Preparation of Poly(ethylene glycol)/Chitosan Membranes by a Glucose-Mediating Process and *In Vitro* Drug Release

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ABSTRACT: Novel pH-dependent chitosan/poly(ethylene glycol) (PEG) membranes were developed for oral drug delivery. The preparation of these membranes involved a solution-mediating process with glucose addition at different pHs. Fourier transform infrared/attenuated total reflectance showed that the Schiff-base reaction was favored at high pHs and high glucose concentrations. X-ray diffraction analysis showed a continuous increase in the glucose addition transformed the chitosan/PEG samples into amorphous polymers. The equilibrium swelling measurements showed that the swelling ratio of the solution-mediated membranes decreased as the glucose concentration increased, and this was demonstrated by degree-of-mediation analysis. The glucose-mediated membranes had different degrees of mediation, which depended on the pH and glucose concentration. The *in vitro* release profiles of theophylline-loaded, pH 6 treated, glucose-mediated membranes showed that the theophylline release decreased as the glucose concentration increased. Also, the release behavior of the theophylline from the glucose-mediated membranes varied with the pH of the release medium, the glucose concentration, and the final pH of the glucose-mediated chitosan/PEG gels. Chitosan/PEG membranes prepared by a basic glucose-mediated process could lead to successful applications in localized drug delivery to the intestine. © 2005 Wiley Periodicals, Inc. J Appl Polym Sci 96: 1083–1094, 2005

Key words: biodegradable; chitosan; drug delivery systems; swelling

INTRODUCTION

Chitosan, a typical biological macromolecule derived from the cuticles of marine crustaceans such as crabs and shrimp, is made of glucosamine and *N*-actyl glucosamine units linked by 1-4 glycosidic bonds. Recently, chitosan has been used in biomedicine because of its favorable characteristics, such as good biocompatibility, and it has been reported to be useful for pharmaceutical preparation.[1]

Chitosan films are usually prepared by chemical crosslinking with glutaraldehyde and so forth.[2,3] These films swell under acidic conditions because of the ionization of amino groups but remain in a shrunken state under a neutral condition. Moreover, chitosan has been reported to prolong the retention of the dosage form in the stomach. Therefore, chitosan films and other dosage forms have been exploited for sustained oral drug delivery in the stomach.[4] The main disadvantages of chitosan in drug-delivery systems are that it is only soluble in dilute acetic acid and has low mechanical properties and its physical properties are highly dependent on the pH. Therefore, it is difficult to control drug-release behavior because of the various pHs of the internal organs of the human body, and it may have negative effects in the human body because of the over-release of drugs.

To improve the hydrophilic character of chitosan derivatives, researchers have blended hydrophilic polymers such as poly(vinyl alcohol) and poly(ethylene glycol) (PEG).[5] PEG has been widely used as a pharmacological product because of its hydrophilicity, biocompatibility, and low biodegradability. Jiang and Han[6] indicated that chitosan/PEG blends are compatible and have attractive intermolecular interactions at various PEG 6000 concentrations. Therefore, applying a suitable amount of PEG would increase the biocompatibility or solubility with tissue.

To improve the mechanical properties of chitosan/PEG blend films, a stabilizer is necessary. However, chemical crosslinking agents may induce toxicity and other undesirable effects. The use of a reduced sugar, such as fructose or glucose, that has aldehydes in the end group as a stabilizer has been developed by our group.[7] The reaction between amino groups and aldehyde groups[8] involves the formation of a Schiff base,

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which is accompanied by color formation; it is called the Maillard reaction. However, the reactivity and stability of the Maillard reaction end product are greatly influenced by the pH of the reaction system. The open-chain form of the sugar and the unprotonated form of the amino groups are favored at higher pHs, but the stability of the end products is still a controversial issue.

Therefore, we studied drug-release behavior with glucose-mediated chitosan/PEG membranes containing theophylline as a model drug at pH 1.2 (stomach) and pH 6.8 (intestine) *in vitro*. The properties of the chitosan and glucose-mediated chitosan/PEG membranes were investigated with Fourier transform infrared/attenuated total reflectance (FTIR–ATR), equilibrium swelling studies, X-ray diffraction (XRD) analysis, degree-of-mediation analyses, *in vitro* drug-release studies, and scanning electron microscopy (SEM).

EXPERIMENTAL

Materials

High-molecular-weight chitosan (degree of deacetylation = 86%, weight-average molecular weight $\sim 4 \times 10^5$) was obtained in a flake form from Fluka (Buchs, Switzerland). PEG (number-average molecular weight = 6000) was purchased from Riedel-de Haen (Seelze, Germany). Anhydrous dextrose was used as a mediating agent and was supplied by J.T. Baker, Inc (Phillipsburgh, NJ). All other reagents were extra-pure-grade and were used as received.

Preparation of the glucose-mediated chitosan/PEG membranes

A chitosan solution with a concentration of 3 wt % was prepared by dissolution in 2 wt % acetic acid. The mixture was stirred for 4 h to obtain a perfectly transparent solution. A chitosan/PEG blend solution was prepared by the mechanical stirring of the filtered chitosan and PEG flakes in a 70:30 ratio at room temperature. The glucose-mediated chitosan/PEG solution was prepared by the mixing of 3, 5, and 10 wt % glucose with the chitosan/PEG solution. The final pH value of the glucose-mediated chitosan/PEG solution was adjusted to 3 by 0.5*M* sulfuric acid and to 6 by 1*M* sodium hydroxide. Then, the glucose-mediated chitosan/PEG solution was thermally treated at 120°C in an oven for 1 h. The film of the resulting polymer blend was obtained via casting into a polystyrene Petri dish and incubation for 2 days in an oven at 68°C. The membrane was neutralized with 10% (w/v) sodium hydroxide, and this was followed by rinsing with deionized distilled water (DDW) and drying at room temperature overnight; it was then cut into 2 mm × 2 mm squares.

Preparation of the drug-loaded, glucose-mediated membranes

A glucose-mediated chitosan/PEG membrane containing a model drug (theophylline; 10 mg) was prepared through the mixing of glucose-mediated chitosan/PEG solutions of various pH values with theophylline in 2% (w/v) acetic acid. The solution (10 mL) was sonicated, left to stand until trapped air bubbles were removed, poured onto a polystyrene Petri dish, and incubated for 2 days in an oven at 68°C. The final drug-loaded, glucose-mediated membrane was stored in a desiccator for characterization.

Extent of the mediation of chitosan/PEG with a pH-treated solution

The primary amine content of mediated and nonmediated membranes, expressed as the mediated percentage of free amino groups in the treated membranes with respect to the nonmediated membrane, was determined with 2,4,6-trinitrobenzenesulfonic acid as a reaction solution, as described by Sheu et al.[9] The resulting solution was diluted with 5 mL of DDW, and the absorbance was measured at 345 nm. The degree of mediation was calculated as follows:

$$\text{Extent of mediation} = 1 - \frac{\text{Absorbance}_{mc}/\text{Mass}_{mc}}{\text{Absorbance}_{nmc}/\text{Mass}_{nmc}} \quad (1)$$

where the subscripts mc and nmc represent the mediated chitosan/PEG membrane and nonmediated chitosan/PEG, respectively.

FTIR–ATR spectroscopy analysis

FTIR–ATR spectra of the films were measured with a Thermo Nicolet Nexus 470 Fourier transform infrared (FTIR) spectrometer (San Diego, CA) to determine the chemical interactions between glucose and chitosan/PEG. The pH-treated, glucose-mediated chitosan/PEG membranes were dried *in vacuo* at 40°C for 24 h before the IR test.

XRD analysis

The XRD measurements of pH-treated, glucose-mediated membranes were carried out with Ni-filtered Cu Kα-radiation on a Rigaku D/max3 Vx X-ray diffractometer (Tokyo, Japan) operating at 30 kV and 30 mA from 10 to 30° (2θ) at a scanning rate of 4° (2θ)/min.

SEM observations

The surface morphology of chitosan, chitosan/PEG, and pH-treated, glucose-mediated chitosan/PEG membranes was observed with a JEOL 5120 scanning

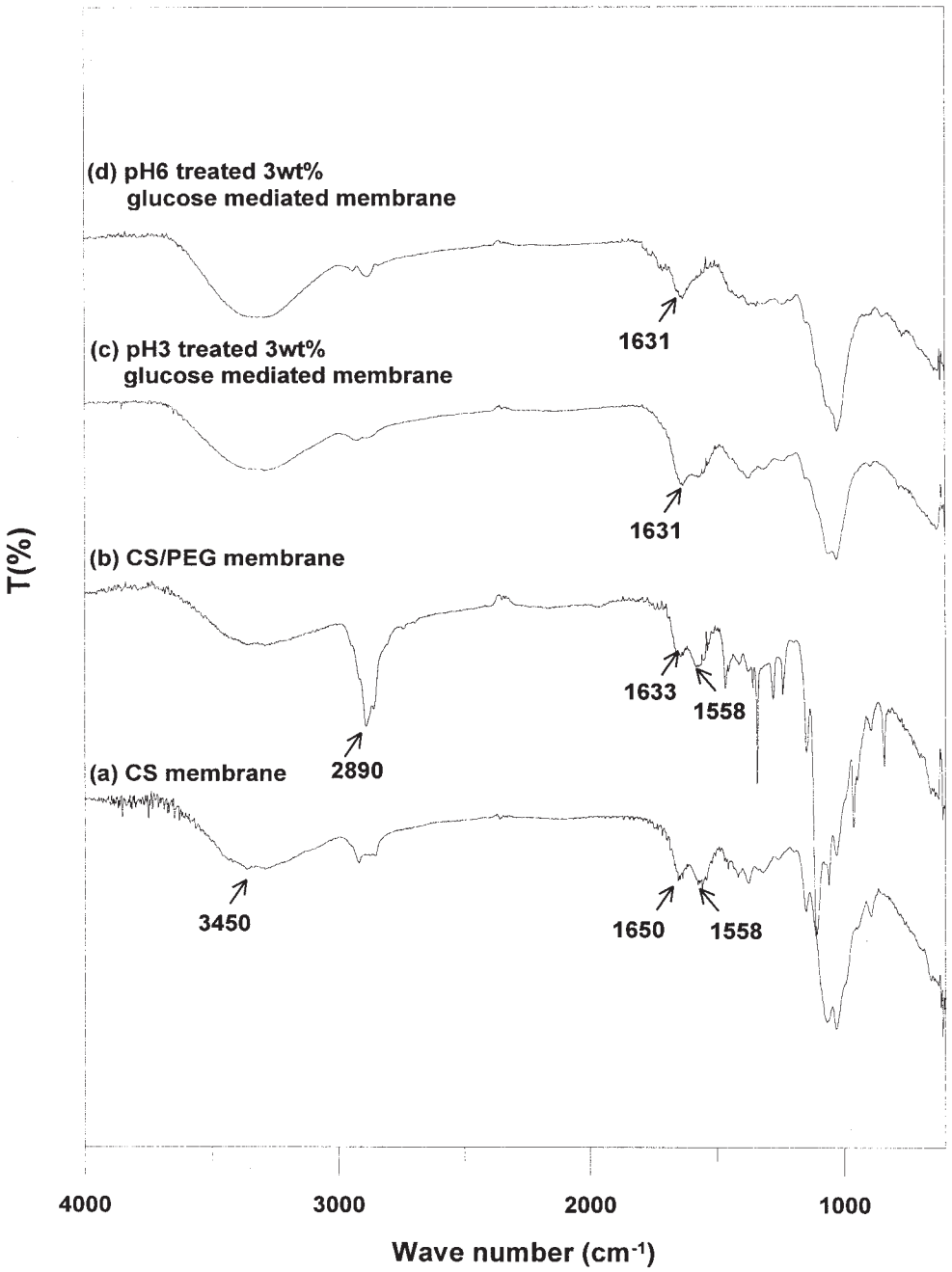

Figure 1 FTIR–ATR spectra: (a) chitosan (CS); (b) CS/PEG; (c) a pH 3 treated, 3 wt % glucose-mediated membrane; and (d) a pH 6 treated, 3 wt % glucose-mediated membrane (T = transmittance).

electron microscope (Tokyo, Japan) at 25 kV. The platinum-coated membrane surfaces were prepared under an argon atmosphere.

Equilibrium swelling studies

The chitosan, chitosan/PEG, and glucose-mediated membrane were equilibrated overnight in 0.1*N* HCl (pH 1.2) and a 0.1*M* phosphate buffer solution (pH 7.4). The samples were washed quickly with tissue to remove excess surface water, were weighed immediately in a microbalance, were placed in a large volume of deionized water to remove the buffer solution, and were dried in a vacuum oven at 30°C for 24 h. The degree of swelling (S) for each sample at time t was calculated as follows:

$$S = \frac{W_t - W_0}{W_0} \tag{2}$$

where W_t and W_0 are the weights of the membrane at time t and in the dry state, respectively. The measure-

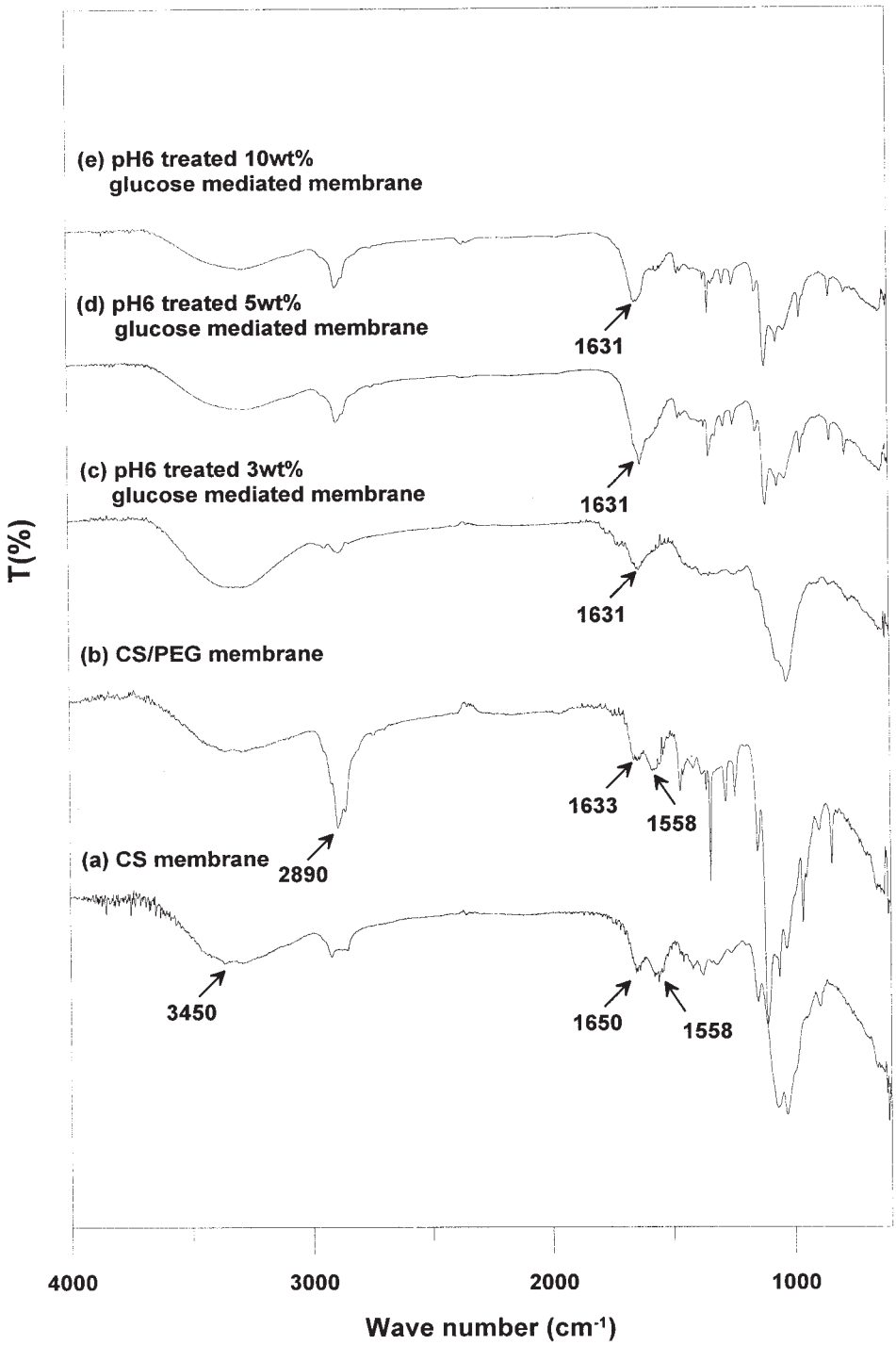

Figure 2 FTIR–ATR spectra: (a) chitosan (CS); (b) CS/PEG; (c) a pH 3 treated, 3 wt % glucose-mediated membrane; (d) a pH 3 treated, 5 wt % glucose-mediated membrane; and (e) a pH 3 treated, 10 wt % glucose-mediated membrane (T = transmittance).

ment was repeated several times to obtain an average value of S for each sample.

In vitro drug-release studies

The *in vitro* release of the entrapped drug theophylline was carried out by the placement of membranes loaded with the drug in 200 mL of an enzyme-free (pH 1.2 or 6.8) phosphate-buffered saline (PBS) buffer solution at 37°C in a water bath incubator with rotating motion (300 rpm). At periodic intervals, 3-mL aliquots were withdrawn and tested at a maximum wavelength of 271 for theophylline with a PerkinElmer Lambda 5 ultraviolet–visible spectrophotometer

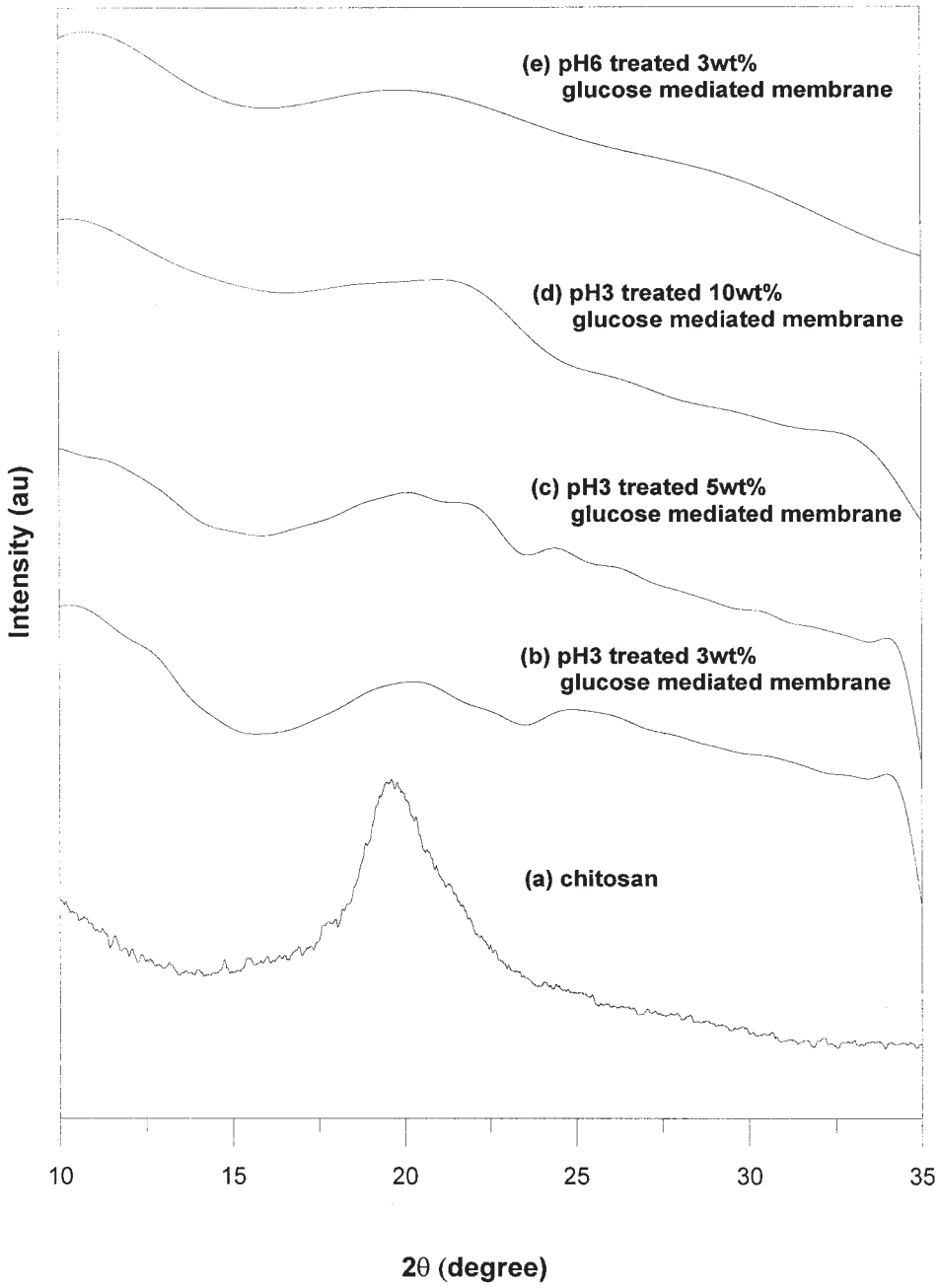

Figure 3 XRD patterns: (a) chitosan; (b) a pH 3 treated, 3 wt % glucose-mediated membrane; (c) a pH 3 treated, 5 wt % glucose-mediated membrane; (d) a pH 3 treated, 10 wt % glucose-mediated membrane; and (e) a pH 6 treated, 3 wt % glucose-mediated membrane.

(Wellesley, MA) for 48 h. The release media were replaced periodically with an equal volume of fresh medium to create an infinite sink condition. The data represent the means and standard deviations from three independent experiments.

RESULTS AND DISCUSSION

FTIR–ATR spectra

To examine the interaction between chitosan/PEG and glucose at different pHs, FTIR spectroscopy in combination with the attenuated total reflectance technique was applied. This analytical method has been demonstrated to be a useful tool for detecting changes in particular functional groups in a polymer molecule.[10] In a preliminary study,[11] we demonstrated by FTIR analysis that glucose could reactivate a chitosan/PEG gel solution and form a Schiff-base product with C═N in the structure. Figure 1 shows the FTIR–ATR spectra of chitosan and pH 3 and 6 treated, 3 wt % glucose-mediated membranes. The spectrum of the chitosan film shows absorptions around 1650 and 1558

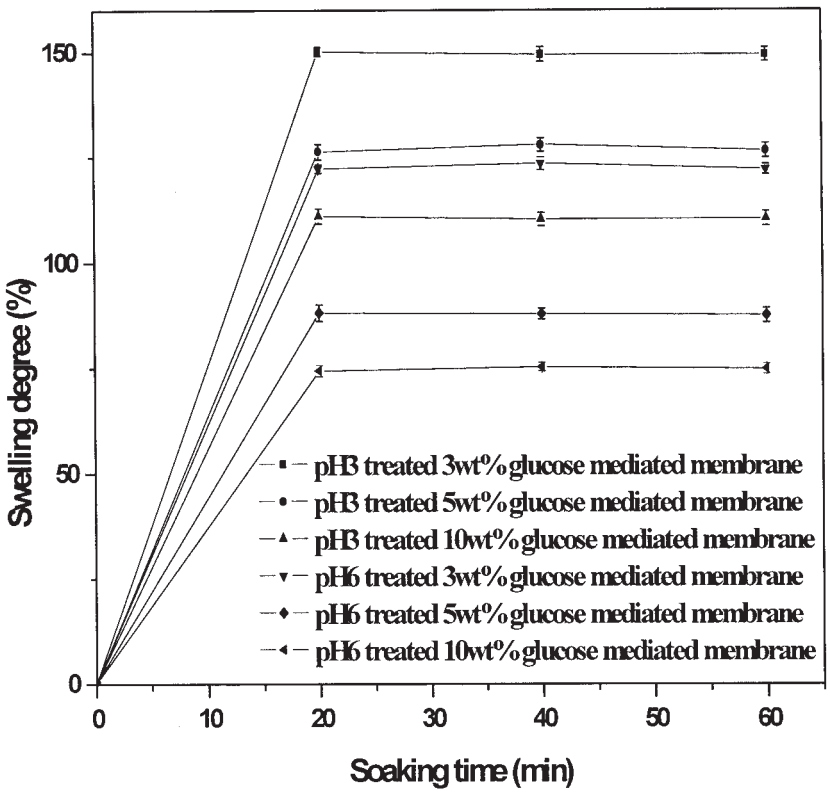

Figure 4 Swelling ratios of glucose-mediated chitosan/PEG membranes as a function of the glucose concentration in an acidic environment (0.1*N* HCl) at different pHs (3 and 6).

cm^{-1}, which represent the amide I and amide II bands, respectively. A broad band appearing at approximately 3310–3450 cm^{-1} corresponds to associated OH stretching vibrations of hydroxyl groups. A relatively high and intense peak at 2890 cm^{-1} corresponds to an aliphatic C—H in the chitosan/PEG membrane. The 843-, 1280-, and 963-cm^{-1} peaks are contributions from the crystalline region in PEG. There are only slight differences between the chitosan/PEG and pH 3 treated, 3 wt % glucose-mediated chitosan/PEG membrane spectra, except that the peak at 1650 cm^{-1} moves to a lower wave number (1633 cm^{-1}) and the absorbance at 1558 cm^{-1} decreases, as shown in Figure 1(c). In contrast to Figure 1(c,d) (pH 6 treated, glucose-mediated membrane), a significant peak at 1631 cm^{-1} and the disappearance of peaks at 1558 cm^{-1} in the spectra are due to the formation of C═N, and this is because of the imine reaction between the amino groups from chitosan and aldehyde groups in glucose. This also implies that the reaction between chitosan and glucose was favored by a pH 6 environment. This result was similar to that of chitosan crosslinking with glutaraldehyde.[12] The effects of the glucose concentration on chitosan/PEG are shown in Figure 2. With increasing glucose concentration, the peak corresponding to 1631 cm^{-1} gradually becomes sharper because of the formation of more imines groups. This implies that as the glucose concentration increased, more aldehyde groups of glucose in a linear form resulted in more Schiff-base product.

TABLE I
Degree of Mediation (%) of Chitosan/PEG with Different Glucose Concentrations and Mediation Conditions

Concentration of glucose (wt %)	Mediation condition[a]	
	pH 3	pH 6
3	67.16 ± 1.22	71.49 ± 1.52
5	86.21 ± 1.41	87.32 ± 1.27
10	92.55 ± 1.12	98.46 ± 1.13

[a] The data represent the means and standard deviations from three independent experiments.

XRD analysis

The crystallinity was studied with XRD. Figure 3 shows the XRD patterns of chitosan and different pH-treated, glucose-mediated membranes. In Figure 3, the XRD pattern of a chitosan sample shows a characteristic peak at $2\theta = 20°$ caused by the presence of (001) and (002). For pH 3 and pH 6 treated, glucose-mediated membranes, the peak at $2\theta - 20°$ disappeared or decreased. The decrease in the crystallinity of the glu-

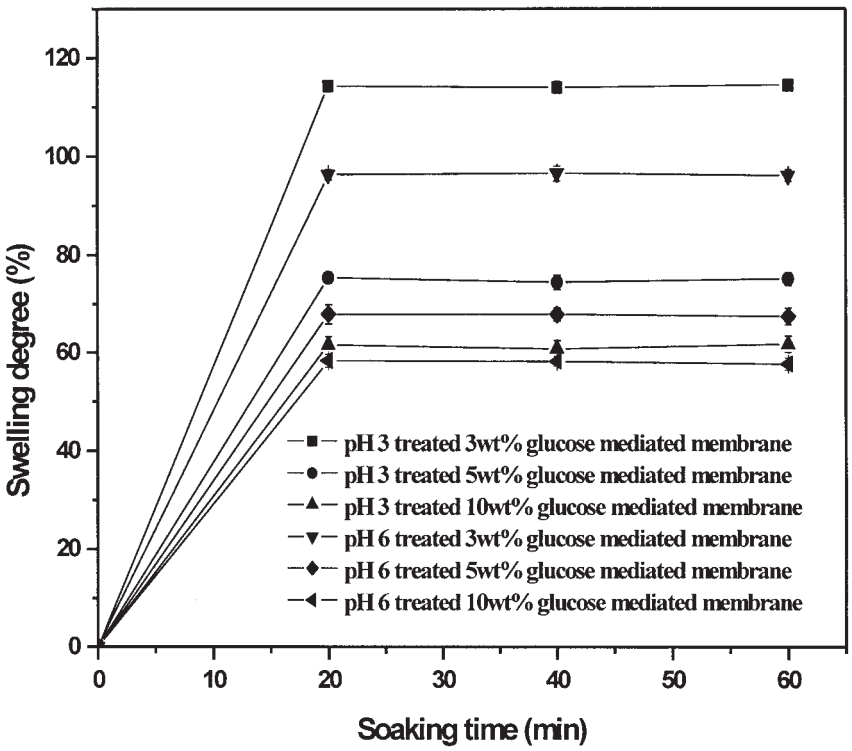

Figure 5 Swelling ratios of glucose-mediated chitosan/PEG polyblends as a function of the glucose concentration in PBS solutions (pH 7.4) at different pHs (3 and 6).

cose-mediated membranes could be attributed to the deformation of strong hydrogen bonds in the chitosan backbone as amino groups reacted with the aldehyde groups of glucose in a linear form. Otherwise, the main peak ($2\theta = 20°$) in the pH 3 treated, glucose-mediated membrane lost its prominence and gradually shifted to the high angle as the glucose concentration increased. This result was similar to that of Claudio et al.'s[13] study about chitosan crosslinking with glutaraldehyde. It suggested that the crystal structure of the glucose-mediated membrane was more distorted because more aldehyde groups were present at high glucose concentrations. In comparison with the crystal structure of the pH 6 and pH 3 treated, 3 wt % glucose-mediated membranes, the broadening of the chitosan diffraction main peak was mainly due to more active glucose in a linear form at a high pH. In addition, for the pH 3 and pH 6 treated, glucose-mediated membranes, the diffractograms did not show any other peak, as illustrated in Figure 3. Thus, in this process, a continuous increase in the glucose addition transformed the chitosan/PEG samples into amorphous polymers.[14]

Swelling studies

The chitosan and chitosan/PEG membranes rapidly dissolved in 0.1*N* HCl (pH 1.2) in 20 min because of the protonation of NH_2 groups of chitosan and hydroxyl groups of PEG. Through the addition of glucose at different pHs, the chitosan/PEG polyblends were expected to reduce the number of —NH_2 groups of chitosan and hence reduce the solubility at pH 1.2. The swelling behavior, as a function of the glucose concentration in pH 1.2 environments, of glucose-mediated chitosan/PEG membranes prepared at different pHs (with a final solution pH of 3 or 6) is shown in Figure 4. Interestingly, as the glucose concentration increased, the swelling degree of the pH 3 treated, glucose-mediated membrane slightly decreased from 149.41 to 118.32% in a pH 1.2 environment, as shown in Figure 4. The result was demonstrated by measurements of the degree of mediation, as shown in Table I; there was a small increase in the degree of mediation as the glucose concentration increased. Moreover, when the glucose concentration was higher than 5 wt %, the degree of mediation of the membrane slightly decreased. This implied that when the glucose concentration was greater than 5 wt %, the Schiff-base reaction product reached the maximum value under the pH 3 reaction condition. According to Lee et al.,[15] the amino groups in chitosan and sulfate ions have a Coulombic interaction, and so they crosslink the chitosan main chain ionically. Guo et al.[16] prepared a sclerox–chitosan cogel, also indicating that the polyelectrolyte complex formation could compete with Schiff-base formation at a lower pH condition. In our study, the low pH value of the mixed chitosan/PEG

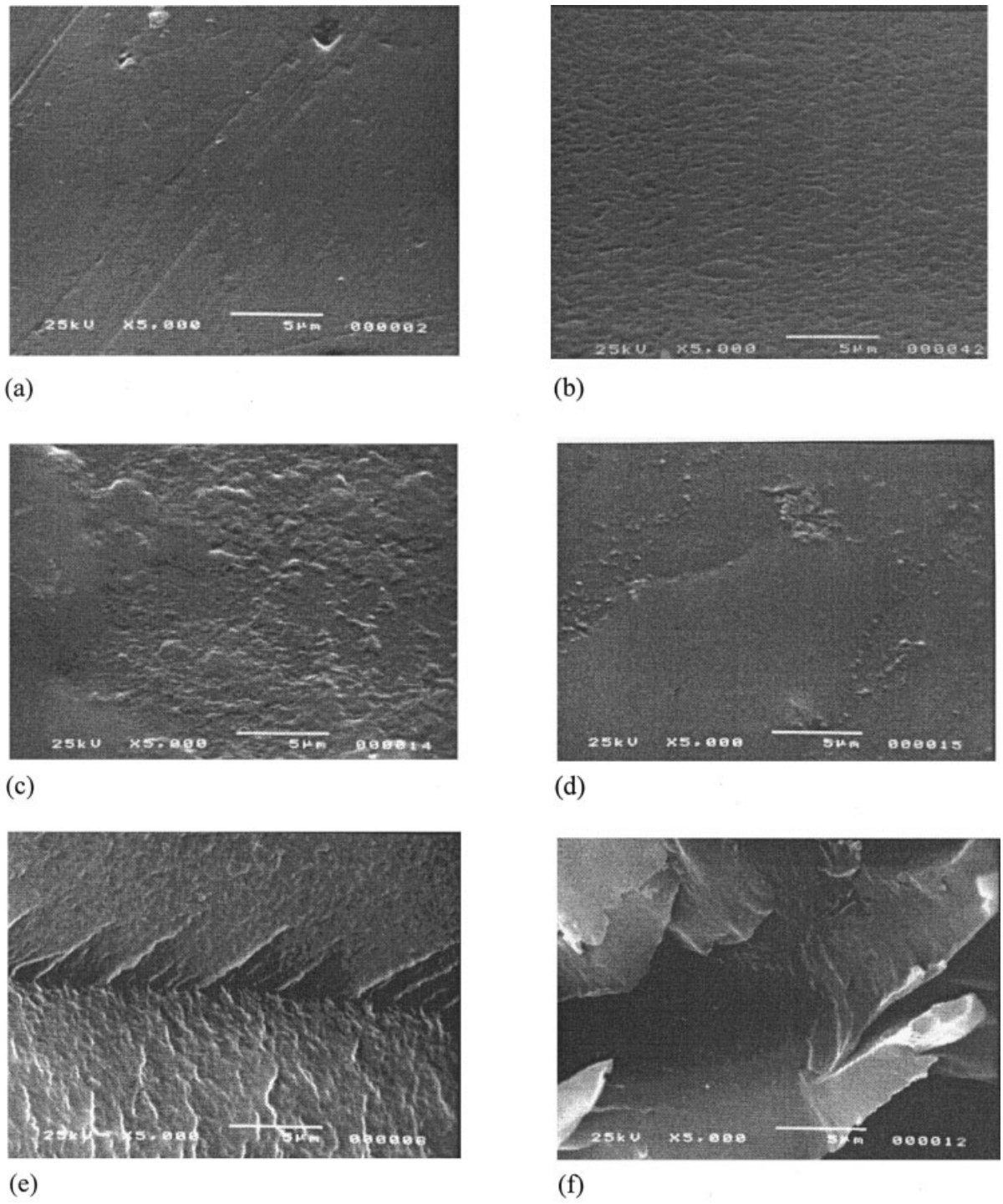

Figure 6 SEM micrographs: (a) the surface of chitosan; (b) the surface of chitosan/PEG; (c) the surface of a pH 3 treated, 3 wt % glucose-mediated membrane; (d) the surface of a pH 6 treated, 3 wt % glucose-mediated membrane; (e) a cross section of the pH 3 treated, 3 wt % glucose-mediated membrane; and (f) a cross section of the pH 6 treated, 3 wt % glucose-mediated membrane.

gel solution was close to 3, and this implied that the mediating effect was complex and could include a Schiff reaction and an ionic reaction. Many protonated amino groups are crosslinked ionically by sulfate ions (chitosan—$^{-}NH_3$—SO_4—H_3N^{+}—chitosan), but the numbers of Schiff-base formed end products (C═N) are much less because of the presence of a stable chair form for most glucose molecules.[17] There was a significant difference in the swelling degree for glucose-mediated membranes prepared in pH 3 and pH 6 mediating conditions. As the glucose concentration increased, the swelling degree of the pH 6 treated,

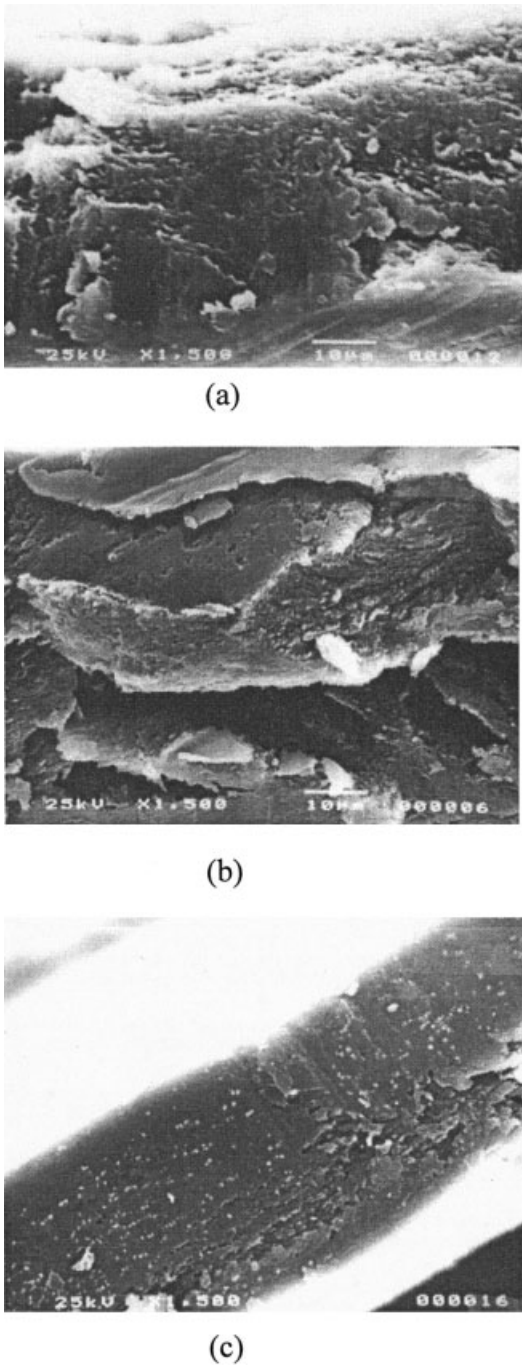

Figure 7 SEM cross-section micrographs: (a) a pH 6 treated, 3 wt % glucose-mediated membrane; (b) a pH 6 treated, 5 wt % glucose-mediated membrane; and (c) a pH 6 treated, 10 wt % glucose-mediated membrane.

glucose-mediated membrane obviously decreased from 122.53 to 75.21% in a pH 1.2 environment, as shown in Figure 4. The swelling behavior of the pH 6 treated, glucose-mediated membrane can be explained as follows. The final pH value of the mixed chitosan/PEG solution, close to 6, implied that more Schiff-base products were formed because of more glucose molecules present in a linear form. Therefore, the sulfate-ion crosslinking effect was suppressed by the Schiff-base formation process, and then the polymer precipitate contained more Schiff-base product and fewer free amino groups. This analysis was supported by

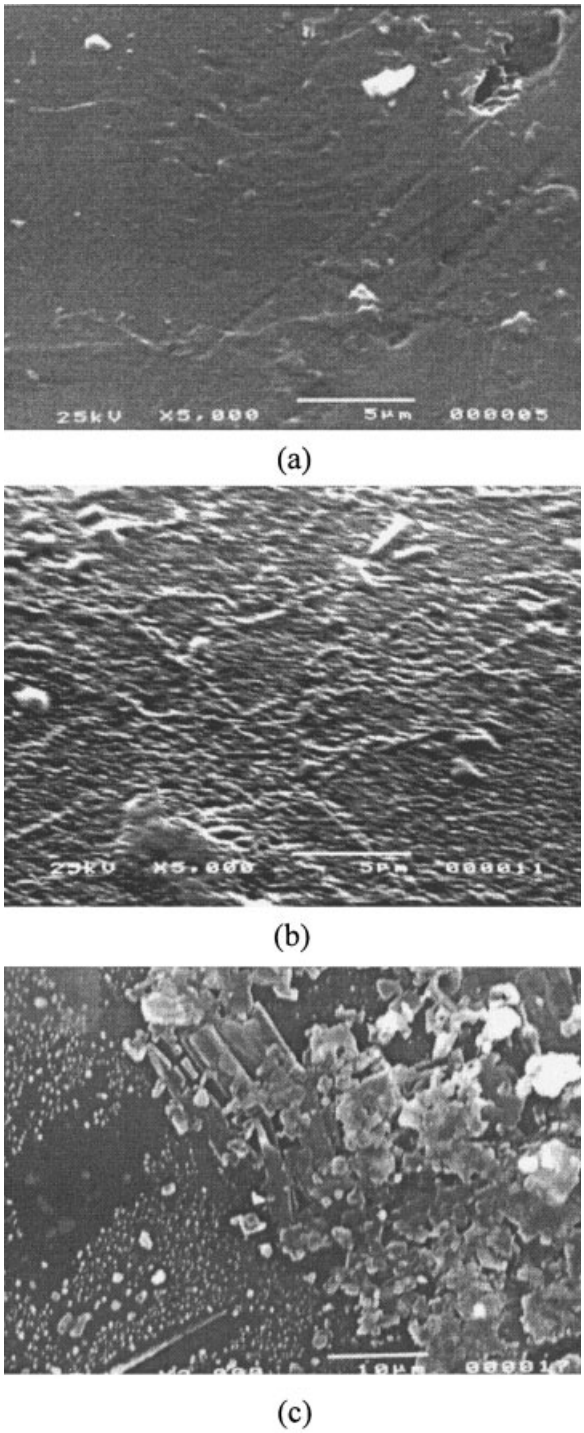

Figure 8 Surface morphology of chitosan/PEG membranes dissolved in a pH 1.2 medium for 6 h: (a) a basic-treated, 3 wt % glucose-mediated membrane; (b) a theophylline-loaded, basic-treated, 3 wt % glucose-mediated membrane; and (c) a theophylline-loaded, basic-treated, 3 wt % glucose-mediated membrane.

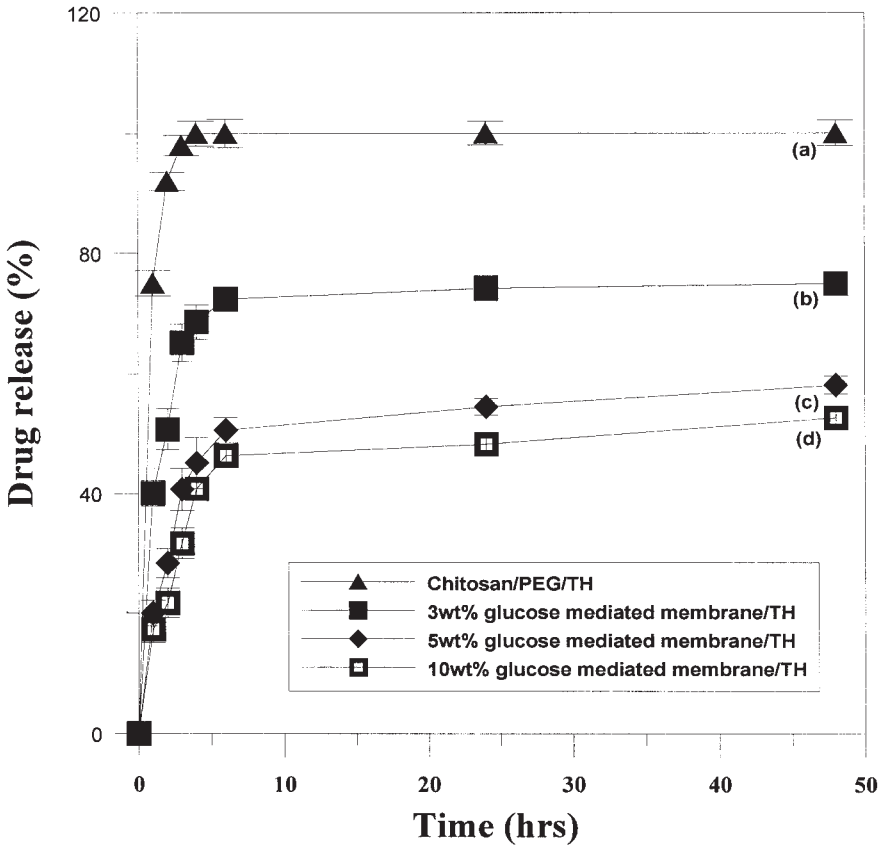

Figure 9 *In vitro* release profiles of membranes in a pH 1.2 medium: (a) a theophylline (TH)-loaded chitosan/PEG membrane; (b) a TH-loaded, basic-treated, 3 wt % glucose-mediated membrane; (c) a TH-loaded, basic-treated, 5 wt % glucose-mediated membrane; and (d) a TH-loaded, basic-treated, 10 wt % glucose-mediated membrane.

measurements of the degree of mediation, as shown in Table I; the degree of mediation increased with an increase in the pH value of the mixture.

In pH 7.4 PBS environments, the swelling degrees of the pH 3 treated, glucose-mediated membranes also were higher than those of the pH 6 treated ones, as shown in Figure 5. The difference in the swelling degree may have been due to the greater stability of the Schiff-base formation product in the neutral environment. Hence, in the pH range of 1.2–7.4, the swelling degrees of pH 3 treated, glucose-mediated membranes were higher than those of pH 6 treated ones. All the membranes swelled at pH 1.2 and shrank at pH 7.4. As expected, glucose could improve the stability of the chitosan/PEG membranes, especially in an acidic environment.

SEM observations

Figure 6 shows the morphologies of chitosan, chitosan/PEG, and pH-treated, glucose-mediated membranes. The chitosan membrane had a smooth surface, but the chitosan/PEG membrane had a rough surface with small, round voids, as shown in Figure 6(a,b), respectively. The pH value of the mediating solution had a great effect on the surface morphology of the chitosan/PEG membrane. For example, the pH 6 treated, 3 wt % glucose-mediated membrane was relatively smooth in comparison with the pH 3 treated, 3 wt % glucose-mediated membrane, as shown in Figure 6(c,d). The cross-sectional micrograph of the pH 3 treated, 3 wt % glucose-mediated membrane shows a dense and rough surface pattern, but the pH 6 treated, 3 wt % glucose-mediated membrane had a denser and more compact surface pattern, as shown in Figure 6(e,f). The pH media had a significant influence on the surface structure, and color of the samples became much deeper. This indicated that the Maillard reaction between chitosan and glucose was favored at a high pH.

In vitro release studies

Because the pH 6 treated, glucose-mediated membranes exhibited a low swelling ratio at equilibrium in pH 1.2 and 6.8 PBS media, the *in vitro* release studies were carried out in both media to achieve localized oral drug delivery to the stomach region. By SEM observations, we found that the interstructure of the pH 6 treated, 3 wt % glucose-mediated membranes

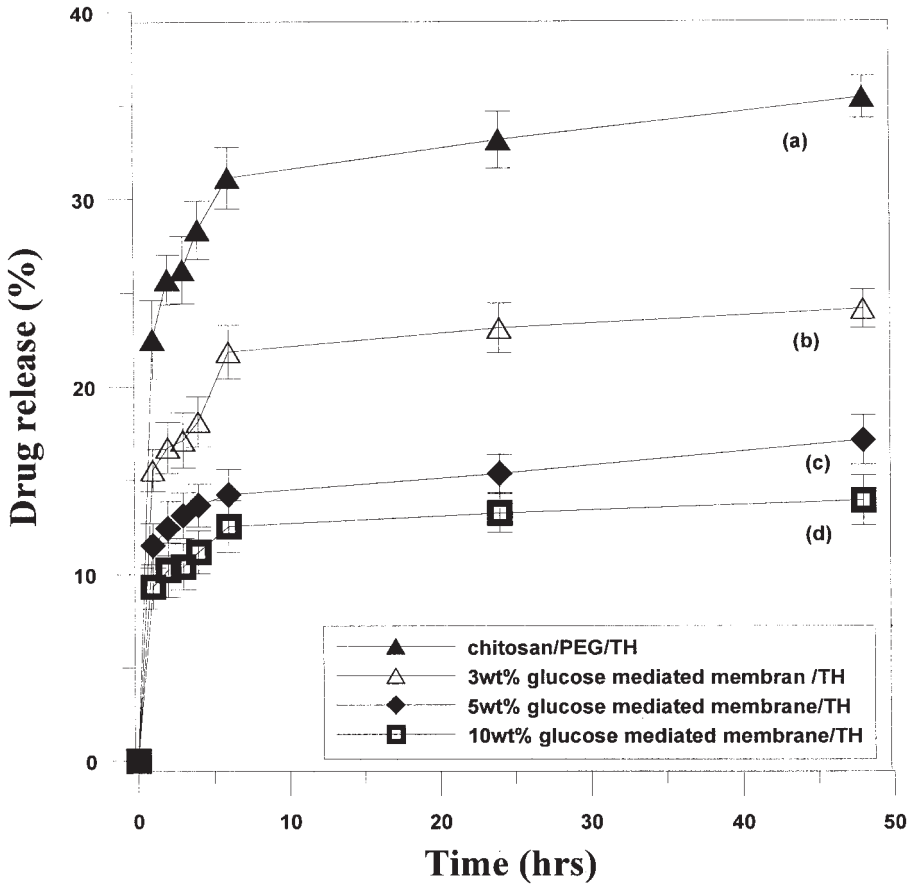

Figure 10 *In vitro* release profiles of membranes in a pH 6.8 medium: (a) a theophylline (TH)-loaded chitosan/PEG membrane; (b) a TH-loaded, basic-treated, 3 wt % glucose-mediated membrane; (c) a TH-loaded, basic-treated, 5 wt % glucose-mediated membrane; and (d) a TH-loaded, basic-treated, 10 wt % glucose-mediated membrane.

had rough micropores, but this structure became more compact as the glucose concentration increased to 5 and 10 wt % [Fig. 7(b,c)]. In addition, SEM showed that pH 6 treated, 3 wt % glucose-mediated membranes had smooth and dense surfaces, but the surfaces became rough with the incorporation of theophylline into the chitosan/PEG membranes [Fig. 8(a,b)]. The morphology of the membranes after they dissolved in a pH 1.2 PBS medium for 6 h was obviously different. Figure 8(c) shows the erosion of the drug crystal on the surface of a theophylline-loaded, pH 6 treated, 3 wt % glucose-mediated membrane in a pH 1.2 medium. The result was attributed to the fact that the glucose in the chitosan/PEG membrane acted not only as a mediator but also as a surface protector of the drug powder.[18]

Figure 9 shows the *in vitro* release profiles of theophylline-loaded chitosan/PEG and pH 6 treated, glucose-mediated membranes. For the theophylline-loaded chitosan/PEG membrane, the theophylline was totally released after 4 h because the chitosan/PEG membrane was easily dissolved in the pH 1.2 medium. This result indicated that the chitosan/PEG membrane was not suitable for use as a long-term drug-delivery system in a gastric environment. On the other hand, the chitosan/PEG membrane mediated by glucose greatly prolonged the theophylline release; the time period for 77% theophylline release was extended from 4 to 6 h after mediation with a 3 wt % glucose solution. Moreover, the theophylline release decreased as the glucose concentration increased; this agreed with the results of the swelling test and SEM observations, as shown in Figure 7. Figure 10 also shows that the amount and percentage of the drug release were much lower in pH 6.8 media than in pH 1.2 media. The result could be attributed to the fact that the release rate depended on the swelling of the glucose-mediated membranes. As previously noted, the swelling of the glucose-mediated membranes in an acidic medium was greater than that in a basic medium.

For a pH 6 treated, 3 wt % glucose-mediated membrane, about 41% of the entrapped theophylline was released in the first hour in an acidic medium. This initial burst effect could be attributed to the diffusion of the drug caused by rapid membrane swelling and also the release of the drug adsorbed toward the surface of the membrane matrix. After 2 h, 50% of the

theophylline was released. This may have been due to the diffusion of the theophylline entrapped in the bulk of the membrane. Afterwards, the theophylline release slowed down, probably because of reduced swelling in the acidic medium, in addition to the lower concentration of theophylline in the membrane matrix. The remaining theophylline in the matrix may have been released in a very slow fashion because of the slow degradation rate of the membrane. The release profiles of the theophylline-entrapped, pH 6 treated, glucose-mediated membrane indicated that this pH-responsive membrane could be exploited for oral drug delivery. By the appropriate chemical modification of degree of mediation of these membranes, the rate of drug release could be modulated. These basic-treated, glucose-mediated membranes exhibited great potential for successful exploitation for the localized delivery of drugs to a gastric environment.

CONCLUSIONS

Novel pH-responsive membranes based on chitosan/PEG were developed for oral drug delivery. The preparation of these membranes was carried out with a solution-mediating process via glucose addition at different pHs. The glucose-mediated membranes had different degrees of mediation, which depended on the pH and glucose concentration. The equilibrium swelling measurements clearly showed that all the glucose-mediated membrane swelled at pH 1.2 and shrank at pH 7.4. The *in vitro* release profiles of the theophylline-loaded, pH 6 treated, glucose-mediated membrane showed that the theophylline release decreased as the glucose concentration increased, and this agreed with the result of swelling studies and measurements of the degree of mediation. Also, the release behavior of the theophylline from the glucose-mediated membranes differed according to the pH of the release medium, the concentration of glucose, and the final pH value of the mixed glucose-mediated chitosan/PEG gels. This investigation of pH-responsive, glucose-mediated membranes indicates that the rate of drug release can be modulated by the appropriate chemical modification of the degree of mediation of these membranes. Therefore, chitosan/PEG membranes prepared by a basic glucose-mediation process may lead to successful applications for localized drug delivery to the intestine.

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