Drug-Release Behavior of Chitosan-*g*-Poly(vinyl alcohol) Copolymer Matrix

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ABSTRACT: Chitosan-*g*-poly(vinyl alcohol) (PVA) copolymers with different grafting percent were prepared by grafting water-soluble PVA onto chitosan. The drug-release behavior was studied using the chitosan-*g*-PVA copolymer matrix containing prednisolone in a drug-delivery system under various conditions. The relationship between the amount of the released drug and the square root of time was linear. From this result, the drug-release behavior through the chitosan-*g*-PVA copolymer matrix is shown to be consistent with Higuchi's diffusion model. The drug-release apparent constant (K_H) was slightly decreased at pH 1.2, but increased at pH 7.4 and 10 according to the increasing PVA grafting percent. Also, K_H was decreased by heat treatment and crosslinking. The drug release behavior of the chitosan-*g*-PVA copolymer matrix was able to be controlled by the PVA grafting percent, heat treatment, or crosslinking and was also less affected by the pH values than was the chitosan matrix.
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Key words: chitosan-*g*-PVA copolymer matrix; prednisolone; swelling ratio; Higuchi's equation

INTRODUCTION

The naturally occurring polysaccharide, chitin, consists mainly of β-(1 $\rightarrow$ 4)-2-acetamido-2-deoxy-D-glucose units, although some deacetylation may take place during isolation. The poly(aminosaccharide), chitosan, may be obtained from chitin by deacetylation using a strong alkaline aqueous solution such as NaOH.[1] Recently, chitosan has been used in the biomedical field because of its favorable characteristics such as good biocompatibility and has been reported to be useful for pharmaceutical preparations.[2,3] Among some interesting applications, use as a drug carrier in drug-delivery systems (DDSs) is especially noteworthy.[4,5] But chitosan's main disadvantages for using in DDSs are that it is insoluble in common organic solvents except for dilute acetic acid and has low mechanical properties and also a high dependency of its physical properties on pH. Therefore, in the case of using chitosan as a drug carrier, especially for oral administration, it is difficult to control the drug-release behavior under various identified pH values of the internal organs of the human body. So, there is quite a possibility that over releasing of the drug may bring about ill effects in the human body. In previous articles,[6,7] we reported the synthesis of a chitosan-*g*-PVA copolymer by grafting PVA with water-soluble and high mechanical properties onto chitosan and its change of physical properties such as solubility and thermal and mechanical properties under various conditions. Hence, the present work was to study the change of the

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drug-release behavior through the chitosan-*g*-PVA copolymer matrix containing prednisolone as a model drug under pH 1.2 (stomach), 7.4 (intestines), and 10 *in vitro*.

EXPERIMENTAL

Materials and Reagents

Chitosan and prednisolone used as model drugs were supplied by the Tokyo Kasei Co. (Tokyo, Japan). PVA was supplied by the Shinyo Pure Chemical Co. (Osaka, Japan) (degree of hydrolysis: 0.89; degree of polymerization: 1200). Ceric ammonium nitrate (CAN) was supplied by Shimakyu's Pure Chemical Co. (Tokyo, Japan). Glutaraldehyde was supplied by the Junsei Chemical Co. All other commercially available chemicals were reagent grade and used without further purification.

Preparation of Chitosan-*g*-PVA Copolymer

The chitosan-*g*-PVA copolymer was prepared by the following method[6]: One gram of chitosan, an appropriate amount of PVA (1,2 diol content identified in the previous article[6]: 1.9%), and 300 mL of 5 wt % acetic acid were charged into a four-necked round flask, equipped with stirrer, reflux condenser, and N_2 inlet and then stirred over 30 min. A CAN solution as an initiator was added into the flask and reacted at 40°C for 3–4 h. The reaction mixture was added to excess H_2O in order to remove unreacted PVA. The precipitated material was filtered off and washed over several times with H_2O. Finally, the chitosan-*g*-PVA copolymer was obtained by drying in a vacuum oven at 40°C for 24 h.

Preparation of Chitosan-*g*-PVA Copolymer Matrix

A chitosan-*g*-PVA solution was prepared by adding 0.1 g of the chitosan-*g*-PVA copolymer to 10 mL of a 5% acetic acid aqueous solution and stirring for 24 h. The solution was filtered off to remove dirt and undissolved copolymer. Accurately weighed prednisolone, 0.1 g, was added to this solution and stirred for over 2 h for the purpose of it having uniform dispersion, then poured into a mold-shaped tablet. Finally, the chitosan-*g*-PVA copolymer matrix containing prednisolone (drug loading percent: 50) was obtained by drying in a vacuum oven. The tablet is rectangular-shaped with dimensions 1.5 × 1.5 × 1.5 cm. The composition and thickness of the drug matrix are shown in Table I.

Table I Composition and Thickness of Copolymer Matrix

Chitosan-*g*-PVA Copolymer		Prednisolone (g)	Thickness (mm)
Grafting %	g		
18.3	0.1	0.1	0.82
48.7	0.1	0.1	0.82
54.0	0.1	0.1	0.82
64.2	0.1	0.1	0.82
0	0.1	0.1	0.84

Heat Treatment of Chitosan-*g*-PVA Copolymer Matrix

The chitosan-*g*-PVA copolymer matrix was treated by heating in an oven at 70°C for 24 h under a N_2 stream.[8,9]

Crosslink of Chitosan-*g*-PVA Copolymer Matrix

The chitosan-*g*-PVA copolymer matrix was crosslinked by submerging it into a 1% glutaraldehyde aqueous solution for 1 min.

Measurement of Swelling Ratio

Chitosan, the chitosan-*g*-PVA copolymer, the heat-treated copolymer, and the crosslinked copolymer were equilibrated overnight in a pH 1.2, 7.4, and 10 buffer solution. The samples were washed quickly with tissue to remove excess surface water and weighed immediately in a microbalance and then placed in a large volume of deionized water to remove the buffer solution and dried in a vacuum oven at 40°C for 24 h. The swelling ratio, S, was calculated as follows:

$$S = \frac{\text{Weight of swollen membrane}}{\text{Weight of dry membrane}}$$

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

Drug-release Profile

The experimental apparatus is illustrated in Figure 1. The matrix shown in Table I was immersed in 1000 mL of a controlled pH buffer solution, maintained at 37°C ± 1°C and rotated at 50 rpm.

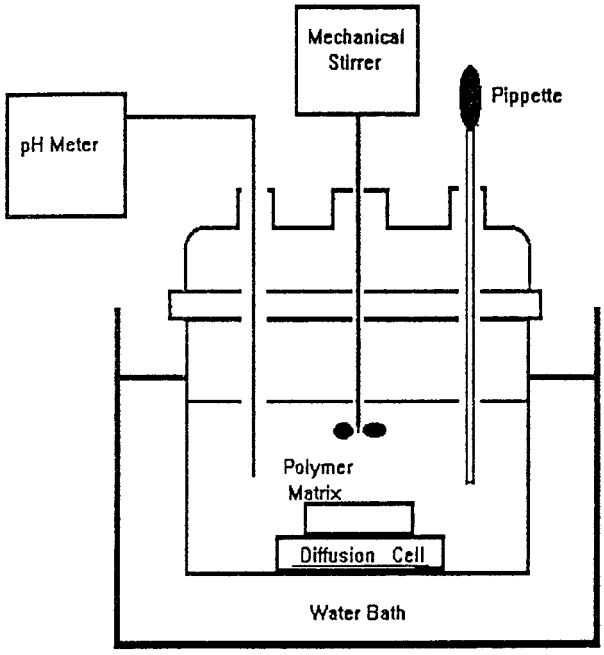

Figure 1 Experimental apparatus for measuring the released drug.

Five milliliters of the solution-released drug was withdrawn at regular intervals for a period of 60 h. Each withdrawal was replaced by 5 mL of fresh medium. The amount of drug released was estimated with an ultraviolet (UV) spectrophotometer at 242 nm.

Characterization and Analysis

The structure of the chitosan-*g*-PVA copolymer was confirmed using a Shimadzu DR-8011 Fourier transform infrared (FTIR) spectroscope and a Bruker ARX-300 carbon (^{13}C)-nuclear magnetic resonance (NMR) spectroscope. FTIR spectra were obtained from KBr pellets of chitosan and the chitosan-*g*-PVA copolymer. Solid-state ^{13}C-NMR spectra were measured from solid-state chitosan and the chitosan-*g*-PVA copolymer. Also, the amount of the drug released was obtained by measurement of the absorbance at 242 nm using a Shimadzu 2201 UV spectrophotometer.

RESULTS AND DISCUSSION

Characteristics of Chitosan-*g*-PVA Copolymer

The chitosan-*g*-PVA copolymer was prepared by the reaction of 1 g of chitosan and 1 g of PVA using 8.83×10^{-3} mol/L of CAN at 40°C for 4 h. The FTIR spectra and the ^{13}C-NMR spectra of chitosan and the chitosan-*g*-PVA copolymer are shown in Figures 2 and 3, respectively. The FTIR spectrum [Fig. 2(B)] shows a new peak at 1660 cm^{-1} due to the C═O of grafted PVA on chitosan. Also, the ^{13}C-NMR spectrum [Fig. 3(B)] shows a new weak peak at 171.2 ppm due to C═O and at

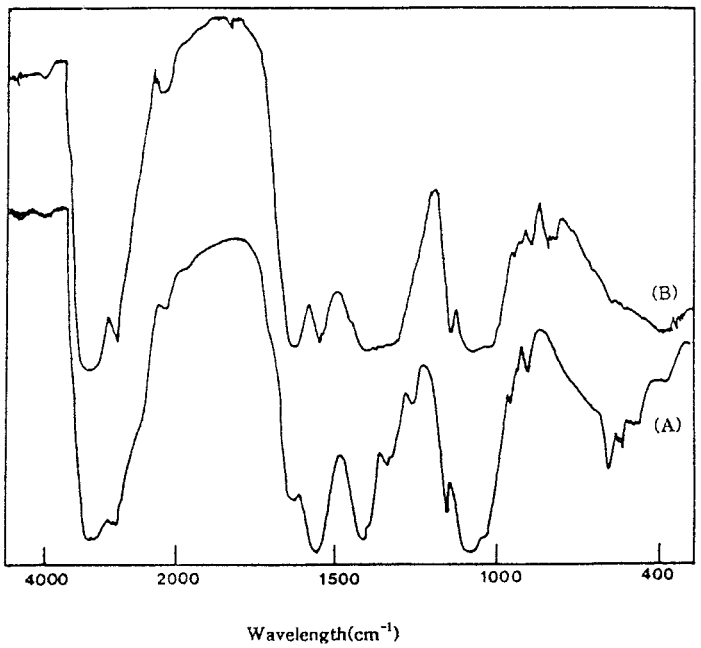

Figure 2 FTIR spectra of (A) chitosan and (B) chitosan-*g*-PVA copolymer.

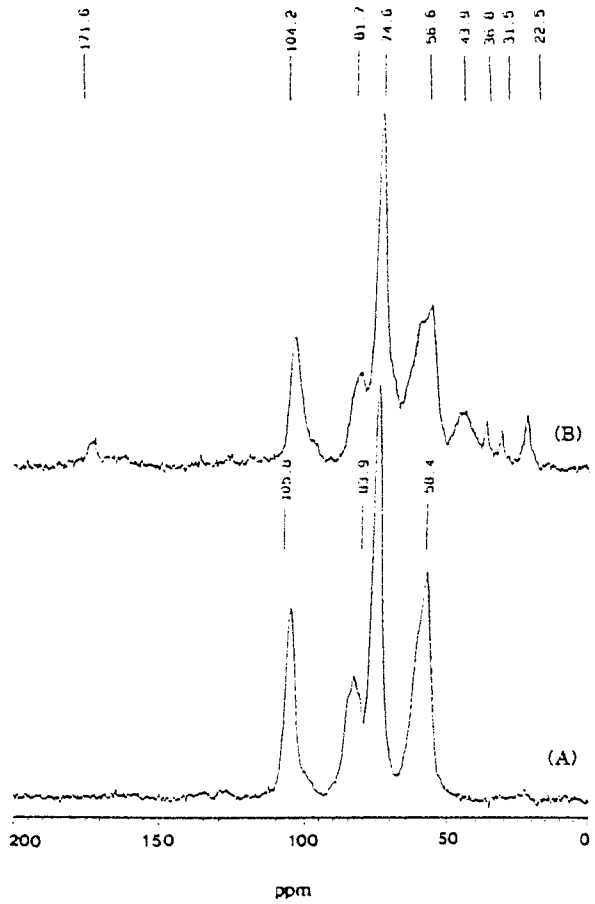

Figure 3 ^{13}C-NMR spectra of (A) chitosan and (B) chitosan-*g*-PVA copolymer.

22.5, 31.3, 36.8, and 43.9 ppm due to individual carbons of grafted PVA.

Swelling Ratio

The swelling ratios of chitosan, the chitosan-*g*-PVA copolymer, the heat-treated copolymer, and the crosslinked copolymer are shown in Figures 4–6, respectively. As shown in Figure 4, it was impossible to measure the swelling ratio for chitosan due to its being soluble in pH 1.2; the swelling ratio of the chitosan-*g*-PVA copolymer was slightly decreased from 8.6 to 8.2 with increase of the PVA grafting % from 18.3 to 64.2. Also, it was decreased from 8.2 to 7.1 and 2.6, respectively, by heat treatment and crosslinking. As shown in Figure 5, while the swelling ratio of chitosan was about 3.9, the swelling ratio of the chitosan-*g*-PVA copolymer was increased from 4.7 to 5.4 with increase of the PVA grafting % from 18.3 to 64.2. Also, by heat treatment and crosslinking, the

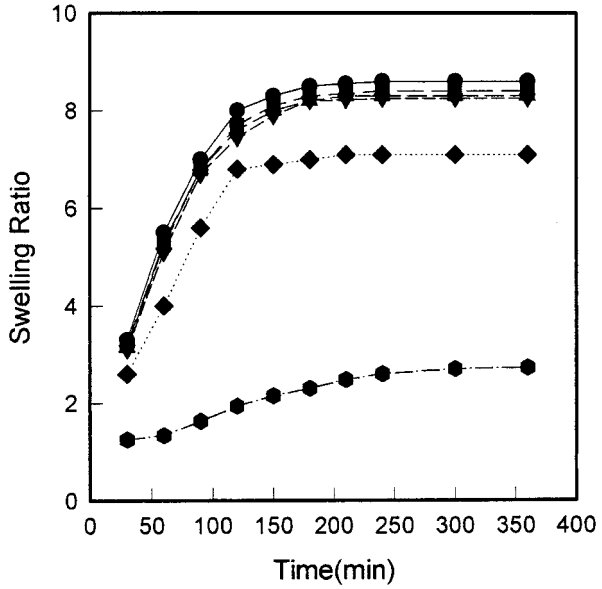

Figure 4 Swelling ratio according to time at pH 1.2: (—●—) copolymer (grafting %: 18.3); (—■—) copolymer (grafting %: 48.7); (—▲—) copolymer (grafting %: 54.0); (—▼—) copolymer (grafting %: 64.2); (—◆—) heat-treated copolymer (grafting %: 64.2); (—⬢—) crosslinked copolymer (grafting %: 64.2); (—○—) chitosan.

swelling ratio decreased from 5.4 to 4.1 and 2.7, respectively. As shown in Figure 6, the swelling ratio of chitosan, the chitosan-*g*-PVA copolymers,

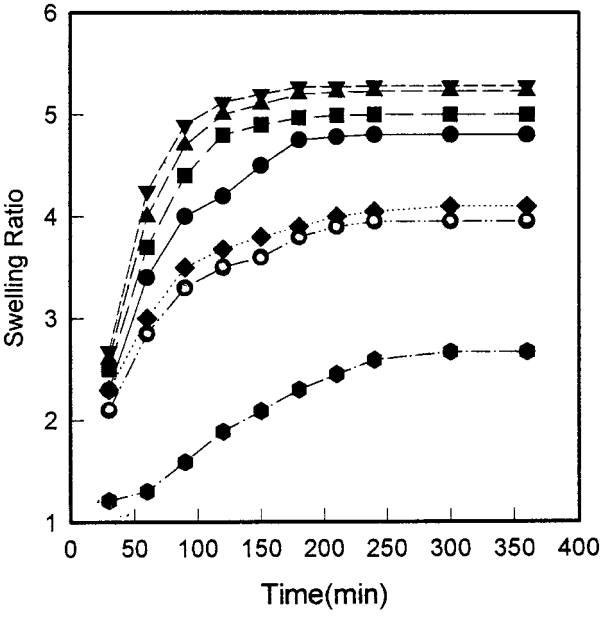

Figure 5 Swelling ratio according to time at pH 7.4. See Figure 4 legend for symbols.

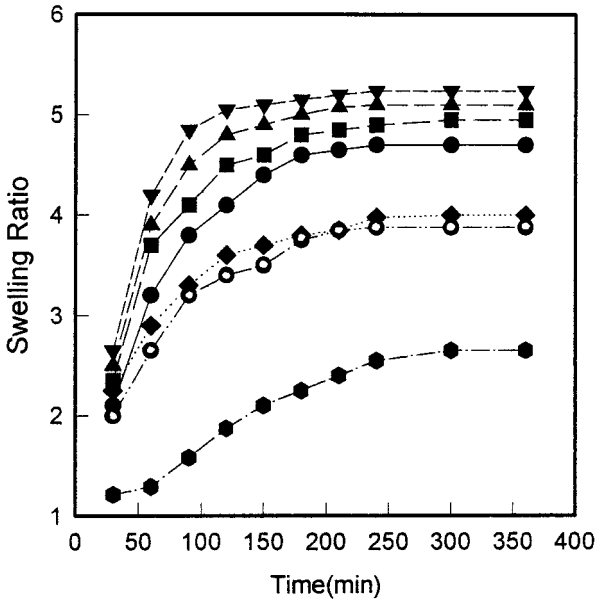

Figure 6 Swelling ratio according to time at pH 10. See Figure 4 legend for symbols.

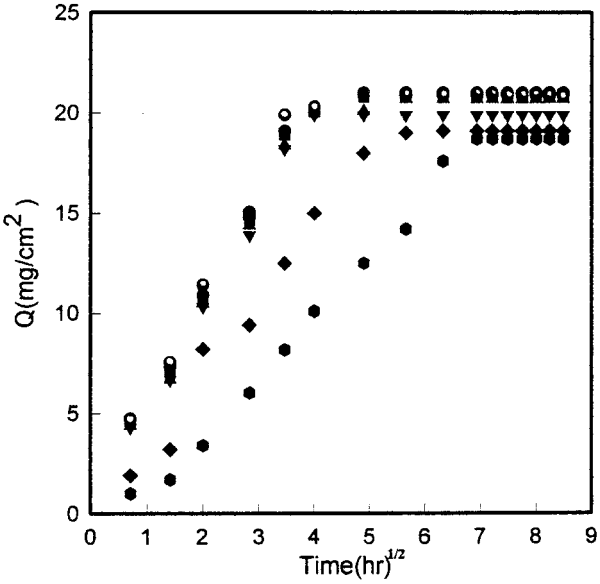

Figure 7 Amount of drug released according to square root of time at pH 1.2. See Figure 4 legend for symbols.

the heat-treated copolymer, and the crosslinked copolymer were almost similar to that of pH 7.4.

Drug-release Behavior

In general, the drug-release behavior through the polymer matrix is described by Higuchi's equation as follows[10,11]:

$$Q = [DC_d(2A - C_d)t]^{1/2} \quad (1)$$

where Q is the amount of the released drug per unit area of the matrix; D, the diffusion coefficient of the drug in the matrix; A, the initial amount of the drug per unit volume of the matrix; C_d, the dissolution concentration of the drug in the matrix; and t, the time. Higuchi's eq. (1) was further developed so that it is applicable to a porous polymer matrix system:

$$Q = [D(\varepsilon/\tau)(2A - \varepsilon C_d)C_d t]^{1/2} \quad (2)$$

where ε is the porosity of the matrix, and τ, the tortuosity factor. Also, Higuchi's equation can be simplified by modification of eqs. (1) and (2), as follows:

$$Q = K_H t^{1/2} \quad (3)$$

where K_H is the apparent release-rate constant (Higuchi constant).

Q was measured in the square root of time to explain the drug-release behavior for the matrix shown in Table I under various conditions using Higuchi's eq. (3). A plot of Q is linear in the

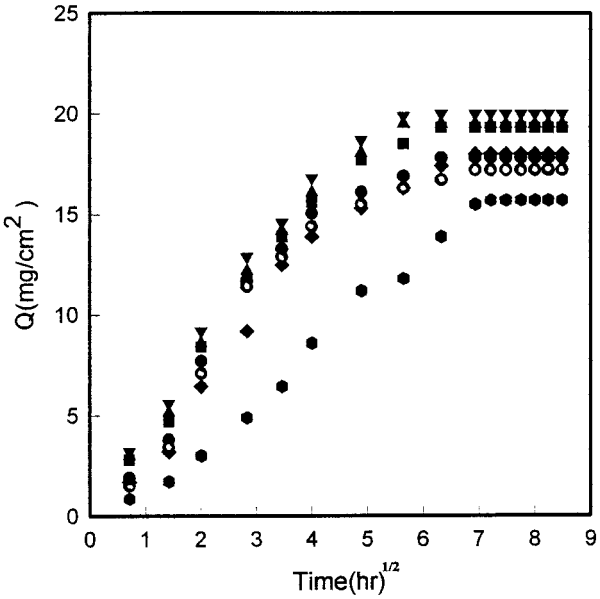

Figure 8 Amount of drug released according to square root of time at pH 7.4. See Figure 4 legend for symbols.

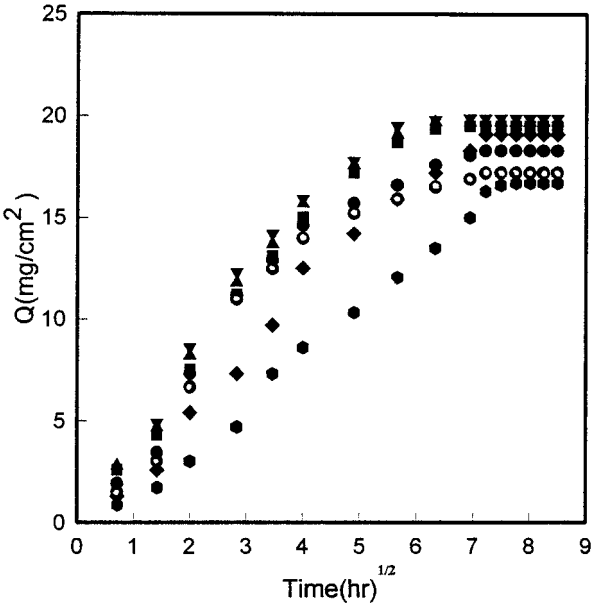

Figure 9 Amount of drug released according to square root of time at pH 10. See Figure 4 legend for symbols.

square root of time. Typical plots to obtain drug-release data such as K_H and t_{LRT} (time to reach until Q is linearly increased) are shown in Figures 7–9. The K_H and t_{LRT} values obtained from Figures 7–9 are summarized in Table II. The K_H of the chitosan matrix are 5.75, 2.88, and 2.81 (mg cm^{-2} day$^{-1/2}$) and the t_{LRT} are 16, 40, and 40 h at pH 1.2, 7.4, and 10, respectively. The K_H of the chitosan-*g*-PVA copolymer matrix was slightly decreased from 5.52 to 5.26 (mg cm^{-2} day$^{-1/2}$) according to the PVA grafting % from 18.3 to 64.2, and t_{LRT} was almost constant at about 16 h regardless of the PVA grafting % at pH 1.2. But K_H was increased from 2.99 to 3.82 (mg cm^{-2} day$^{-1/2}$) according to increase of the PVA grafting % from 18.3 to 64.2, and t_{LRT} was short at about 24 h regardless of the PVA grafting percent at pH 7.4 than that of chitosan. Also, the drug-release behavior of pH 10 is almost similar to that of pH 7.4. These were supposed to be results showing that the swelling ratio of the chitosan-*g*-PVA copolymer was slightly decreased at pH 1.2, but increased at pH 7.4 and 10 according to increase of the PVA grafting percent.

Also, the drug-release behavior of the chitosan-*g*-PVA copolymer matrix was less affected by the pH values than was that of the chitosan matrix. Additionally, by the crystallization of PVA in the chitosan-*g*-PVA copolymer with heat treatment or crosslinking with glutaraldehyde, K_H and t_{LRT} were decreased or delayed at pH 1.2, 7.4, and 10. These were supposed to be results showing that the increased crystalline region in the chitosan-*g*-PVA copolymer by heat treatment disturbs the release of the drug in the matrix or that the swelling ratio of the copolymer was decreased by crosslinking, which makes it difficult to release the drug in the matrix. Also, the drug release behavior of the heat-treated and crosslinked chitosan-*g*-PVA copolymer matrix was less affected by the pH values than was the chitosan matrix. For oral administration, if the physical properties of a drug carrier are sensitive to pH values and difficult to control; the human body will be harmed owing to overreleasing the drug. Hence, if the chitosan-*g*-PVA copolymer were used as a

Table II Apparent Release Rate Constant (K_H) and Linear Release Rate Time (t_{LRT}) of Chitosan and Chitosan-*g*-PVA Copolymer Matrix

Sample	Grafting %	K_H (mg cm^{-2} day$^{-1/2}$)			t_{LRT} (h)		
		pH 1.2	pH 7.4	pH 10	pH 1.2	pH 7.4	pH 10
Chitosan	0	5.75	2.88	2.81	16	40	40
Chitosan-*g*-PVA copolymer	18.3	5.52	2.99	2.98	16	24	24
	48.7	5.46	3.62	3.52	16	24	24
	54.0	5.32	3.69	3.59	16	24	24
	64.2	5.26	3.82	3.64	16	24	24
Heat-treated copolymer	64.2	3.69	2.80	2.70	32	40	40
Crosslinked copolymer	64.2	2.69	2.50	2.23	48	48	52

drug carrier for oral administration, the possibility of a bad effect could be diminished because the drug-release behavior can be controlled by the PVA grafting percent or by heat-treatment and crosslinking.

CONCLUSIONS

The drug-release behavior of the chitosan-*g*-PVA copolymer matrix containing prednisolone was studied under various conditions. According to the increase of the PVA grafting % from 18.3 to 64.2, the apparent release rate constant, K_H, was slightly decreased from 5.52 to 5.26 (mg/cm^2 day$^{1/2}$) at pH 1.2, but increased from 2.99 to 3.82 (mg/cm^2 day$^{1/2}$) at pH 7.4. While the drug-release behavior of the chitosan matrix was sensitive to the pH values and difficult to control; that of the chitosan-*g*-PVA copolymer matrix was less affected by the pH values and, also, could be controlled by the PVA grafting percent or heat-treatment and crosslinking. From these results, we found that the chitosan-*g*-PVA copolymer is a much better candidate than is chitosan as a drug carrier in DDSs.

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