for the symmetric deformation of $—NH_3+$ formed from the primary amino groups as Ch was dissolved in acetic acid solution during blend preparation.[25] An absorption was also shown at 3300–3500 cm^{-1} for O—H stretching, reflecting the extensive hydrogen bonding in case of Ch, PVA, and ChVA1. However, ChVA1 seems to possess relatively higher extent of hydrogen bonding than the separate components of the blend.[26] The intensity of the O—H band decreases upon irradiation of Ch/PVA blends up to 20 Kgy, compared with the nonirradiated films and inversely related to the irradiation dose, which is in good agreement with results in the literature.[26] This means that radicals are formed on the macromolecules resulted in self-crosslinking of PVA chains during irradiation and the extent of these effects depends mainly on the irradiation dose.[27]

It has been suggested that alkoxy radicals formed by γ-irradiation of PVA decay mainly by formation of α-carbon radicals or by formation of an aldehyde and terminal alkyl radicals, which can readily converted into α-carbon radical.[18] Such radicals can undergo intermolecular crosslinking by which both molar mass and size of the resulting polymer increase and/or intramolecular crosslinking, causing collapse of a linear or branched polymer chain.[28] Scheme 1 represents the obtained polymeric network after chemical crosslinking of chitosan with glutaraldehyde and after γ-irradiation crosslinking (mainly of PVA).

SEM investigations

The surface morphology of the interpolymeric films prepared from Ch/PVA blends loaded with 24 mg/g matrix of FU as a model drug has been investigated with the aid of scanning electron microscopy (SEM). Three samples were chosen to be investigated including a blank sample of 1:1 Ch/PVA blend (ChVA1) and loaded samples with FU before and after 24 h of the drug release in pH 7.4 at 37°C.

From Figure 1, a big difference can be noticed between the three investigated samples. The surface morphology of the blank film indicates that it is integrated, dense, and smooth [Fig. 1(a)], while loading with the drug causes some roughness and surface

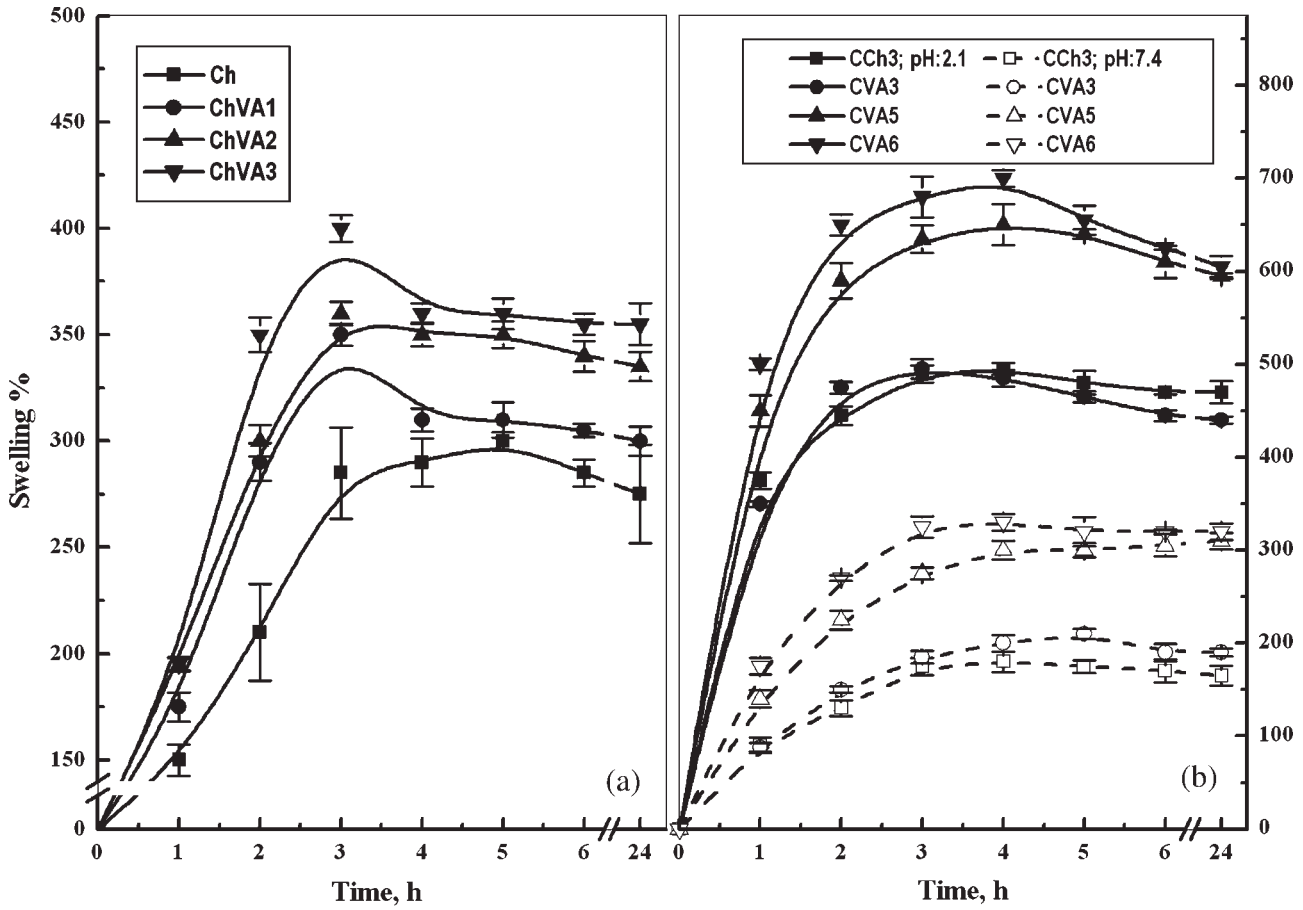


Figure 3 Time dependence of swelling percent of (a) uncrosslinked and (b) crosslinked Ch/PVA blends with different PVA content in pH 2.1 and 7.4 at 37°C.

deficiencies, which has been noticed over most of the sample surface [Fig. 1(b)]. After 24 h of the drug release in pH 7.4 at 37°C, the film surface has been converted into a highly porous matrix as a result of releasing the loaded amount of FU over 24 h under the abovementioned conditions [Fig. 1(c)].

XRD patterns

The crystallinity of FU-loaded Ch/PVA blends has been investigated with the aid of 2D-XRD, compared with the unloaded blends in addition to the single components of the blend (i.e., Ch and PVA). The diffractogram of Ch film showed three major crystalline peaks at 2θ of 8.38°, 11.49°, and 18.25° in addition to many weak and broad crystalline peaks. This diffraction pattern reflects high degree of crystallinity for Ch. The diffractogram of PVA film has two major crystalline peaks at 2θ of 11.49° and 19.55° together with two other broad bands with 2θ of 22.80° and 29.78°. Investigation of a 1:1 Ch/PVA blend (ChVA1) indicated that the main characteristic peaks of the blend components are still noticeable in the diffractogram, but suffer some weakness and broadness. This may be attributed to the H-bonding between amino and hydroxy groups of Ch in one side with the hydroxy groups of PVA in the other side, leading to some degree of compatibility within the blend. The diffractograms of the investigated samples are shown in Figure 2.

Upon loading of 5 wt % FU, the resultant film was still transparent with some uniform feathery aggregations that tend to refer to a possible formation of H-bonding between the drug molecules and the polymer chains. In addition, the characteristic crystalline peaks for single Ch and PVA were weak or approximately disappeared reflecting the lower crystallinity of the loaded polymer blend.[13]

Equilibrium swelling characteristics

Most of factors affecting the equilibrium swelling properties are related to mobility restriction of chains between crosslinks and the polymer composition.[1] In following context, equilibrium swelling is referred to as swelling percent.

Effect of PVA content

Figure 3(a) shows the direct time dependence of the equilibrium swelling of the noncrosslinked films pre-

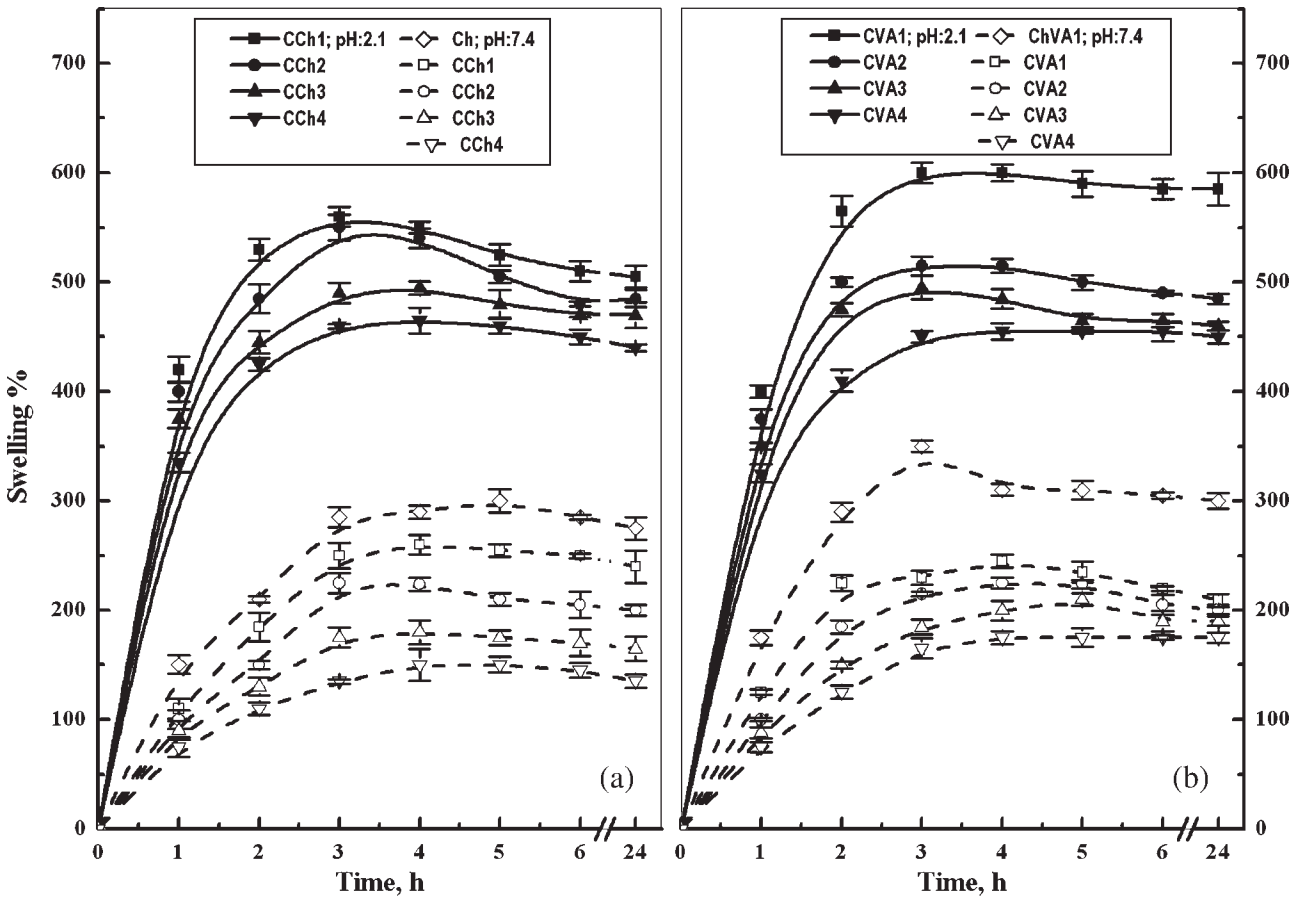


Figure 4 Time dependence of swelling percent of crosslinked (a) chitosan films and (b) 1 : 1 Ch/PVA blends in pH 2.1 and 7.4 at 37°C.

pared from Ch/PVA blends of different PVA content at 37°C and pH 7.4. Swelling percent of Ch was ~270% while it increased to 300%, 340%, and 360% upon blending with 50%, 60%, and 75% PVA, respectively. This is expected, as PVA is a highly hydrophilic water-soluble polymer which increases consequently the hydrophilic nature of the blend, leading to higher swelling at equilibrium. Figure 3(b) shows also the direct time dependence of the swelling percent attained for the crosslinked samples of similar PVA content, namely, CVA3, CVA5, and CVA6 at 37°C in pH 2.1 and 7.4 showing higher swelling percent in pH 2.1 than in pH 7.4. This can be attributed to the tendency of Ch moieties to be more highly dissolved in acidic medium (pH = 2.1) than in the neutral or faint alkaline medium (pH = 7.4). The noncrosslinked blends have not been investigated in pH 2.1, as the samples are soluble in this acidic medium.

Effect of crosslinker content

Figure 4 shows the direct time dependence of swelling percent of Ch and Ch/PVA blend films crosslinked with varying amounts of glutaraldehyde at 37°C where the swelling percent depends inversely on glutaraldehyde content but more significant in case of Ch/PVA blends up to 10% after which the dependence is nearly similar. In both cases, swelling behavior at lower pH (2.1) was less sensitive to glutaraldehyde content compared with that at higher pH (7.4). It can be concluded from Figure 4(a) that by increasing the glutaraldehyde content from 5% to 35%, the extent of crosslinking increases and consequently the swelling percent decreases from 550% to 450% and from 270% to 150% in pH 2.1 and 7.4, respectively in case of the crosslinked Ch films. Figure 4(b) represents a similar behavior for 1 : 1 Ch/PVA blends crosslinked with varying amounts of glutaraldehyde at both pHs 2.1 and 7.4. It can be noticed also that crosslinking of Ch with 5% of glutaraldehyde has practically slight effect on swelling percent compared with the noncrosslinked film.

Effect of irradiation dose

The swelling percent of Ch/PVA films of varying PVA content and crosslinked upon exposure to (a) 10 KGy and (b) 20 KGy dose of γ-irradiation has been determined. Figure 5(a) shows the time dependence of swelling percent of such samples, and it can be concluded that, at the same pH, more crosslinking occurs upon

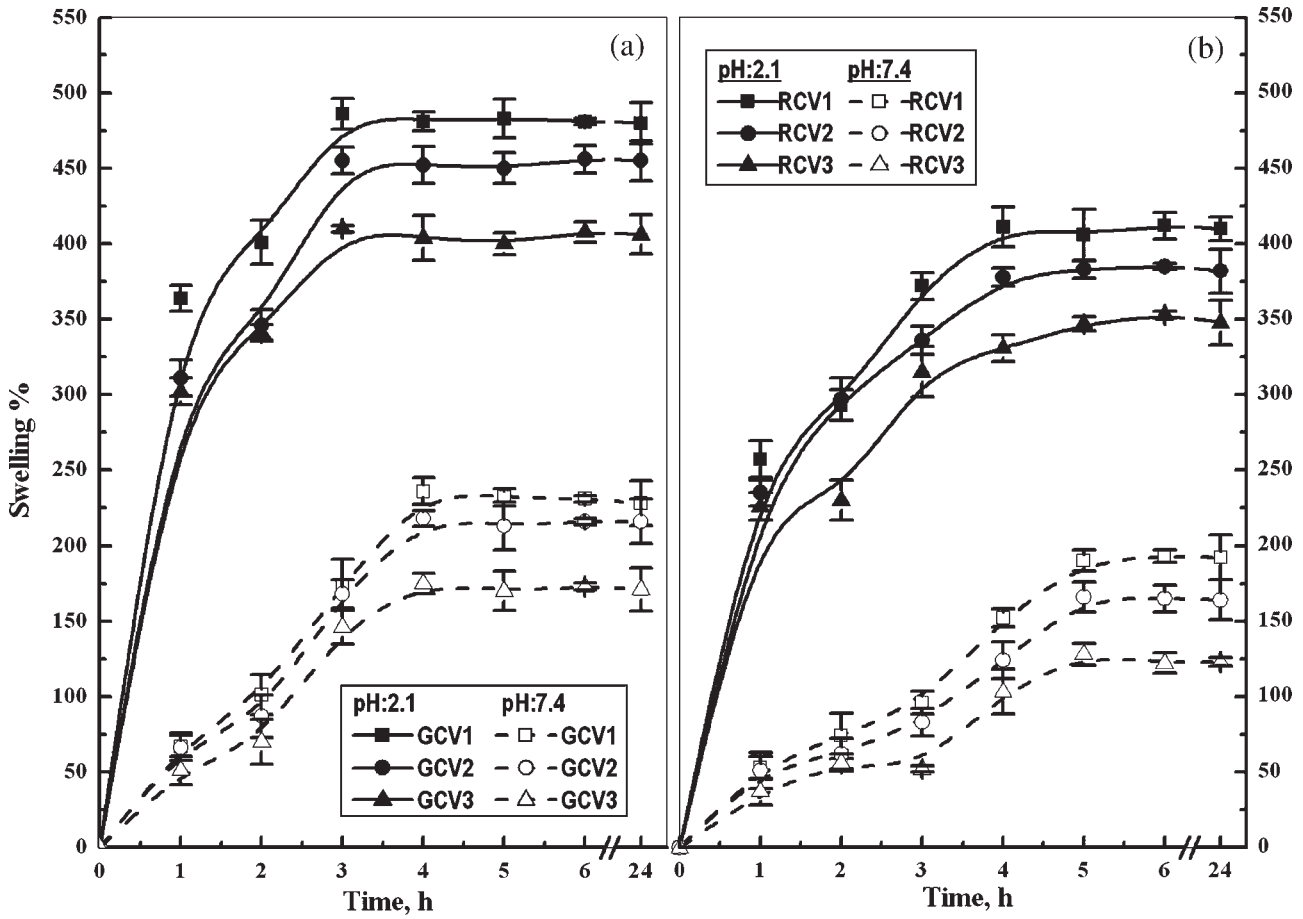


Figure 5 Time dependence of the swelling percent of (a) 10 KGy and (b) 20 KGy γ-irradiated Ch/PVA films of different blend ratios in pH 2.1 and 7.4 at 37°C.

irradiation as the content of PVA increases. This is due to the mobility restriction of chains between crosslinks, which leads to a remarkable decrease in the swelling percent at equilibrium. Such swelling percent (450%, GCV2) was attained in approximately 3 h in pH 2.1, while the time required for equilibrium swelling percent (210%, GCV2) increased up to 4 h in case of pH 7.4. Figure 5(b) behaves similarly for a higher γ-irradiation dose of 20 KGy, but the swelling percent was of lower limits. The equilibrium swelling percent (380% and 150%, RCV2) was attained after about 4 and 5 h in pH 2.1 and 7.4, respectively. On the other hand, the direct dependence of the Gel fraction percent representing the crosslinking extent on both γ-irradiation dose and PVA content in the films confirms that PVA role in crosslinking was predominant (see Table II).

From all the above discussed results, it is noticeable that the swelling percent was higher at acidic medium (pH 2.1) than for the slightly alkaline one (pH 7.4). This sensitivity towards pH can be attributed to the chemical structure of chitosan where protonation can occur favorably at the NH_2 groups of chitosan in the acidic medium, leading to dissociation of the hydrogen bonds involving these groups. This consequently facilitates the entrance of swelling fluids into the film matrix and a higher extent of swelling percent will be attained. In addition, this facilitates ionization of amino groups in the acidic buffer solution.[22,29] On the other hand, the swelling process will be hindered at pH 7.4 due to the increased hydrophobic nature of the chitosan-based gel films dominating at higher pH values, thus preventing faster swelling in neutral and alkaline media.[30]

Cumulative release measurements

The release patterns of a drug from a polymeric matrix depend mainly on its swelling behavior. Thus, factors

TABLE II
Gel Fraction Percent of γ-Irradiated Ch/PVA Films of Different PVA Contents in pH 7.4 at 37 °C

	PVA content (%)		
Irradiation dose (KGy)	50	60	75
10	40.2	52.0	59.5
20	51.0	56.0	61.1

affecting the DS are consequently influencing the cumulative release profile of a drug from such matrix. In the next subsection, the effect of PVA and crosslinker contents as well as the irradiation dose is discussed for samples loaded with a 24 mg FU/g matrix. However, samples loaded with different amounts of FU (14 and 40 mg/g matrices) were prepared to investigate the dependence of release percent on the initial concentration of FU in the matrix.

Effect of PVA content

The cumulative release of FU from the noncrosslinked films of Ch/PVA blends in pH 7.4 at 37°C was investigated, and the dependence of the release percent of FU on the PVA content in the films was realized. A gradual increase in the released percent of FU was observed for the PVA-free sample while an initial burst release in the first hour was observed for samples containing PVA. Release of FU becomes faster and the release percent attains higher values at equilibrium as the content of PVA in the blend increases, and nearly most of the accessible FU is released from the films within 2.5 h; hence, the plateau level was attained. The noncrosslinked chitosan blends have not been investigated at pH 2.1 as it can be dissolved in acidic medium. The release percent of FU for the crosslinked Ch/PVA blends at 37°C in pH 2.1 and 7.4 was investigated and the direct dependence on the content of PVA in the blend and pH of the releasing medium was remarkable. For instance, the release percent increased from ~84% to ~96% and from ~57% to ~70% for samples released in the medium of pH 2.1 and 7.4, respectively, by increasing the PVA content from 50% (CVA3) to 75% (CVA6) in the films loaded with 24 mg FU/g matrix. The time required for release of most accessible FU was 5 h in both cases (Table III).

TABLE III
Release Percent (*R*%) at Equilibrium of FU from Ch and Ch/PVA Films with Initial Concentration (Ei) of 14, 24, and 40 mg FU/g matrix in pH 2.1 and 7.4 at 37°C[a]

			R %			
Sample	Ei; mg/g	E %	pH 2.1	t, h	pH 7.4	t, h
Ch	14	78.0	—	—	72.5	2.5
	24	70.9	—	—	76.0	—
	40	73.2	—	—	77.8	—
ChVA1	14	73.5	—	—	76.9	—
	24	68.0	—	—	80.4	—
	40	66.4	—	—	82.1	—
ChVA2	14	82.3	—	—	85.0	—
	24	69.7	—	—	87.0	—
	40	71.6	—	—	88.2	—
ChVA3	14	69.4	—	—	88.0	—
	24	67.8	—	—	91.6	—
	40	74.7	—	—	90.8	—
CCh1	14	83.0	92.1	6.0	76.1	6.0
	24	82.1	95.0	—	76.0	—
	40	83.3	96.8	—	76.8	—
CCh2	14	86.7	81.3	—	60.2	—
	24	86.9	83.2	—	61.0	—
	40	85.1	83.7	—	61.7	—
CCh3	14	86.4	76.1	—	48.4	—
	24	85.1	80.0	—	50.2	—
	40	87.5	84.5	—	50.0	—
CCh4	14	91.7	80.7	—	45.3	—
	24	92.4	80.0	—	46.0	—
	40	90.8	82.3	—	46.1	—
CVA1	14	85.1	92.6	5.0	62.8	5.0
	24	86.0	94.0	—	63.0	—
	40	85.3	95.3	—	64.1	—
CVA2	14	87.4	87.1	—	63.9	—
	24	88.2	87.0	—	63.5	—
	40	88.9	89.0	—	65.2	—
CVA3	14	87.3	83.2	—	54.7	—
	24	88.0	84.0	—	57.0	—
	40	87.1	84.6	—	59.3	—
CVA4	14	88.5	81.4	—	50.0	—
	24	87.2	83.0	—	51.2	—
	40	85.8	85.2	—	53.0	—
CVA5	14	92.3	95.0	—	61.1	—
	24	90.9	95.0	—	63.0	—
	40	90.7	96.6	—	65.2	—
CVA6	14	94.2	96.9	—	76.8	—
	24	93.0	96.0	—	70.0	—
	40	94.8	98.2	—	74.6	—

[a] E % is the percent of FU entrapped in the matrix.

Effect of crosslinker content

The equilibrium release percent of FU from Ch and Ch/PVA films was varied according to the amount of glutaraldehyde used for crosslinking in pH 2.1 and 7.4. The inverse dependence on the degree of crosslinking can be concluded. Table III showed that, for instance, ~95% FU was released up to equilibrium from 5% glutaraldehyde-crosslinked chitosan (CCh1), which was lowered to 80% in the case of 35% glutaraldehyde-crosslinked chitosan (CCh4) in pH 2.1. A slight or nearly no difference was observed in the release percent at equilibrium from the 25% (CCh3) and 35% (CCh4) crosslinked samples. A similar behavior was observed in pH 7.4 at 37°C and all samples attained a state of equilibrium release after ~6 h, that is, longer than that for the noncrosslinked films (<2.5 h).

For the crosslinked 1 : 1 Ch/PVA blends, the release percent of FU up to equilibrium decreased from 94% to 83% as the amount of glutaraldehyde increased from 5% for CVA1 to 35% and for CVA4 while no significant difference was observed at equilibrium between CVA3 and CVA4 (25% and 35% glutaraldehyde, respectively) at pH 2.1 at 37°C. Similar release patterns were obtained for the same samples (CVA1-4) in pH 7.4. In both media (pH 2.1 and 7.4), the release percent from the FU-loaded samples (CVA1-4) attained its equilibrium value after nearly 5 h, that is, in less time than that for the crosslinked Ch samples (~6 h). This can be attributed to the higher swelling

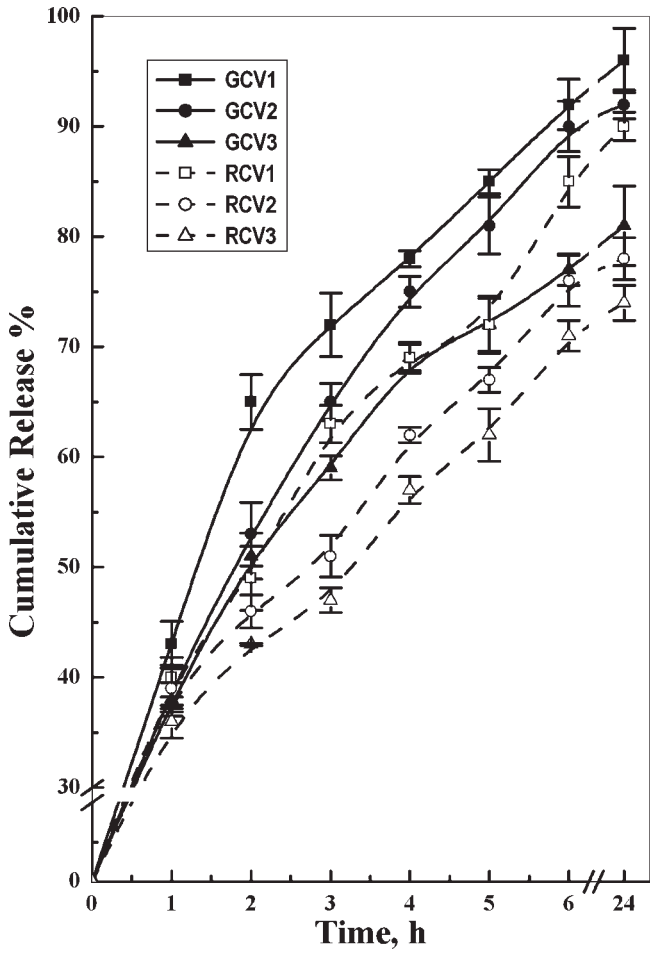


Figure 6 Release percent of FU from γ-irradiated Ch/PVA films of different PVA contents in pH 2.1 at 37°C.

ability of the crosslinked Ch/PVA films relative to that for Ch films.

Effect of irradiation dose

The cumulative release behavior of FU from Ch/PVA films subjected to a dose of 10 KGy and 20 KGy of γ-irradiation in pH 2.1 and 7.4 at 37°C was investigated. Figure 6 shows the direct time dependence of the release percent of FU on the PVA content in the film. The inverse effect of PVA content on the release percent of FU at equilibrium is recognizable as well. This can easily be explained by the fact (derived in the subsection ''Effect on irradiation dose'' above) that more radiation-induced crosslinking occurs by increasing the γ-irradiation dose and/or the content of PVA in the film. This will lead, of course, to swelling and consequently the release percent of FU will be dimensioned.

Effect of initial concentration of loaded FU

The release percent of FU from all the investigated films irrespective their composition was much higher in acidic medium (pH 2.1) than that in the neutral or weakly alkaline one (pH 7.4). This may be attributable to the dependence of the release rate on the degree of swelling of the gel, where the release is mainly diffusion-limited. This conclusion can be supported by the results obtained by investigating the release patterns of FU from samples loaded with different amounts (14, 24, and 40 mg/g matrix) of FU. From Table III, it can be noted that the release percent of FU was directly related to the initial concentration of FU loaded in the matrix. This may tend to refer to the role played by the hydrophilic nature of the entrapped materials in increasing the rate of release. However, the variation in the released amount of the drug upon increasing its initial concentration is not significant enough to reflect a strong role of drug hydrophilicity. At the same time, it confirms that the mechanism of release is mainly diffusion-limited through the swollen gel. Moreover, a marked effect of the pH of the release medium over the effect of the PVA content in the gel was revealed. This may be attributed to the chemical structure of chitosan, where the amino groups are responsible for such pH sensitivity.

CONCLUSIONS

1. Chemical crosslinking of Ch blends can be achieved through the formation of imine bonding upon condensation with glutaraldehyde, with the exclusion of the possible acetal or hemiacetal formation between PVA and glutaraldehyde.
2. Irradiation of Ch/PVA blends resulted in self-crosslinking of PVA chains; therefore, more crosslinking occurs as the content of PVA increases leading to a remarkable decrease in the equilibrium swelling.
3. Equilibrium swelling of all films depends directly on time and increases with the content of PVA, while it depends inversely on the crosslinker content.
4. The release percent of FU depends directly on the content of PVA and more significantly on the pH of the releasing medium, where it was faster in an acidic medium than in a neutral or weakly alkaline one.
5. For γ-irradiated samples, the irradiation dose has an inverse effect on the release percent of FU from Ch/PVA blends; hence, more crosslinking occurs with increased γ-irradiation dose.

The authors would like to cordially thank Dr. DRK Harding at IFS, Massey University, Palmerston North, New Zealand for facilitating the SEM investigations, elemental analysis, and XRD measurements through gainful collaboration.

References

1. Kossmehl, G. A.; Abdel-Bary, E. M.; Sarhan, A. A.; Abdelaa1, M. Y. Angew Makromol Chem 215, 1994, 59–77.
2. Abdelaal, M. Y. J Polym Sci Pt A: Polym Chem 40, 2002, 3909–3915.
3. Abdelaal, M. Y.; Abbas, Y. A. Monatsh Chem 127, 1996, 1131–1136.
4. Abbas, Y. A.; Abdelaal, M. Y. Polymer Bull 36, 1996, 273–278.
5. Kurita, K. In Chitin in Nature and Technology; Muzzarelli, R.A.A.; Jeuniaux, C.; Gooday, G.W., Eds.; Plenum Press: New York, 1986, p 287–293.
6. Hirano, S.; Seino, H; Akiyama, Y.; Nonaka, I. In Progress in Biomedical Polymers; Gebelin, C. G. & Dunn, R. L., Eds.; Plenum Press: New York, 1990; p 283–290.
7. Muzzarelli, R.; Baldassarre, V.; Conti, F.; Ferrara, P.; Biagini, G.; Gazzanelli, G.; Vasi, V. Biomaterials 9, 1988, 247–252.
8. Wang, P. F.; Wu, S. H. K.; Shi, X. Y.; Deng, B. M.; Sun, C. J Mater Sci 33, 1998, 1753–1757.
9. Xie, W. M.; Xu, P. X.; Wang, W.; Liu, Q. Carbohyd Polym 50, 2002, 35–40.
10. Sannan, T.; Kurita, K.; Iwakura, Y. Macromol Chem 177, 1976, 3589–3600.
11. Martien, F. L. In Encyclopedia of Polymer Science and Engineering, Vol. 17, Wiley: New York, 1986; p 167.
12. Roberts, G. A. F.; Taylor, K. E. Makromol Chem 1905, 1989, 951–960.
13. Wang, Q.; Du, Y.; Fan, L. J Appl Polym Sci 96, 2005, 808–813.
14. Bhattacharya, A. Prog Polym Sci, 25, 2000, 371–401.
15. Jabbari, E.; Nozari, S. Eur Polym J 36, 2000, 2685–2692.
16. Rosiak, J. M.; Ulanski, P. Radiat Phys Chem 55, 1999, 139–151.
17. Park, S. E.; Nho, Y. C.; Lim, Y. M.; Kim, H. I. J Appl Polym Sci 91, 2004, 636–643.
18. Zainuddin, Z.; Hill, D. J. T.; Le, T. T. Radiat Phys Chem 62, 2001, 283–291.
19. Roberts, G. A. F. Solubility and solution behaviour of chitin and chitosan, In: Roberts, G.A.F. (Ed.), Chitin Chemistry, MacMillan, Houndmills, 1992, pp. 274–329.
20. Abdelaal, M. Y.; Elmorsy, S. S. Angew Makromolek Chemie 233, 15–21. 1995,
21. Roberts, G. A. F.; Domszy, J. G. Int J Biol Macromol 4, 1982, 374–377.
22. El-Sherbiny, I. M.; Lins, R. J.; Abdel-Bary, E. M.; Harding, D. R. K. Eur Polym J 41, 2005, 2584–2591.
23. Kasaai, M. R.; Arul, J.; Charlet, G. J Polym Sci, B: Polym Phys 38, 2000, 2591–2598.
24. Lapasin, R.; Princl, S. In: Rheology of industrial polysacharides: Theory and application, Blackie Academic & Professional: New York, 1995.
25. Wang, T.; Turhan, M.; Gunasekaran, S. Polym Int 53, 2004, 911–918.
26. Abd-Alla, S. G.; Said, H. M.; El-Naggar, A. M. J Appl Polym Sci 94, 2004, 167–176.
27. Huglin, M. B.; Zakaria, M. B. J Appl Polym Sci 31, 1986, 457–475.
28. Wang, B.; Kodama, M.; Mukataka, S.; Kokufuta, E. Polym Gels and Networks 6, 1998, 71–81.
29. Kim, S. J.; Park, S. J.; Kim, S. I. React Funct Polym 55, 2003, 53–59.
30. Gupta, K. C.; Kumar, M. N. V. R. J Appl Polym Sci 76, 2000, 672–683.