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Swelling Behavior and Drug Release of Poly(vinyl alcohol) Hydrogel Cross-Linked with Poly(acrylic acid)

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Abstract: Thermal cross-linking method of poly(vinyl alcohol) (PVA) using poly(acrylic acid) (PAA) was carried out on PVA/PAA hydrogels. The level of gelation was measured in the PVA/ PAA hydrogels with various PAA contents. The swelling behavior at various pHs showed that the swelling kinetics and water contents of the PVA/ PAA hydrogels reached equilibrium after 30 h, and the time to reach the equilibrium state decreased with increasing PAA content in the hydrogel. The water content increased with increasing pH of the buffer solution. The permeation and release of the drug were tested using indomethacin as a model drug. The permeated and released amounts of the drug increased with decreasing the PAA content because of the low free volume in the hydrogel due to the higher cross-linking density. The kinetic profile of drug release at various pHs showed that all samples reached the equilibrium state within the 5 h.

Keywords: poly(vinyl alcohol), poly(acrylic acid), thermal cross-linking, hydrogel, swelling, drug release.

Introduction

Hydrogels are hydrophilic three-dimensional polymer networks capable of absorbing a large volume of water or other biological fluid. Hydrogels have become increasingly important materials for pharmaceutical and biomedical applications,[1-4] because of their biocompatibility with the human body and their characteristics similar to natural tissue.

This research deals with the thermal cross-linking method of poly(vinyl alcohol) (PVA) using the direct reaction between carboxylic acid of poly(acrylic acid) (PAA) and hydroxyl group of PVA. Conventional methods include the repetitive freezing and thawing cycles, which entangle networks through the physical junctions of PVA, and forming the interpenetrating networks (IPN) through the polymerization of acrylic acids in the presence of PVA.[5-10] PVA has been known as excellent mechanical strength, good film forming, and long-term temperature and pH stability.[11,12] Furthermore, PVA is bio-compatible and nontoxic, and exhibits minimal cell adhesion and protein absorption, as desired in biomedical applications requiring contact with bodily fluid.

PAA was used to cross-link the PVA, because the carboxyl groups can be used to be reactive site and also to chemically alter its properties under mild reaction conditions. In addition, the carboxyl group of PAA has influenced on the pH-responsive behavior, because pH-sensitive hydrogels usually contain either acid or basic pendent groups in the network.[13-15] Its carboxylic groups are ionized and swell

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considerably above the pKa of 4.7. In the case of pH-dependent drug delivery systems using hydrogels, researches have focused on swelling properties of hydrogels. The acidic or basic components in the hydrogels led to reversible swelling/deswelling because they changed from the neutral state to the ionized state in response to the change of pH. Peppas *et al.* studied the structure, characteristics and drug diffusion of PVA and Ende *et al.* studied the characteristics of PAA and solution diffusion at various pHs.[5,8,16]

The present study discusses the swelling behaviors of crosslinked PVA/PAA films at various PAA contents of 5 through 9 %, which were considered to be best, particularly under the various pH conditions. In addition, the permeation of Indomethacin through the prepared films was measured at different operating temperatures. Finally, the drug release behaviors at various pH conditions will be discussed in more detail.

Experimental

Materials. PVA (average molecular weight, Mw = 89,000-98,000, degree of hydrolysis = +99%) and PAA (average molecular weight, Mw = 2,000) was purchased from Aldrich Chemical Co. (Milwaukee, WI, USA). Indomethacin (1-[*p*-chlorobenzoyl]-5-methnowl-2-methylindole-3-acetic acid) which had a hydrophobic property was used as a model drug. Buffer solutions (pH 3-7) were purchased from Duksan Chemical Co. Water was first treated with Younglin Pure Water System (Seoul, Korea). Other chemicals were reagent grade and used without any further purification.

Preparation of Membrane. PVA power was dissolved in doubly deionized water with concentration of 10 wt% at 90 °C for 6 h. The dissolved PVA solution was mixed with 10 wt% PAA aqueous solution for at least 1 day at room temperature. The mixing ratios of PAA in the solution were ranged from 5 to 9 wt% (see Table I). Homogeneously mixed solutions were cast onto a Plexi-glass plate using a Gardner knife with predetermined drawdown thickness. The cast solutions were dried at room temperature, and completely dried hydrogels were then peeled off. To thermally cross-link the hydrogel, the dried membranes were heated in a vacuum oven at 150 °C for 1 h.

Gelation Content. To measure the gelation content, preweighed dry samples were immersed in deionized water to remove the not cross-linked parts of the hydrogel. After 1 day, the washed hydrogel was dried in the vacuum oven at 25 °C until the weight of sample was fixed. The gelation content was calculated using the following formula:

$$\text{Gelation content (\%)} = (W_c / W_i) \times 100$$

where, W_c is the weight of hydrogel after washing and drying in a vacuum oven for two days, and W_i is the initial weight of hydrogel without washing with water.

Measurement of Water Content. A swelling study was conducted on the hydrogels to observe the behavior as functions of the temperature and pH in the swelling medium. To measure the water content, pre-weighed dry samples were immersed in deionized water (pH 5.4) or buffer solutions (pH 3-7). When the samples reached at the equilibrium state, the weight of swollen samples was measured after the excessive water on the surface was removed with filter paper. The water content is defined as the following equation:

$$\text{Water content} = [(W_s - W_d) / W_d]$$

where, W_s and W_d are the weights of the sample at the sufficiently swollen and dried states, respectively.

Measurement of Drug Permeation. Drug permeation studies were conducted on the diffusion cell using Indomethacin, as a model drug (see Figure 1). Two separated chambers were filled with Indomethacin solution and pH 7 buffer solution, respectively. The hydrogel was inserted between two chambers. Three-mL aliquots sampled periodically from the medium were analyzed using a UV spectrophotometer at 270 nm, and then returned back into the medium solution. The permeation coefficient was calculated using the following formula:

Table I. Compositions and Gelation Content of PVA/PAA Hydrogels

Sample	Weight (%)		Gelation Content (%)
	PVA	PAA	
5% PVA/PAA	97	3	61.84
7% PVA/PAA	93	7	63.98
9% PVA/PAA	91	9	65.13

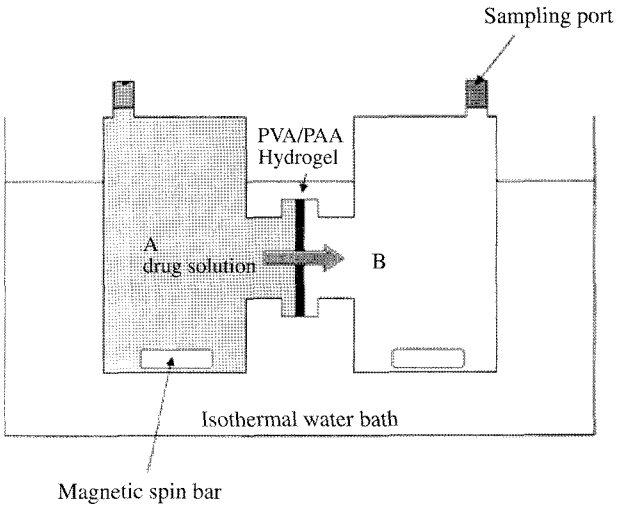

Figure 1. Drug permeation behaviors using the diffusion cell and Indomethacin as a model drug.

$$P = \frac{d}{A(1/V_A + 1/V_B)t} \ln\left|\left(1 + \frac{V_A}{V_B}\right)\frac{C_t}{C_0} - \frac{V_A}{V_B}\right|$$

where, V and A are the volume and the surface area of A and B chamber, and C_0 and C_t are the concentration of Indomethacin at initial and t time.

Drug Release Behaviors. IMC (1-[*p*-chlorobenzoyl]-5-methnowl-2-methylindole-3-acetic acid) was used and loaded as a model drug in the hydrogel. Swelling-loaded technique was used to load the drug into dried hydrogels. An appropriate amount of IMC was saturated with ethyl alcohol and stirred to dissolve at room temperature. Each sample (size = $1 \times 1 \times 0.02$ cm^3) was soaked into aqueous drug solution for two days at 25 °C. The film containing drug solution was blotted with filter paper to eliminate the surface water and dried at room temperature.

Drug-released behaviors were evaluated at various pHs under gentle stirring. The amount of released drug was periodically analyzed by using a UV spectrophotometer (SMART PLUS SP-1900PC). The UV absorbance of IMC was measured at λ_{max} = 270 nm. Solutions with known concentrations of IMC in deionized water were used to calibrate and to obtain a quantitative curve equation, which was $C = 0.00288\ A + (-1.61167 \times 10^{-4})$, where A is absorbance and adequately describes the increment in IMC concentration from 0.32 to 15.23 mg/mL actual dose.

Statistical Analysis. The data were analyzed by ANOVA using SAS (Release 6.12, SAS Institute Inc., Cary, NC, USA) and differences among mean values were processed by Duncan's multiple range tests. Values of $p<0.05$ were statistically considered.

Results and Discussion

Gelation Content and Water Content of Hydrogels with Various PAA Contents. Table I shows the gelation content as a function of PAA contents in the hydrogels. The gelation content increases with the PAA content because the number of carboxylic groups, which can be reacted with hydroxyl groups of PVA, increases with the PAA content in the hydrogels. Even though the samples are the solid state, the cross-linking between hydroxyl groups and carboxylic groups can occur at the high temperature around 150 °C. It means that the gelation content increases with the PAA content because the number of carboxylic groups, which can be reacted with hydroxyl groups of PVA, increases with the PAA content in the hydrogels.

Swelling Behaviors. Figures 2 and 3 show the swelling kinetics of thermally crosslinked PVA/PAA hydrogels in deionized water and various pH conditions. In the swelling kinetics, all PVA/PAA hydrogels reached an equilibrium after about 30 h.

In the deionized water, water contents of the hydrogels at the equilibrium state decreased with the increasing PAA contents in the hydrogel, indicating that the higher cross-linking density occurred after adding the PAA. The PAA chains were used as a cross-linking agent and thermal cross-linking was conducted between carboxylic groups of PAA and hydroxyl groups of PVA.

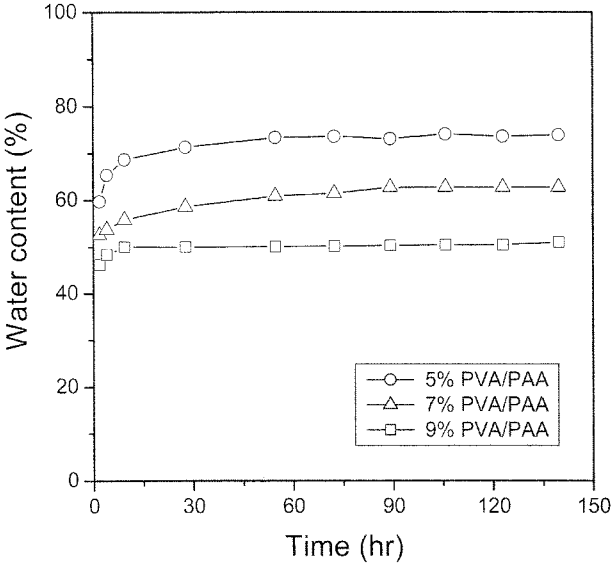

Figure 2. Water content of hydrogels for the various PAA contents at 37 °C.

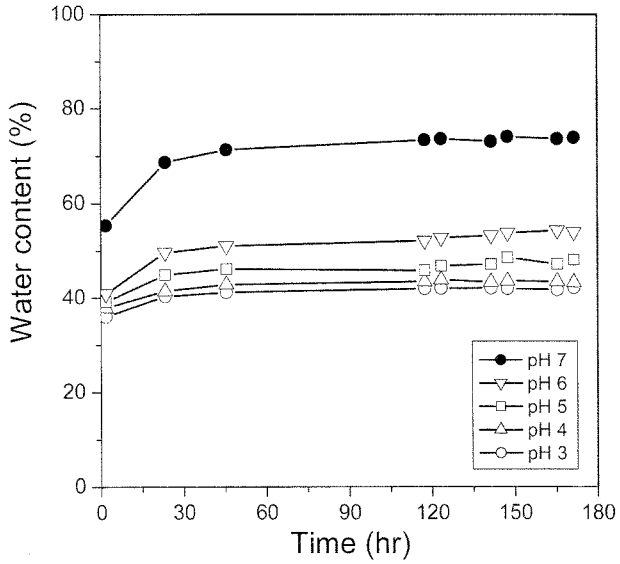

Figure 3. Water content of 5% PVA/PAA hydrogels at various pHs (at 37 °C).

Figure 3 shows pH-sensitive characteristics of hydrogels, which are investigated by swelling test under various pH ranges between 3 and 9. In the swelling kinetics of PVA/PAA hydrogels, all PVA/PAA hydrogels reached an equilibrium after about 30 h. The water contents increased with pH of buffer solution. At pH 7, the water content drastically increased due to the ionization of carboxylic acid group in

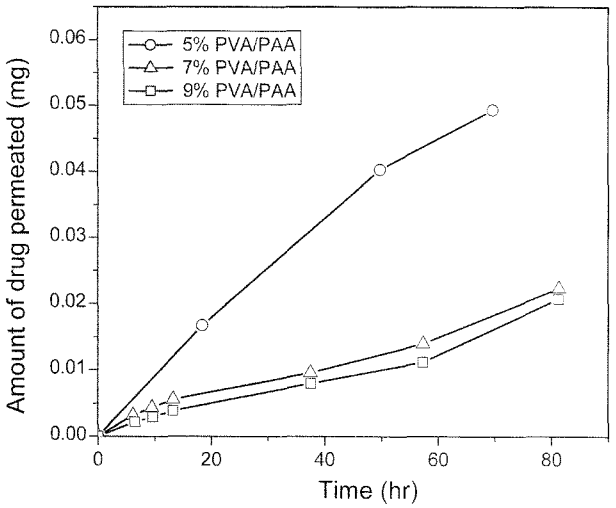

Figure 4. Indomethacin permeation through PVA/PAA hydrogel (at 37 °C and pH 7).

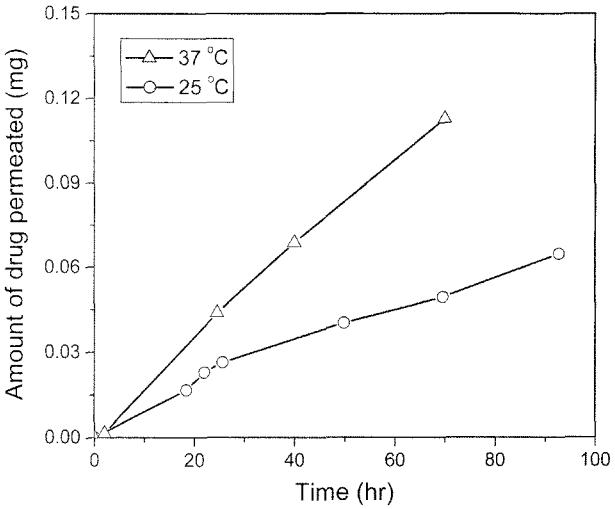

Figure 5. Indomethacin permeation through 5% PVA/PAA hydrogel (pH 7).

the hydrogel. Thus, the ionic repulsion caused by the formation of carboxylation, donated the swelling behavior.

The pH sensitivity is mainly affected by carboxylic groups, which is a weak acid with an intrinsic pK_a of about 4.7; namely, the hydrogels swelled at high pH due to the ionic repulsion of the protonated carboxylic groups, and collapsed at low pH because of the influence of unprotonated carboxylic groups. As the pH value of the buffer solution decreases, ionized COO^- groups become COOH groups, and the resulting neutralization of ionic groups causes the hydrogels to be precipitated.

Drug Permeation Behavior. Drug permeation behaviors were investigated using the diffusion cell and Indomethacine as a model drug. Figure 4 shows typical plots of the mass of solute transported through PVA/PAA hydrogels as a function of time. It can be seen that there was generally a short initial induction time during which the permeation rate varied, followed by a steady rate of permeation through the hydrogel. The permeated amount of drug increased with decreasing the PAA contents because of the low free volume in the hydrogel due to the higher crosslinking density.

Figures 5 and 6 show the Indomethacin transported through PVA/PAA hydrogels as functions of temperature and pH, respectively. The permeated amount of drug increased with temperature of buffer solution. The permeability coefficient increased with pH of buffer solution due to the carboxyl group of PAA, because pH-sensitive hydrogels usually contain either acid or basic pendent groups in the network.

Drug Release Behavior. A solvent sorption method was adopted to load the Indomethacin into the polymer gels. The method has advantages over the simultaneous method in which the drug is incorporated during polymerization. The

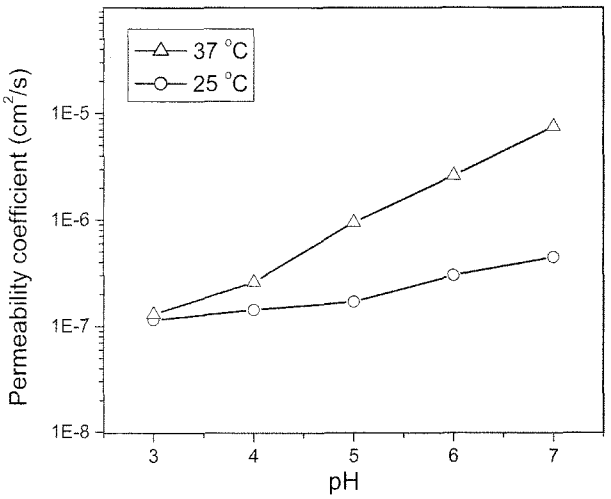

Figure 6. Permeation coefficient through 5% PVA/PAA hydrogel with various pH values and temperatures.

unreacted materials can be removed before drug loading and the loading amount of the gel can be adjusted by controlling the concentration of drug solution and degree of swelling.

Figure 7 shows the kinetic profile of drug release at the various PAA contents. All sample reached at the equilibrium state within the 5 h. The released amount of drug decreased with increase of PAA contents in the hydrogel due to the low swelling ratio in loading the drug.

Figure 8 shows the kinetic profile of drug release at various pHs. All sample reached at the equilibrium state within the 5 h. At the pH 7, the released drug sharply increased because of the pK_a of PAA (pK_a = 4.28). At the higher pK_a, the released amount of drug has the three-folds in comparison with that below pK_a.

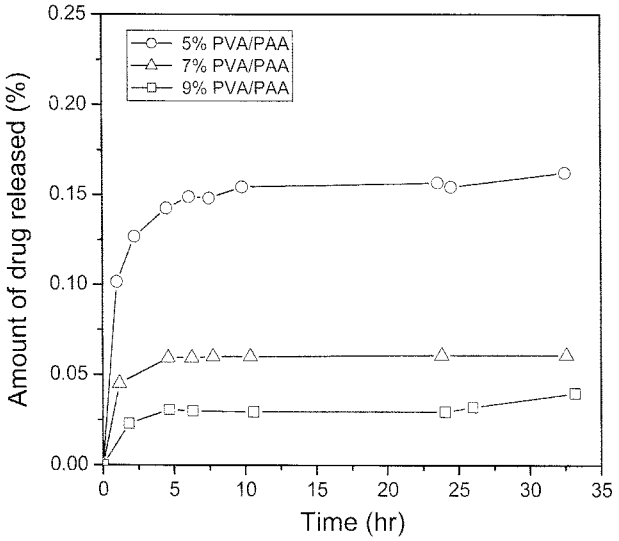

Figure 7. Release of Indomethacin from hydrogels for various PAA contents (at 37 °C and pH 7).

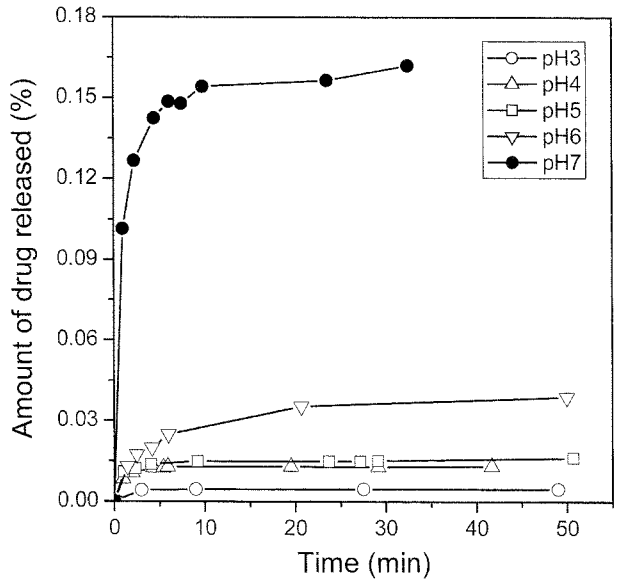

Figure 8. Permeation coefficient from 5% PVA/PAA hydrogel with various pH values.

Conclusions

PVA hydrogel was prepared using the thermal cross-linking method in the solid state. The gelation content increases with the PAA content because the number of carboxylic groups increases with the PAA content in the hydrogels. In the swelling kinetics, all PVA/PAA hydrogels reached an equilibrium after about 30 h. Water contents of the hydrogels at the equilibrium state decreased with the increasing PAA contents in the hydrogel because the higher cross-linking density occurred after adding the PAA. The water contents increased with pH of buffer solution and, in particular, the water content at pH 7 drastically increased due to the ionization of carboxylic acid group in the hydrogel. The permeated amount of drug increased with decreasing the PAA contents because of the low free volume in the hydrogel due to the higher cross-linking density. The permeated amount of drug increased with temperature of buffer solution. The permeability coefficient increased with pH of buffer solution due to the carboxyl group of PAA. In the kinetic profile of drug release at various pHs, all sample reached at the equilibrium state within the 5 h. and the released amount of drug sharply increased at pH 7.

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