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Polymer 41 (2000) 4589–4598

polymer

Novel pH-sensitive chitosan hydrogels: swelling behavior and states of water

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Received 3 August 1999; received in revised form 1 September 1999; accepted 13 September 1999

Abstract

Physically crosslinked chitosan hydrogels were synthesized by grafting d,l-lactic acid (LA) and/or glycolic acid (GA) with different feed ratios. The physical crosslinking was formed due to the hydrophobic side chains aggregation and intermolecular interactions through hydrogen bonds between side and main chains. The crystallinity of original chitosan decreased by grafting LA and GA. The structural change of the hydrogels in different pH buffers was characterized by FT-IR method and the results were interpreted. Differential scanning calorimetry (DSC) was used to probe the states of water in the chitosan hydrogels. Three types of water were found in the samples, i.e. freezing water (namely free water), non-freezing water (namely bound water), and freezing bound water, while there are variations in the amount of bound water for different hydrogels. The effect of hydrophobic side chains on water state and swelling behavior were discussed.

Keywords: Chitosan; d,l-Lactic acid; Glycolic acid

1. Introduction

Hydrogels are three-dimensional networks which will swell in water and aqueous solutions. In the swollen state they are soft and rubbery, resembling a living tissue, and some of them also possess excellent biocompatibility [1]. Ongoing investigations on natural and synthetic hydrogels have established their potential for use in several biomedical applications such as drug delivery systems [2,3], soft contact lenses [4], and implants [5]. Other practical applications include the immobilization of enzymes, food processing technology, electrophoresis, and phase transfer catalysis [6,7]. Because of the presence of certain functional groups along the polymer chains, hydrogels are often sensitive to the conditions of the surrounding environment, which are referred to as "intelligent materials". For example, the water uptake of these materials may be sensitive to temperature [8], pH [9], or to the ionic strength [10] of the swelling solutions or even to the presence of a magnetic field [11] or ultraviolet light [12].

Numerous workers have studied the states of water in hydrogels. Water in polymer systems is known to be affected by specific interaction with polymer chains. The investigations on the state and role of water have been focused on poly(vinyl alcohol) [13], poly(2-hydroxyethyl methacrylate) [14,15] as well as chitosan [16,17]. According to their results, the water in hydrogels can be generally classified into three species: freezing water (namely free water), non-freezing water (namely bound water), and freezing bound water. It is convincing that a study on the physical state of water in the hydrogels might provide useful information on their microstructure and behavior.

The hydrogel forming ability through physical crosslinking of several natural polymers such as gelatin [18], cellulose [19], starch [20] and chitosan [21,22] have been well documented. We have synthesized pH-sensitive hydrogels by graft copolymerization of specifically d,l-lactic acid (LA) onto chitosan (CS) [23]. In this paper, we considered the incorporation of glycolic acid (GA), with d,l-lactic acid at different feed compositions. Their chemical structures are shown in Scheme 1 (chemical structure of glycolic acid, lactic acid, chitosan and graft chitosan). The GA side chains, which are more hydrophilic than those of the LA, will not only affect the crystallinity, but also have a strong impact on the swelling behavior of the synthesized chitosan hydrogels. The preparation and characterization of the hydrogels are reported. The structural change of the hydrogels in different pH buffers was analyzed. Furthermore, the effect of hydrophobic side chains on the water state in hydrogels is discussed. These pH-sensitive hydrogels are of general

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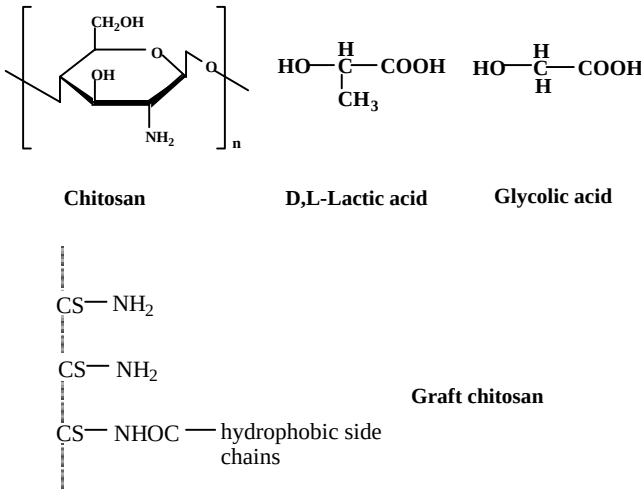
PII: S0032-3861(99)00685-0



Scheme 1.

interest for biomedical applications, such as artificial muscles or switches, biochemical separation systems, and controlled-release systems.

2. Experimental

2.1. Materials

d,l-Lactic acid (LA) (99%), glycolic acid (GA) (99%) from Lancaster (England) and chitosan (CS) (M_w = 70,000) from Fluka (Switzerland) were used for the preparation of the hydrogels. Acetic acid and sodium phosphate for the preparation of buffers were purchased from Merck. The degree of deacetylation (88%) of chitosan was determined by the IR spectroscopy method [24]. All these chemicals were used as-received, without further purification.

2.2. Preparation of chitosan hydrogels

The synthesis of hydrogels was carried out by direct copolycondensation in the absence of catalysts similar to the method already reported [23]. In short, chitosan powder (1 g) dispersed in water, was dissolved by adding d,l-lactic and/or glycolic acid at different feed ratios. The solutions were poured on a Teflon dish with 15.0 cm diameter and dried at 80°C. This was followed by extraction with methanol in a Soxhlet apparatus for 24 h.

2.3. Fourier transform infrared transmission spectra

The Fourier transform infrared (FT-IR) transmission spectra were obtained from the film samples on a Perkin–Elmer FT-IR 1725X spectrometer.

2.4. Wide-angle X-ray diffraction measurements

Wide-angle X-ray diffraction (WAXD) measurements were carried out at room temperature by using a D/MAX-YA diffractometer with a CuK_α tube, 40 kV, 100 mA, made by Rigaku Co., Japan. The diffraction patterns were determined over a range of diffraction angle $2\theta = 3$ to 40°.

2.5. Degree of substitution

Degree of substitution (DS) of the chitosan amino groups was determined by formation of *N*-salicylidene chitosan [18] by reacting salicylaldehyde with the amino groups remaining after grafting. An accurately weighed methanol extracted and dried sample was immersed for 24 h in 100 ml 0.02 M solution of salicylaldehyde in methanol/1% acetic acid aqueous solution (80/20, v/v). After 24 h, the mixture was filtered, a portion of the filtrate diluted 400 times and the UV absorbance at 255 nm measured to determine the residual concentration of salicylaldehyde (SA) by comparison to the blank SA solutions.

2.6. Elemental analysis

The contents of C, H and N were determined for virgin and methanol-extracted grafted chitosan samples. In this case the total nitrogen content was determined according to Dumas with a Carlo Erba NA 1500 instrument. All analyses were performed by Mikro Kemi AB, Uppsala, Sweden.

2.7. Thermogravimetric analyses

Dynamic thermogravimetric (TG) analyses were carried out with a METTLER TGA/SDTG 851[e] system. All the thermogravimetric analyses were performed with 4–5 mg

Table 1
Graft copolymerization of glycolic and d,l-lactic acid onto chitosan

Sample	CS (g)[a]	GA (g)	LA (g)	$COOH/NH_2$ (mol/mol)	Yield (g)	DP of side chains[b]	DS of side chains[c] (%)
GA/CS = 0.5	1.0	0.5	–	1.24	0.86	1.71	7
GA/CS = 2	1.0	2.0	–	4.96	0.94	3.85	16
GA/LA/CS = 1/1/1	1.0	1.0	1.0	4.58	0.95	2.91	13
LA/CS = 2	1.0	–	2.0	4.19	1.02	1.95	14
LA/CS = 0.5	1.0	–	0.5	1.05	0.86	0.99	6

[a] Water-soluble chitosan with 88% deacetylation was used.
[b] Degree of polymerization of side chains measured by elemental analysis.
[c] Degree of substitute measured by residual salicylaldehyde.

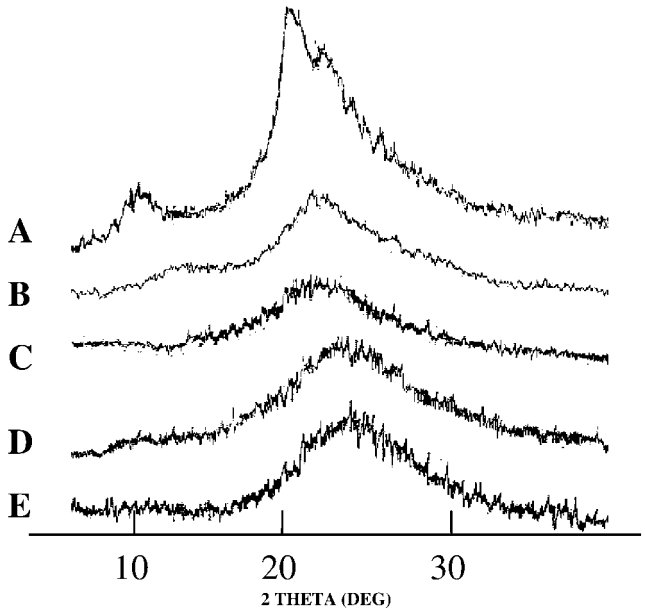


Fig. 1. X-ray spectra of sample: (A) chitosan; (B) LA/CS = 2; (C) GA/LA/CS = 1/1/1; (D) GA/CS = 2; (E) GA/CS = 0.5.

of finely cut sample pieces in an Al_2O_3 crucible (70 μl) under a dynamic nitrogen atmosphere flowing at 50 ml min^{-1}. The experiments were run at a scanning rate of 10°C min^{-1}.

2.8. Differential scanning calorimetry

A Mettler Toledo differential scanning calorimetry (DSC) 820 calorimeter fitted with a cooling accessory was used for all DSC experiments. The samples were cut into small pieces and put into aluminium vessels. The vessels were heated from room temperature to 500°C at a heating rate of 10°C min^{-1}.

To study the Water State in hydrogels, hermetically sealed aluminum DSC sample vessels were used for all experiments. The samples dried in vacuum overnight were cut into small pieces (about 5 mg) and put into aluminum vessels, excess distilled unionized water was added to the sample and allowed to evaporate until the desired water content was obtained. The sample vessels were weighed again before and after the experiment to ensure that no weight loss had occurred during the experiment. The vessels were cooled first from room temperature to −60°C and then heated to 25°C at a rate of 10°C min^{-1}. The specific solution content or weight uptake of hydrogels was expressed by the following equation:

Specific solution content (water uptake) (W)

$$= (W_s - W_d)/W_d$$

where W_d and W_s are the weights of the samples in the dry and swollen states, respectively.

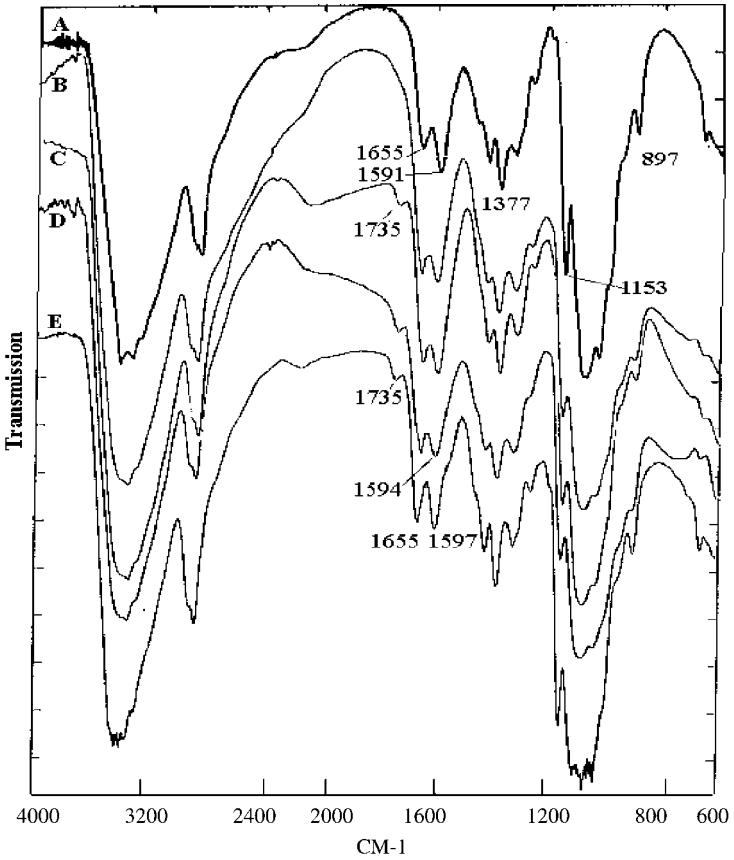


Fig. 2. FT-IR spectra of sample: (A) chitosan; (B) GA/CS = 0.5; (C) GA/CS = 2; (D) GA/LA/CS = 1/1/1; (E) LA/CS = 2.

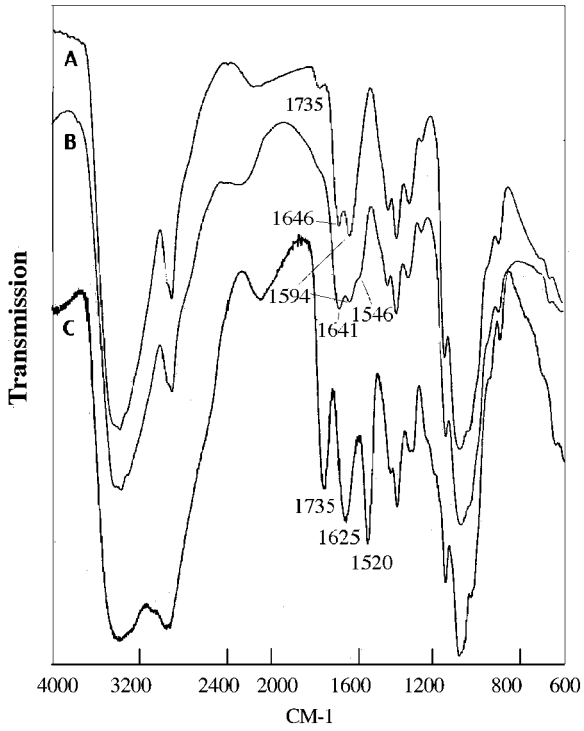


Fig. 3. FT-IR spectra of: (A) sample GA/CS = 2 in dry state; (B) swollen in pH 7.4 buffer and dried; (C) swollen in pH 2.2 buffer and dried.

2.9. Swelling of the hydrogels

To determine the effect of pH on hydrogel swelling kinetics, McIlvaine buffer [25] with the same ionic strength, $I = 0.5$ M, and various pH was used in this work [citric acid/Na_2HPO_4 (pH 2.2–7.4), and 0.5 M NaOH/KCl (pH 12.0)]. The samples (approximately 0.05 g) were immersed into 200 ml of buffer solution, the weight of solution absorbed by the gels was calculated from the weights of the gel before and after vacuum drying at room temperature.

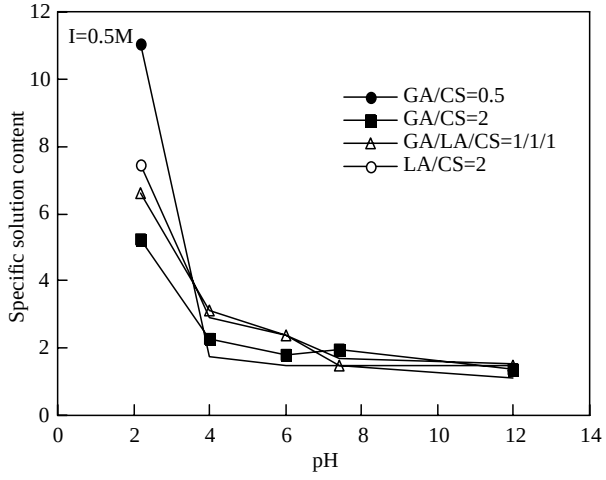


Fig. 4. Equilibrium specific solution content of hydrogels as a function of buffer pH.

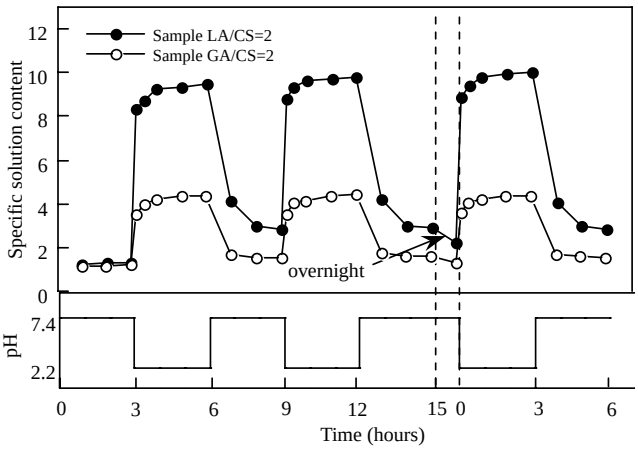


Fig. 5. Specific solution content of hydrogels as a function of time under repeated abrupt change of pH between 7.4 and 2.2.

The specific solution content or weight uptake of hydrogels was expressed by the above equation.

The swelling reversibility of the chitosan hydrogels was measured in the pH 2.2 and pH 7.4 buffers. The films were brought into a swelling equilibrium at pH 7.4 for 3 h and then transferred to a solution at pH 2.2 so that an abrupt swelling was ensured. After obtaining swelling equilibrium, the samples were placed back into the pH 7.4 buffer. The exchange of buffers was repeated at 3-h intervals and the specific solution content was measured as a function of time.

3. Result and discussion

The pH-dependent swelling behavior and kinetics of hydrogels based on d,l-lactic acid (LA) and chitosan (CS) are already reported in our previous articles [23]. In this article, we report on the grafting of another monomer, glycolic acid (GA), alone or in combination with d,l-lactic acid onto chitosan. Compared to LA, the chemical structure of GA also has a hydroxyl and carboxylic group but no methyl group. The oligomer and polymer of GA are reported to be more crystalline, but also more hydrophilic and thus easier to hydrolyze in aqueous solution than those of the LA [26,27]. The graft chitosan could form hydrogels in aqueous solutions due to the physical crosslinking through hydrogen bonding and dipole–dipole interactions between neighboring ester groups and chitosan chains, as well as the hydrophobic side chain aggregation. Desbriéres et al. [28] reported that chitosan which are substituted with alkyl chains having a minimum of six carbon atoms demonstrate hydrophobic interactions in solution.

3.1. Characterization of chitosan hydrogels

Table 1 gives the monomer-to-chitosan feed ratios, yields and grafted side chain data of the chitosan hydrogels. The average side chain length (DP) and degree of substitution (DS) were calculated from the results of the elemental

Table 2
Evaporation temperatures of water inside chitosan and its derivatives measured by TG and DSC

	Chitosan	GA/CS = 0.5	GA/CS = 2	GA/LA/CS = 1/1/1	LA/CS = 2	LA/CS = 0.5
DTG_{max} (°C)	61.36	80.30	109.79	119.96	109.75	95.28
DSC_{min} (°C)	89.33	110.33	128.33	123.83	122.33	116.17
Wt. Loss (%)	7.09	7.55	8.59	8.17	7.28	6.40

analysis and the residual salicylaldehyde method [29]. The DS of chitosan $-NH_2$ groups increases with the feed ratio of LA or GA to CS. Compared to the lactic acid, grafting with glycolic acid will give higher values of the side chain length, but comparable degrees of substitution.

The X-ray pattern of ungrafted chitosan film shows two crystalline peaks at around $2\theta = 10$ and 20° as shown in Fig. 1a [30,31]((while both the crystalline peaks decrease with grafting lactic acid (Fig. 1b). The grafting by d,l-lactic acid will take place at random along the chitosan chains in solution, giving rise to a random graft chitosan and destroying efficiently the regular packing of the original chitosan chains. Finally it will result in the formation of totally amorphous graft chitosan [23]. With the incorporation of glycolic acid, the crystalline peak of chitosan at $2\theta = 20°$ shifts to 22° (GA/LA/CS = 1/1/1) and then to 23° (GA/CS = 2), which is the peak position for the crystal structure of glycolic acid oligomer and polymer according to the literature [32]. This would indicate that the glycolic acid side chains from different chitosan main chains might aggregate and even crystallize in spite of the low DP and DS values. No significant difference exists between the samples GA/CS = 0.5 and GA/CS = 2 and the reason for it is unclear. The glycolic acid grafted chitosan samples are opaque after methanol extraction, while the lactic acid grafted samples are always transparent.

The FT-IR spectra of chitosan and the graft chitosan samples are shown in Fig. 2. The spectra of graft copolymers (Fig. 2B–E) are similar to those of the original chitosan (Fig. 2A), while a new peak appeared at 1735 cm^{-1} which could be assigned to the ester or carbonyl groups in the side chains [23,29]. The intensity increased with the increase of GA/CS feed ratio. After the reaction, the amide I peak (1655 cm^{-1}) of chitosan increases, which indicates the increase of amidation by reacting chitosan with GA and/or LA, but no significant difference exists between each grafted sample in spite of the different DS values (see Table 1). The peak of the amino groups shifted slightly from 1591 to 1594 cm^{-1} for GA/CS = 2 and then to 1597 cm^{-1} in the case of LA/CS = 2, suggesting hydrogen bonding between the side chains and chitosan. In addition, it can be supposed that chemical crosslinking does not occur at the relatively mild graft copolymerization conditions (80°C) used since no new peak corresponding to ether groups from the reaction between the hydroxyl groups of CS and LA and /or GA was found in the IR spectra. However, the reaction between the hydroxylic groups of CS and the carboxylic groups of LA and/or GA may occur to some extent under the present conditions according to literature [33].

3.2. Structural changes of chitosan hydrogels

The chitosan hydrogels are pH-sensitive and their structural change depends on the buffer pH. This change was analyzed by FT-IR and the results are shown in Fig. 3. After the sample GA/CS = 2 had been swelled in pH 7.4 buffer for 30 min and vacuum dried, its IR spectrum (Fig. 3B) is similar to that of the original sample (Fig. 3A). The carbonyl peak at 1735 cm^{-1} becomes a shoulder due to the increase of 1646 cm^{-1} peak intensity. But a new shoulder, which could be assigned to the deformation of NH_3^+ groups,

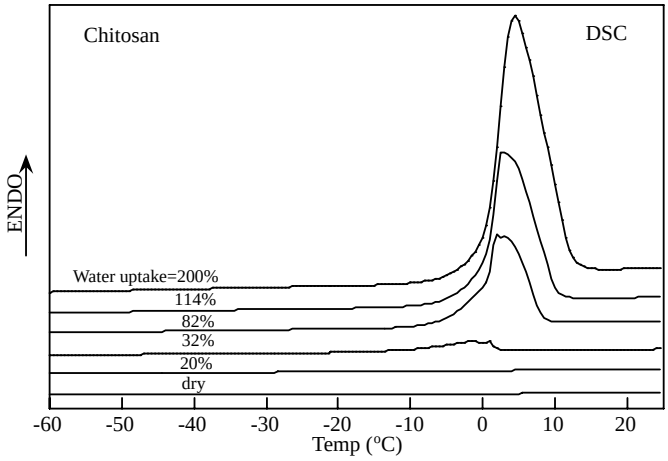


Fig. 6. Representative DSC heating curves of chitosan/water system as a function of temperature, recorded at 10°C min^{-1}.

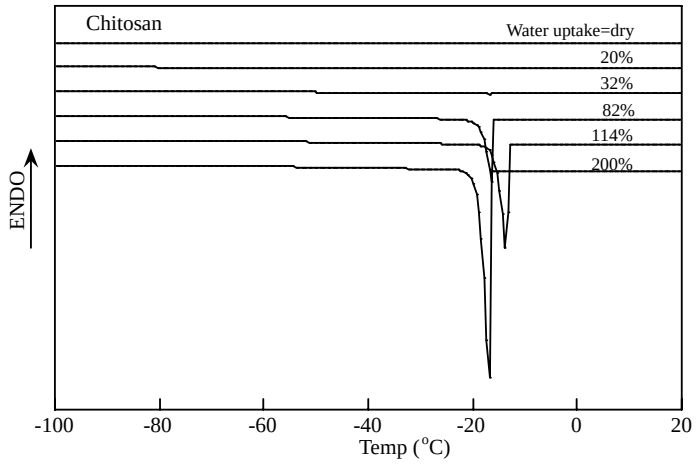


Fig. 7. Representative DSC cooling curves of chitosan/water system as a function of temperature, recorded at 10°C min^{-1}.

appeared at 1546 cm^{-1}. It shows that the residual $-NH_2$ group of the grafted copolymers would be partly ionized by the weak acid in pH 7.4 buffer [17]. A major part of the amino groups would not be protonated at pH 7.4 since the pK_b for CS hydrogels is in the range of 4.0–6.0 as we reported previously.

After 30 min in pH 2.2 buffer followed by vacuum drying, two new and strong peaks, which are related to the deformation of NH_3^+ groups of chitosan, appeared at 1625 and 1520 cm^{-1} in the spectrum (Fig. 3C) [16]. All of the amino groups have been protonated in pH 2.2 buffer. The ionization causes the electrostatic repulsion between adjacent ionized residual $-NH_2$ groups of chitosan leading to chain expansion, which eventually increases the water uptake of the gel. Meanwhile, the peak of the carbonyl group at 1735 cm^{-1} increases significantly which indicates that the gel had formed ionic complex with the acid in the buffer.

3.3. Swelling reversibility of chitosan hydrogels

The equilibrium water uptakes of the samples except LA/CS = 0.5 (reported in the previous paper [23,29]) are shown in Fig. 4. The highest water uptake values were obtained in the pH 2.2 buffer in all cases, while all samples have similar values above the pK_b of CS hydrogels in the range of 4.0–6.0. It means that the side chains and the degree of substitution have less effect on sample swelling above pK_b. These results could be interpreted by the pH-dependent structure change of hydrogels due to charge repulsion at low pH buffers as we explained in the last paragraph.

It is worth noting that the water uptakes of chitosan hydrogels decrease significantly when pH increases from 2.2 to 4.0, while the pK_b of chitosan in aqueous solutions has been reported to be in the range of 6.5–6.7 depending on the degree of deacetylation [24]. According to our experimental results, the pK_b of chitosan hydrogels decreases form 6.5–6.7 to 4.0–6.0 due to partial substitution of amino groups and crosslinking. Similar deswelling behavior of other chitosan hydrogels have also been reported in the literature [17,21,22].

Fig. 5 shows the swelling reversibility of the chitosan hydrogels GA/CS = 2 and LA/CS = 2 between pH 2.2

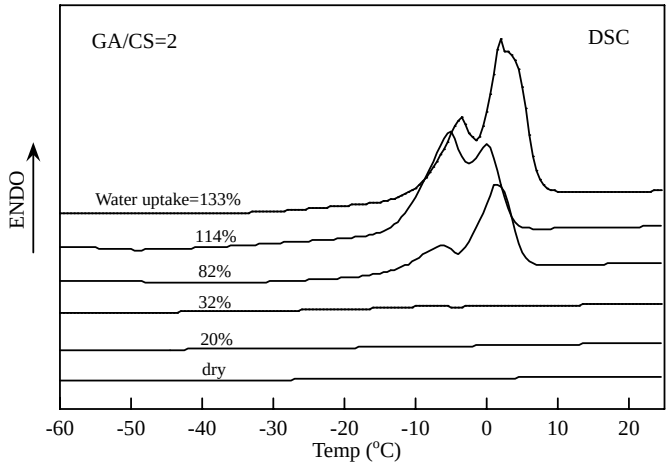


Fig. 8. Representative DSC heating curves of sample GA/CS = 2/water system as a function of temperature, recorded at 10°C min^{-1}.

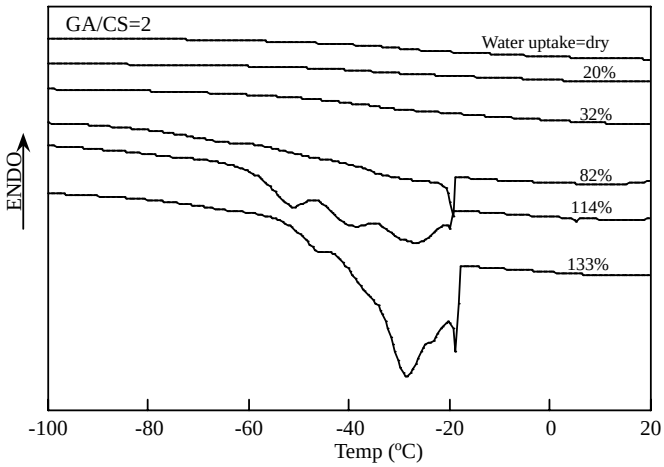


Fig. 9. Representative DSC cooling curves of sample GA/CS = 2/water system as a function of temperature, recorded at 10°C min^{-1}.

and pH 7.4 buffers. The results demonstrated that the samples changed their ability to absorb solution when the environmental pH is altered. It seems that the time for swelling is much shorter than for the deswelling of the hydrogels. This is reasonable since both swelling and deswelling processes start from the surface of the hydrogels. During the swelling, the amino groups of the sample surface are ionized first. Thus the surface will swell due to the electrostatic repulsion between adjacent ionized amino groups. The water and acid will easily penetrate inside the sample. While during the deswelling, the surface will deswell first, then it will take longer time for the deprotonation of the ionized amino groups inside the hydrogels. The acid is more difficult to transport to the buffer solutions compared to the swelling process. The reversibility toward the pH changes was retained even after prolonged treatment (overnight). Meanwhile, although both sample LA/CS = 2 and GA/CS = 2 have similar water uptake in the pH 7.4 buffer, the sample LA/CS = 2 appeared to have higher water uptake values in the pH 2.2 buffer. The reason for this difference is unclear, but it might be due to the stronger GA side chains aggregation and intermolecular interactions. The water permeability, which should increase with sample hydration, can also be converted in response to a change in the environmental pH. It would be a desirable characteristic for a pH-sensitive controlled-release system with controllable swelling ability.

3.4. States of water in chitosan hydrogels

In the initial swelling process, water molecules first disrupt the intermolecular hydrogen bonds and then bind to the hydrophilic sites. These water molecules, which are isolated and uniformly distributed throughout the polymer, have greatly restricted mobility and are referred to as bound or non-freezing water. Above a certain level of bound water, the additional water is preferentially oriented around the bound water and the polymer network structure as a secondary or tertiary hydration shell, which is in a form generally called ‘clusters’. These cage-like structures result from the

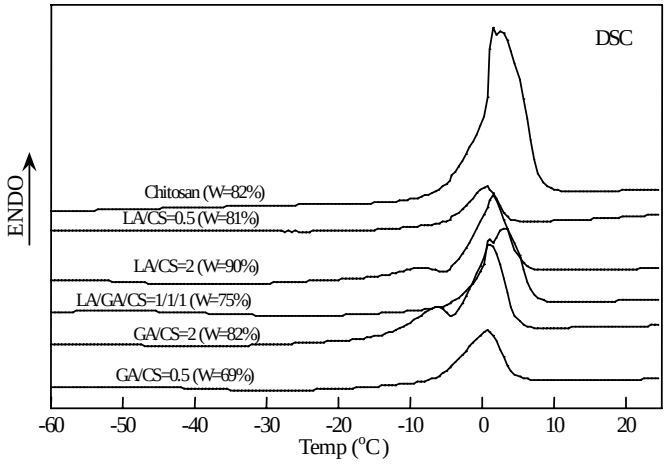


Fig. 10. Representative DSC heating curves of various systems with water uptake 70–90% as a function of temperature, recorded at 10°C min^{-1}.

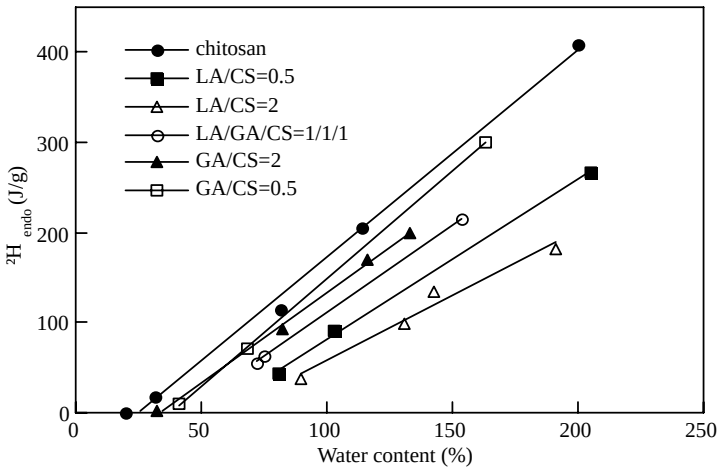


Fig. 11. Dependence of ΔH_{endo} per unit sample weight on water uptake.

tendency of water molecules to form the maximum amount of hydrogen bonds among them in the available space. This type of water is called freezing bound water. As the water uptake further increases, the splitting of the melting peak becomes more apparent in the DSC curves, suggesting the existence of two states of freezing water (freezing bound and freezing water) in the hydrogels. It is already known that the freezing bound water exhibits lower melting and higher freezing temperatures than the freezing water, as stated in the three-state water model. The freezing water portion becomes more and more predominant as the hydrogels gradually approach the equilibrium water uptake [34–36].

The evaporation temperatures and weight loss of water in the samples measured by DSC and TG are given in Table 2. Both TG and DSC results show that water in chitosan derivatives has higher evaporation temperatures than that in chitosan. It could be explained by the decrease of chitosan crystallinity after grafting the hydrophobic side chains. The water molecules could penetrate inside the chitosan derivatives more easily, and have much stronger interactions with hydrophilic chitosan chains. The evaporation temperature of water in chitosan derivatives increases by about 20–50°C compared to those in chitosan.

Representative DSC heating and cooling curves for the water/chitosan systems with various water uptakes are shown in Figs. 6 and 7, respectively. Hysteresis is observed for both melting and freezing of water and there is significant depression of the freezing temperature with $\Delta T = 15$–20°C. It has been suggested that only non-freezing water exists in the polymer network up to a certain percentage of water uptake before freezing water can be detected [37]. In the water/chitosan system, the freezing or melting of water is not observed at water uptake below 24–28%, with only non-freezing water present, whereas both freezing and non-freezing water exist in the system at water uptake above 24–28%.

Figs. 8 and 9 show the corresponding DSC heating and cooling curves for sample GA/CS = 2 with various water uptakes. No peaks are recorded on heating until the water

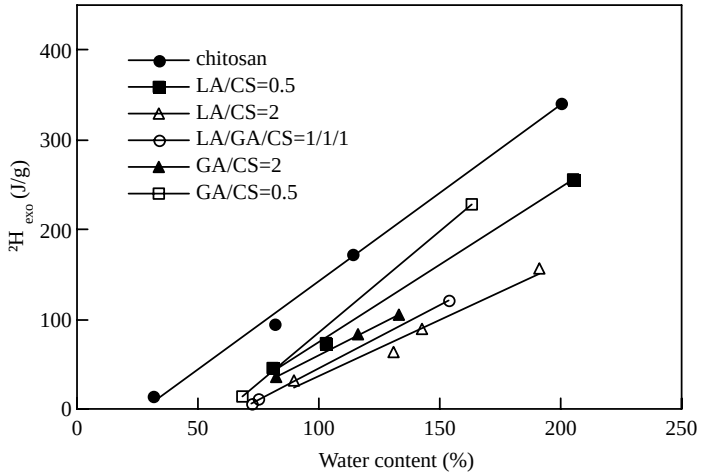


Fig. 12. Dependence of ΔH_{exo} per unit sample weight on water uptake.

Table 3
The results of linear fit in Figs. 11 and 12

Sample	Cooling process		Heating process	
	W_{NF} (%)	ΔH_{cryst} (J/g)	W_{NF} (%)	ΔH_{fusion} (J/g)
Chitosan	28.2	257.7	24.4	289.1
LA/CS = 0.5	57.4	173.2	54.6	178.0
LA/CS = 2	69.1	133.2	60.1	144.4
LA/GA/CS = 1/1/1	66.2	140.4	42.4	192.3
GA/CS = 2	56.7	139.1	33.3	201.0
GA/CS = 0.5	62.7	227.5	37.7	231.7

uptake has reached approximately 82%. The hydrogels with water uptake above 82% exhibit two endothermic peaks, suggesting the existence of two states of freezing water. The peak below 0°C corresponds to the melting of freezing bound water. The magnitude of peak above 0°C does not reach a plateau, but increases in height in proportion to the amount of water progressively added to the system. This peak corresponds to the melting of free water in the hydrogels. The trends of the cooling curves closely follow those described for the heating curves in Fig. 8, although several peaks are recorded for sample GA/CS = 2 with water uptake above 114%. The sharp peaks at −19°C correspond to the freezing of freezing bound water, while the peaks lower than −19°C correspond to the freezing of free water [38].

The formation of different states of water within a polymeric network takes place in the following order: non-freezing, freezing bound and freezing water, i.e. the freezing water is the last type of water emerging after the non-freezing and freezing bound waters have reached their final maximum contents [39,40]. However, our observations are not in accordance with this proposal, since the magnitude of freezing bound water peak in Figs. 8 and 9 increases with the water uptake from 82 to 114%, and then reaches a plateau. Meanwhile, we do not intend to compute the proportion of these peaks since most of them are not symmetric.

The heating DSC curves for chitosan and its derivatives with water uptakes in the range 70–90% are shown in Fig. 10. An endothermic peak below 0°C is recorded in both GA/CS = 2/water and LA/CS = 2/water systems. The melting peak for the chitosan/water system is significantly higher than that of the chitosan derivatives/water systems with similar water uptakes, suggesting the bound water portion in chitosan is lower than that in the other samples. The areas under the DSC peaks represent the changes in enthalpy associated with the freezing or melting of freezing water, and are plotted as a function of water uptake in Figs. 11 and 12, respectively. The slopes of the linear plots give the differential heat associated with the freezing water and the intercepts on the horizontal axis are the maximum amounts of non-freezing water (W_{NF}) in the hydrogels. The values obtained are given in Table 3.

In general, the portion of bound water of the chitosan/water system is about 25%, which is much lower than that of the other systems. The neutral chitosan film used in this study is highly crystalline as shown in Fig. 1. When the water uptake of chitosan is below 25%, water is closely associated with the amorphous regions of chitosan chains and is non-freezing. After grafting lactic acid or glycolic acid, the crystallinity of chitosan decreases and the portion of amorphous regions in chitosan increases, especially in sample LA/CS = 2, GA/CS = 2, and probably also in sample GA/LA/CS = 1/1/1. More water molecules could easily penetrate inside the polysaccharide matrix and form bound water with chitosan chains. As shown in Table 3, the ΔH_{cryst} and ΔH_{fusion} values for the chitosan/water system are around 258 and 289 J g^{-1}, which are close to those of bulk water (276 and 305 J g^{-1}, experimentally determined in this work). The values of the chitosan derivatives/water systems decreases even below 200 J g^{-1}. It means that the water molecules crystallize incompletely in these systems, and freezing bound water certainly exists in these hydrogels.

4. Conclusions

Chitosan could form pH-sensitive hydrogels by grafting glycolic acid and lactic acid. The residual amino groups of chitosan will be ionized in acidic buffers, which contributes to the electrostatic repulsion between adjacent ionized residual $-NH_2$ groups of chitosan leading to chain expansion and eventually increases the water uptake of the gels. The hydrophobic side chains will aggregate and the physical crosslinking is formed. The evaporation temperatures of water in chitosan derivatives increase by about 20–50°C compared to that in chitosan, suggesting the stronger hydrogen bonding between water and chitosan chains after grafting. Both bound water and freezing water exist in the chitosan/water system. The portion of bound water is about 25%, which is lower than that of chitosan hydrogels/water systems. Meanwhile, freezing bound water also exists in these systems except bound water and freezing water. The ΔH_{cryst} and ΔH_{fusion} decrease even below 200 J g^{-1} for chitosan hydrogels/water systems, suggesting that the water molecules crystallize incompletely in these systems, and freezing bound water certainly exists in the hydrogels.

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