
Preparation and swelling behavior of chitosan-based superporous hydrogels for gastric retention application

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Received 6 September 2004; revised 7 June 2005; accepted 8 June 2005

Published online 28 October 2005 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/jbm.a.30533

Abstract: Chitosan and glycol chitosan hydrogels were prepared, and their swelling behaviors in acidic solution were studied to investigate their application for gastric retention device. The optimum preparation condition of superporous hydrogels was obtained from the gelation and blowing kinetics measured at varying acidic conditions. Both the swelling rate and swelling ratio of glycol chitosan hydrogels were higher than those of chitosan hydrogels. Swelling behaviors were significantly affected by not only foaming/drying methods but also crosslinking density, as

the sizes and structures of pores generated were highly dependent on those preparation conditions. The prepared superporous hydrogels were highly sensitive to pH of swelling media, and showed reversible swelling and de-swelling behaviors maintaining their mechanical stability. The degradation kinetics in simulated gastric fluid was also studied. © 2005 Wiley Periodicals, Inc. *J Biomed Mater Res* 76A: 144–150, 2006

Key words: hydrogel; swelling; chitosan; foaming; pore

INTRODUCTION

A number of controlled drug delivery systems^{1–4} have been developed for prolonging and controlling the release of drugs for a period of times to enhance their curing efficiency. The drugs for oral delivery have its own convenience in easy and economic administration, but the weakness in the loss of their functions due to the short residence in the body. About 80% of drugs administrated are reported excreted without being absorbed.^{5,6} Many attempts^{7,8} have been proposed to prolong the residence time of drugs in the body for complete absorption, but not many systems have been successfully applied in practice.

Hydrogels are three-dimensional networks of hydrophilic polymers that are not soluble but swelling in water. When pores with size of hundreds of micrometers are present in the hydrogels, these are called superporous hydrogels, distinguished from other types of porous hydrogels such as microporous, mesoporous, and macroporous hydrogels.^{9–11} Because of their specific pore structures, the superporous hydro-

gels accommodate lots of water in very short time, and this high swelling kinetics led one to developing them as gastric retention devices for controlled release. When applied as drug carriers, those highly swollen hydrogels may remain in stomach for a long time, releasing almost all drugs loaded as their volumes are too big to transport through the pylorus. To be used as an effective gastric retention device, the hydrogels are required to possess not only fast swelling but also the following properties: biocompatibility, biodegradability, high swelling capacity, high mechanical strength, and stability in an acidic condition of pH 1.2.⁵ Although a number of superabsorbent polymers^{12,13} have been reported on their high swelling performance in water, those are not enough to be used as gastric retention devices as their swelling performance is poor in acidic media.

Chitosan (CS), a natural polysaccharide, is a biocompatible, biodegradable, and nontoxic material.^{14,15} Because chitosan has abundant amine groups within polymer chain, it dissolves in acidic solution and forms a gel with dialdehydes such as glutaraldehyde and glyoxal.^{16–18} Thus, in the low pH solution, chitosan hydrogels swell due to the presence of the positive charges in the network.¹⁹ Glycol chitosan is a 6-(2-hydroxyethyl)ether derivative of chitosan and dissolves much more in water than chitosan.^{18,20} In this study, glycol chitosan (GCS) superporous hydrogels were developed using glyoxal as a crosslinking agent. Both freeze drying and gas blowing

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Contract grant sponsor: Korean Research Foundation funded by the Korean government (MOEHRD); contract grant number: KRF-2005-005-D00064

techniques were used for the preparation of superporous hydrogels. Swelling properties of superporous hydrogels prepared were measured and analyzed to test the possibility of their application for a gastric retention device.

MATERIALS AND METHODS

Materials

Chitosan was purchased from Fluka (St. Gallen, Switzerland) and glycol chitosan (DP 2500) from Aldrich-Sigma Chemical Company (Milwaukee, WI). Glyoxal (40% water solution, Aldrich) was used as a crosslinking agent and NaHCO_3 (Aldrich) as a gas blowing agent. Acetic acid, a pH controlling agent, was purchased from Daejung Chemical Company (Japan).

Synthesis of hydrogels

Both chitosan and glycol chitosan hydrogels as shown in Figure 1 were prepared. To prepare each stock solution of 2 wt %, chitosan and glycol chitosan were dissolved in 0.1M acetic acid and distilled water, respectively. The amount of 5 g of stock solution was placed in a test tube (ID = 2 cm), and then 10 wt % glyoxal aqueous solution was added to induce network structures where the crosslinking ratios ranged from 1 to 8 wt %. After the gelation reaction (Schiff base reaction) as shown in Figure 2 was conducted for 12 h, the hydrogels were completely dried in a freeze drier for at least 24 h.

To prepare superporous hydrogels by a gas blowing method, the pH of glycol chitosan stock solution was adjusted to 5 by adding acetic acid. NaHCO_3 powder (40 mg), a blowing agent, was added to the stock solution and the mixture was vigorously stirred for 10 to 30 s. Foaming started immediately after the addition of blowing agent, and the gelation was completed in 30 s to 2 min. The foamed hydrogels were placed at room temperature overnight, and then dried using a freeze drier.

Swelling experiments

The hydrogels prepared were allowed to swell in the acidic solutions at 37°C. The samples swollen in the acidic media were periodically weighed until no weight increase was observed. The swelling capacity of the hydrogels was determined by swelling ratio (Q) calculated according to Equation (1):

$$Q = W_t / W_0 \quad (1)$$

Here, W_0 and W_t are weights of dried and swollen samples at the initial and arbitrary time, respectively.

Degradation kinetics

The degradation kinetics of the prepared hydrogels was examined measuring swelling ratio and weight loss (%). The

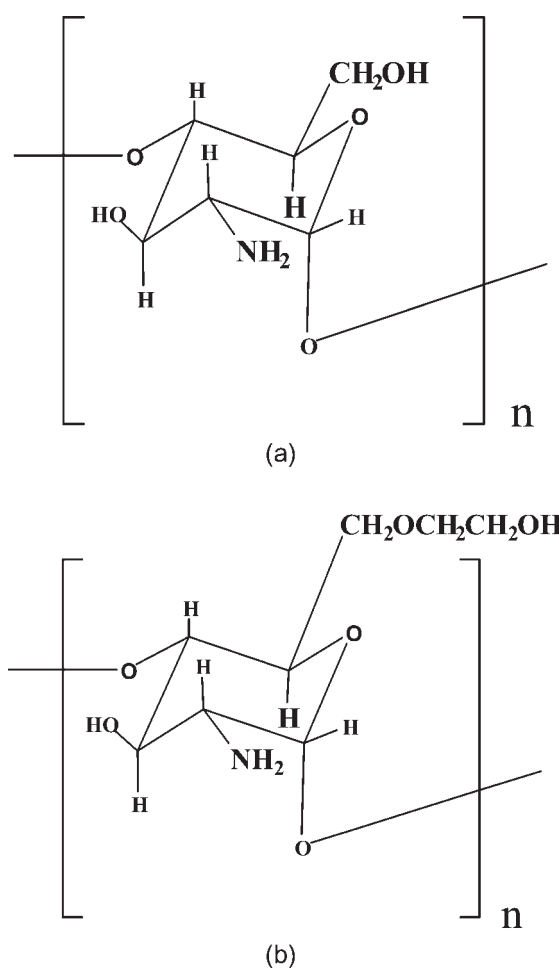


Figure 1. Chemical structure of (a) chitosan and (b) glycol chitosan.

hydrogels were placed in pH 1.2 solution at 37°C for 12 h, and then the samples were periodically weighed at 6 h interval. The percentage weight loss of the sample was determined by the percentage ratio of weight loss to initial weight in swollen state.

Pore structure and size

The structure and size of pores in hydrogels prepared were examined using the scanning electron microscopy (ESEM, XL-30, Philips, Netherlands). Before taking the photographs, the samples were quenched and fractured in liquid nitrogen, and the fractured surface was palladium coated using an ion coater (IB-3, Eiko, Japan).

RESULTS AND DISCUSSION

Preparation conditions of superporous hydrogels

Foaming and gelation reactions should take place simultaneously to obtain well-established porous

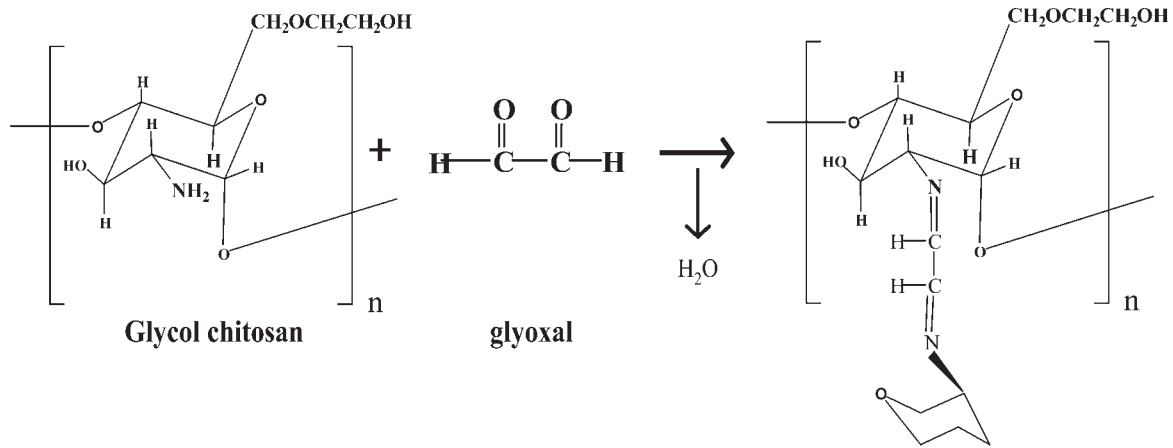


Figure 2. Schematic of the synthesis of glycol chitosan hydrogel using glyoxal as a crosslinking agent.

structures. Figure 3 shows the gelation induction time, the duration time from the addition of crosslinking agent to the start of gelation, as a function of pH values of reactant system. The gelation reaction took place only at the pHs higher than 6, and the fastest reaction was observed at pH 7. When gelation times are not short enough, bubbles are not stabilized but collapsed during gelation reaction. On the other hand, the foaming reaction took place only at the acidic conditions (pH lower than 6). As NaHCO_3 is decomposed to release CO_2 gas in acidic conditions and this decomposition reaction neutralizes the medium (increases the pH), the addition of certain amount of NaHCO_3 eventually induced the gelation reactions at medium pH. Figure 4 shows the amount of blowing agent to adjust the stock solution to pH 7, the fastest (optimum) gelation condition, in this study. The appropriate amount of blowing agent was determined at different the acidic conditions of stock solution to adjust its pH to 7.

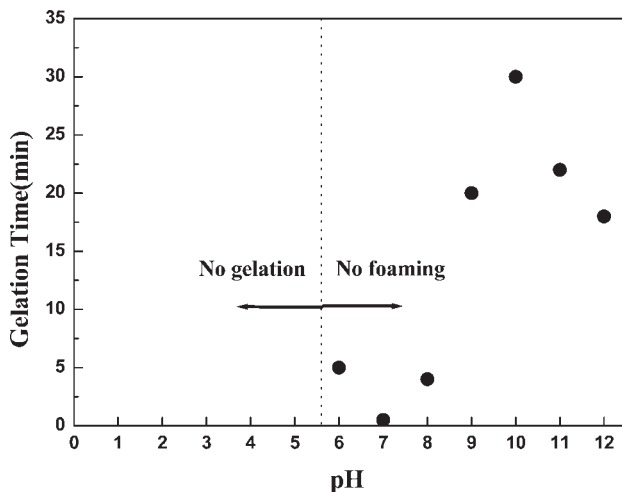


Figure 3. Gelation completion times at varying pH conditions of monomer stock solutions.

Swelling behaviors of chitosan and glycol chitosan hydrogels

Swelling behavior of chitosan hydrogels prepared by freeze drying method was compared with that of glycol chitosan by the same method. Figure 5(a,b) show the equilibrium and dynamic swelling behaviors of the two systems in distilled water and simulated gastric fluid of pH 1.2, respectively. For both cases, the swelling rate and equilibrium swelling amount of glycol chitosan hydrogels were higher than those of chitosan hydrogels, simply because the glycol chitosan is more hydrophilic than chitosan due to the presence of glycol groups. In acidic environment, both the chitosan and glycol chitosan hydrogels showed higher swelling ratio than in distilled water. It was because the amine groups in the chitosan molecules are ionized to ammonium ion (NH_3^+) in acidic aqueous media and these cationic charges in gel phase act as cationic repulsive forces between polymer molecules.

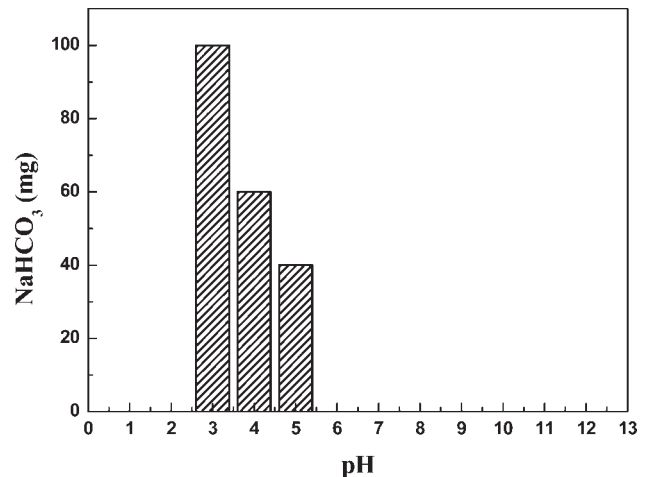


Figure 4. Amounts of blowing agent added to adjust the pH of stock solution to 7.

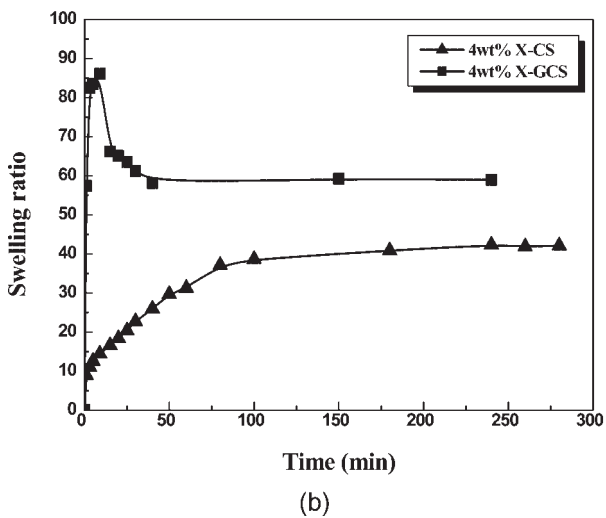
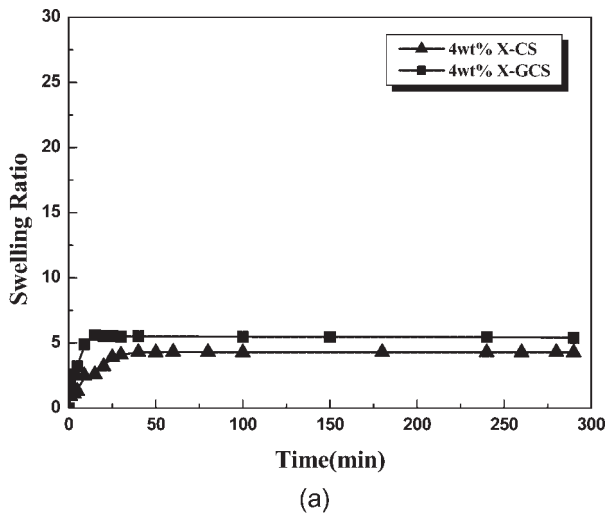


Figure 5. Swelling behaviors of chitosan and glycol chitosan hydrogels in (a) distilled water and (b) SGF, respectively.

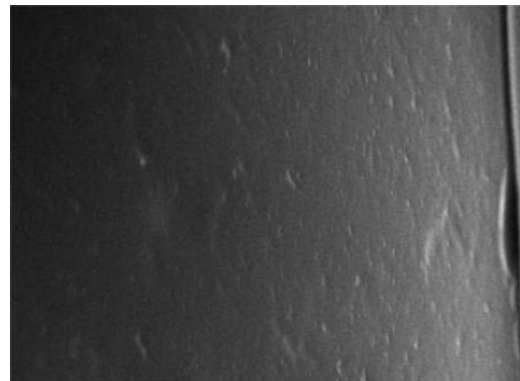
Effect of drying method on the swelling behavior

Figure 6 shows the SEM microphotographs of hydrogels dried by different methods: air drying and freeze drying. The hydrogels prepared by freeze-drying method possessed numerous pores in dried states, while air-dried hydrogels did not. The pore sizes of superporous hydrogels shown in Figure 6(c) were even larger than those of freeze-dried hydrogels as the pores were generated not only by evaporation of solvent but also by blowing of bubbles. Different pore size and porosity of hydrogels led to different dynamic and equilibrium swelling behaviors. As the pores of freeze-dried samples are connected each other, they have higher swelling rate than air-dried samples. As the pore size of superporous hydrogels (freeze-dried/gas-blown hydrogels) was even larger than that of freeze-dried hydrogels, the equilibrium swelling ratios of the first samples were higher than

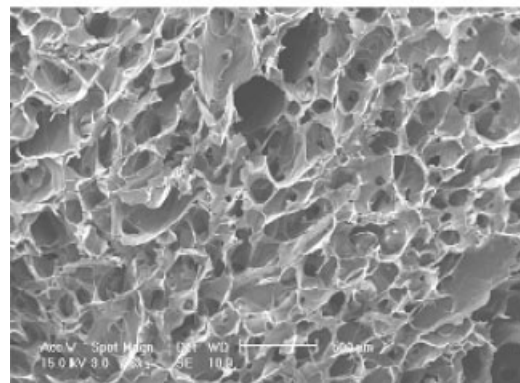
the last ones. The blowing effect was negligible for the air-dried samples, as the bubbles generated were easily collapsed during drying process in air (refer to Fig. 7).

Effect of crosslinking density on the swelling behaviors

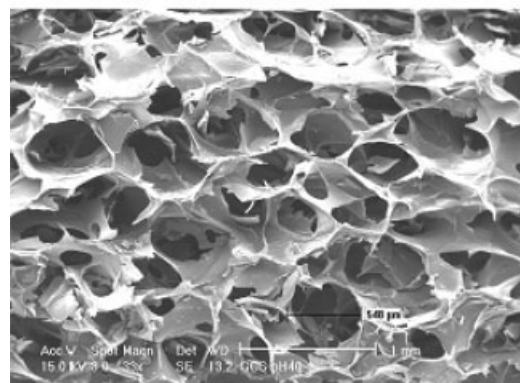
Figure 8 shows the crosslinking density effect on the swelling behavior of superporous hydrogels in simu-



(a)



(b)



(c)

Figure 6. SEM photographs of hydrogels prepared by different drying methods: (a) air drying, (b) freeze drying, and (c) gas blowing and freeze drying, respectively.

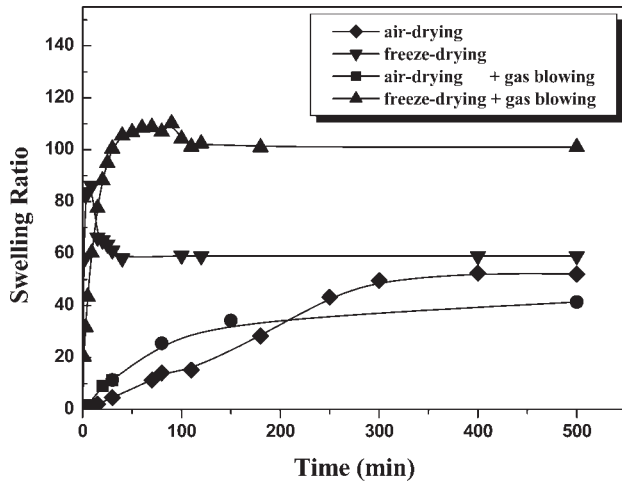


Figure 7. Swelling behaviors of hydrogels prepared by different drying methods: (a) air drying, (b) freeze drying, and (c) gas blowing and freeze drying, respectively.

lated gastric fluid (SGF). The superporous hydrogels crosslinked with 1 and 2 wt % glyoxal were mechanically so weak that the samples were cracked during the swelling process. For this reason, the suitable amounts of crosslinking agent in this study were higher than 2 wt %. At the crosslinking ratios higher than 2 wt %, the swelling ratios of superporous hydrogels decreased with increasing crosslinking density, as much tighter networks were formed at higher concentration of crosslinking agents.

This swelling behavior was complimented by SEM microphotographs, shown in Figure 9. Smaller pores were observed for more crosslinked superporous hydrogels. At 2 wt % crosslinking ratio, the pores were so large that the samples might not have enough strength to absorb lots of water in short time. The presence of larger pores in less crosslinked hydrogels

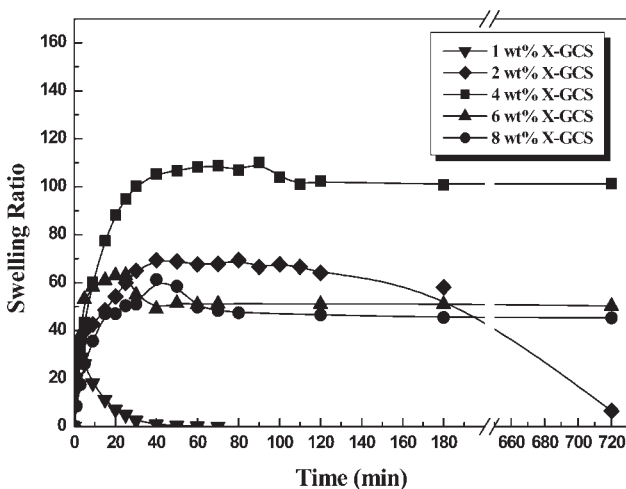
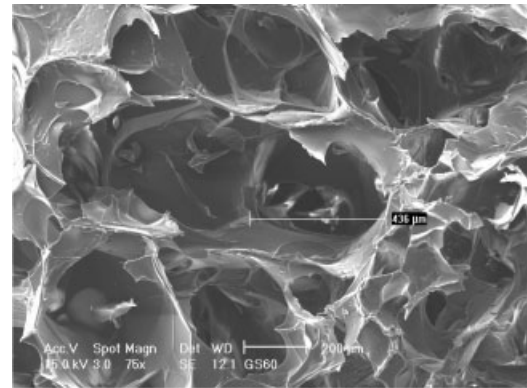
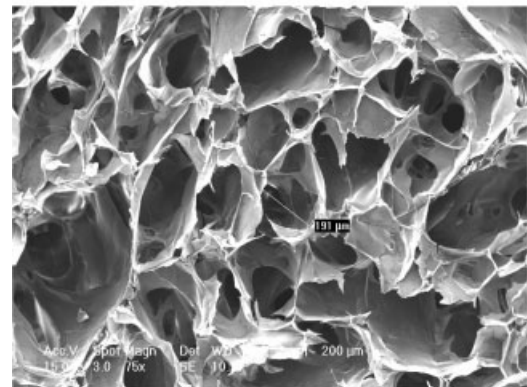


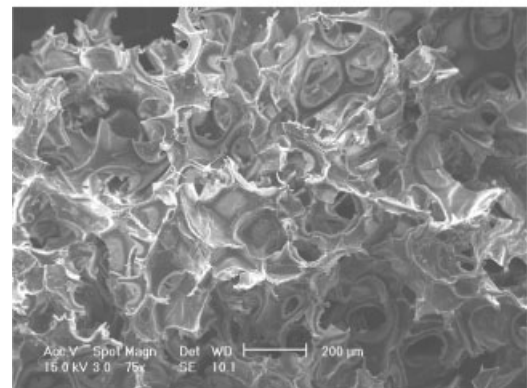
Figure 8. Crosslinking density effect on the dynamic swelling behaviors of glycol chitosan superporous hydrogels.



(a)



(b)



(c)

Figure 9. SEM photographs of superporous hydrogels prepared with different concentrations of crosslinking agent of (a) 4, (b) 6, and (c) 8 wt %, respectively.

is another factor resulting in a high swelling ratio as well as high swelling kinetics.

The glycol chitosan superporous hydrogels showed clear pH sensitive swelling behavior. As shown in Figure 10, higher swelling ratios were observed at lower pHs, for example, a higher acidic condition, as the amine groups in polymer molecules are much more easily cationized at higher acidity. For all pH environments, the crosslinking density effect on the swelling behavior was similar to the previous results.

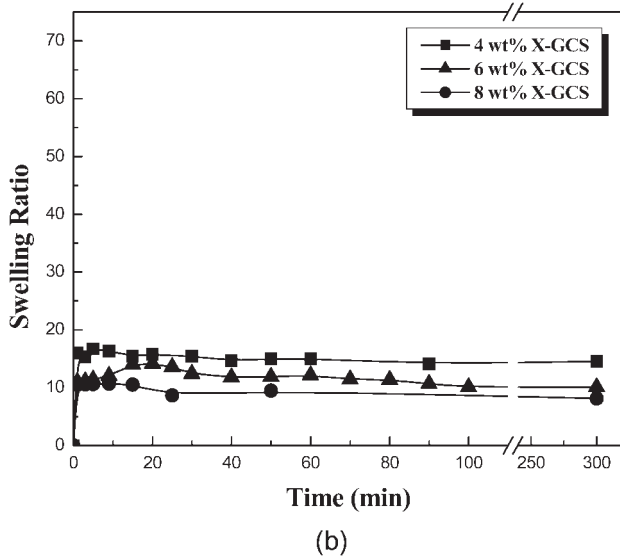
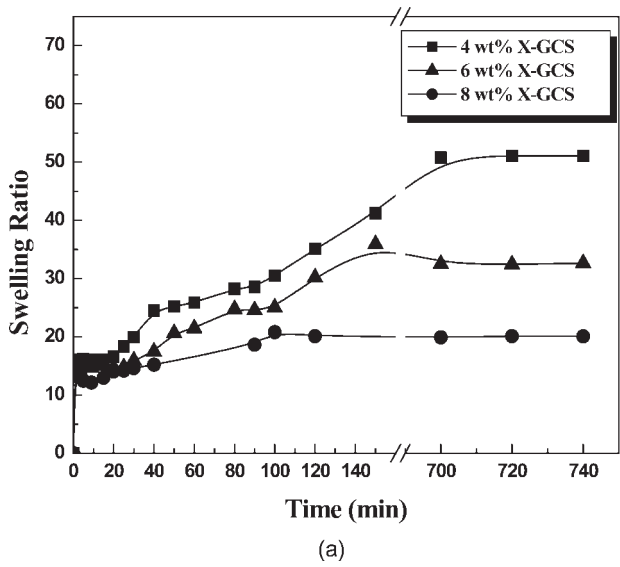


Figure 10. Swelling behaviors of glycol chitosan superporous hydrogels with 4, 6, and 8 wt % crosslinking ratio in (a) pH 4.0 and (b) pH 7.0 solution, respectively.

Figure 11 shows the swelling and de-swelling behaviors of superporous hydrogel. The hydrogel was swollen and de-swollen reversibly depending on the pH conditions of media. Highly pH sensitive swelling behaviors maintaining mechanical stability were clearly observed.

Degradation kinetics of superporous hydrogels

As shown in Figure 12, the weight loss of glycol chitosan hydrogels occurred after 12 h. In acidic environment, superporous hydrogels kept equilibrium swelling ratios for a certain period of time, being protonated as ammonium ions. D-Glucosidic linkages

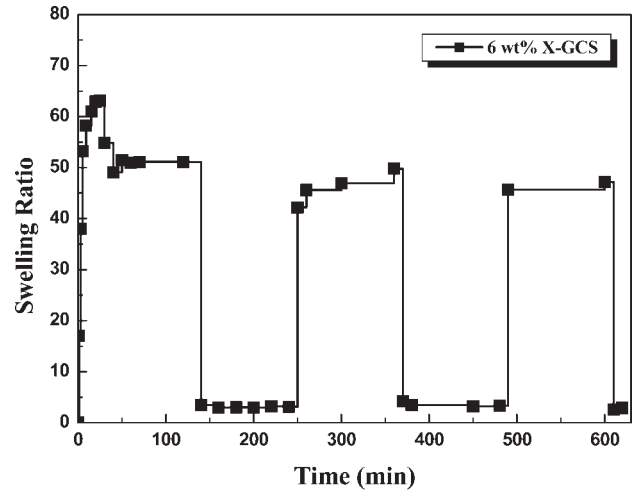


Figure 11. Swelling and de-swelling behaviors of glycol chitosan superporous hydrogels (crosslinking ratio of 6) in different acidic swelling media.

in glycol chitosan were slowly cleaved by acid hydrolysis. As amine groups stabilize D-glucosidic linkages cleaved by acids, a part of glycol chitosan oligomers, especially not highly crosslinked, were slowly dissolved in the swelling media, inducing the weight loss of samples.

CONCLUSION

The optimum gelation and blowing conditions for the preparation of superporous hydrogels were obtained by determining the amount of blowing agent needed to adjust the pH of a stock solution for fastest gelation. The swelling behaviors of chitosan and glycol chitosan were compared in an acidic environment. Both the swelling rate and swelling ratio of glycol

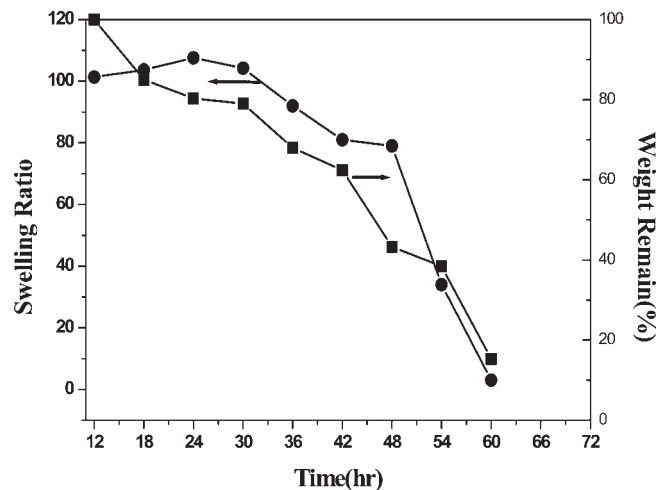


Figure 12. Degradation kinetics of glycol chitosan superporous hydrogels (crosslinking ratio of 4) in SGF.

chitosan hydrogels were higher than those of chitosan hydrogels because of the presence of highly hydrophilic groups, glycols in glycol chitosan. In acidic environment both the chitosan and glycol chitosan hydrogels showed higher swelling ratio than in distilled water because of the cationization of amine groups in acidic condition. At crosslinking ratios higher than 2 wt %, the swelling ratios of superporous hydrogels decreased with increasing crosslinking density, as not only much tighter networks but also much smaller pores were formed at higher concentration of crosslinking agents. The hydrogels were swollen and de-swollen reversibly, depending on the acidity of media. The degradation kinetics investigated in this study will be another important aspect for applying the present materials to a gastric retention device.

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