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pH-sensitive Swelling Behavior of Poly(vinyl alcohol)-hyaluronic Acid Polymer Hydrogel Membranes

Hye Won Ji, Se Won Chon, Tae Il Yoon, Ho Sang Hwang, Ji Young Kwon, Seung Hoon Shin, Sung Il Chung, and Ji Won Rhim†

Department of Chemical Engineering, Hannam University, Daejeon 306-791, Korea

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Abstract: Poly(vinyl alcohol)(PVA) and hyaluronic acid(HA) hydrogel membranes were prepared with varying HA contents from 10 to 50 wt% of PVA. The water contents of the resulting PVA-HA hydrogel membranes in various pH conditions were measured. And the permeation coefficient of indomethacin was determined using several PVA-HA hydrogel membranes at various pH conditions and also 37°C.

Keywords: *poly(vinyl alcohol), hyaluronic acid, glutaraldehyde, crosslinking, water content, permeation coefficient*

1. Introduction

Hydrogels are hydrophilic polymer networks which may absorb from 10-20% up to thousands of times their dry weight in water. Hydrogels may be chemically stable or they may degrade and eventually disintegrate and dissolve. They are called 'reversible' or 'physical' gels when the networks are held together by molecular entanglements, and/or secondary forces including ionic, H-bonding or hydrophobic force[1]. It is important that the character of the water in a hydrogel can determine the overall permeation of nutrients into and cellular products out of the gel.

Hydrogels of stimuli responsive polymers have promising potential as materials which show structural and physical changes to environmental signals such as temperatures, pH, ionic concentrations, electric field, and light. A number of attempts to control swelling changes in hydrogel through external modulation by stimuli have been reported. Recently, polymer hydrogels have been studied for various applications, including diagnostic, therapeutic, and implanting devices (e.g. catheters, biosensors, artificial skin, controlled release drug delivery systems, and contact lenses)[2].

Selection of hydrogels applied in such processes depends on the characteristics of the gel and the drug or protein. Hydrogels have several important characteristics to be considered in drug diffusion including ionization of the gel, swelling ratio, and reaction to the external environments such as temperature, ionic strength, and pH of the swelling agent)[2]. Among these, pH and thermosensitive polymers receive much attention because these two factors are the most available environments inside the human body.

Hyaluronic acid (HA) is a naturally occurring linear polysaccharide with a high molecular weight. It has a repeating disaccharide structure, consisting of 2-acetamide-2-deoxy-β-D-glucose and β-D-glucuronic acid residues, linked by alternating (1-3)- and (1-4)-glucoside bonding [3,4]. HA is a weak polyacid with a very low charge density for two residues. HA has a high lubrication capacity, water sorption, water retention, and influences several cellular functions, such as migration, adhesion and proliferation[5].

Poly(vinyl alcohol) (PVA) is a water-soluble poly-

†Author for all correspondences
(e-mail : jwrhim@hannam.ac.kr)

hydroxy polymer, employed in practical applications because of its easy preparation, excellent chemical resistance and physical properties, and due to its complete biodegradability[6]. Chemically cross-linked PVA hydrogels have received increasing attention in biomedical and biochemical applications because of their permeability, biocompatibility and biodegradability[7,8]. It is also suitable for ion sensing, and can be applied as a solid support for optical sensors as a result of its ability to form very homogeneous high quality films[9].

In this study, PVA-HA hydrogels were prepared and the swelling behavior and stimuli-sensitive properties in various pH environments were studied. Then, the permeation of indomethacin was measured in terms of the permeation coefficient for the prepared PVA-HA hydrogel membranes at various pH conditions and 37°C.

2. Experimental

2.1. Materials

Fully hydrolyzed PVA with average molecular weight of 89,000-98,000 and indomethacin were purchased from Aldrich (USA). HA (sodium salt, M_v = 1.70×10^7) was provided by Pacific Chemical (South Korea). Glutaraldehyde (25 wt% solution in water) (GA) and hydrochloric acid (HCl) were purchased from Junsei Chemical Co. (Japan). All other chemicals were reagent grade and used without further purification.

2.2. Preparation of PVA-HA Hydrogel Membranes

Aqueous 10 wt% PVA solutions were prepared by dissolving preweighed quantities of dry PVA in ultrapure water and heating at 90°C for at least 6 h. Aqueous 1 wt% HA solutions were prepared. Then two solutions were mixed together by varying HA compositions, 10, 30, and 50% of PVA to form a homogeneous solution for at least 1 day at room temperature. After mixing, the PVA was crosslinked in the presence of HA, using GA (1 wt% of PVA) and HCl (5.0×10^{-4} mol) as the crosslinking agent and catalyst, respectively. This solution poured into a petri dish, and dried at room temperature for 1 day. The dried film was cut into 3 cm×3 cm pieces, then immersed in an acetone-water mixture (9:1 (v/v)). The film was washed with deionized water for 2 days and dried in a 40°C vacuum oven for 1 week.

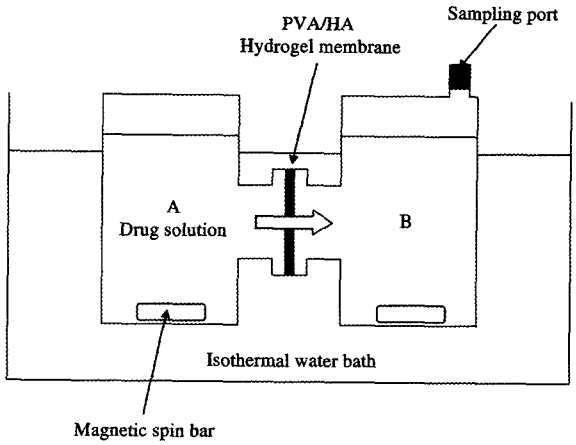

Fig. 1. Two chamber diffusion cell used to measure drug permeability through PVA-HA hydrogel membranes.

2.3. Swelling Properties of PVA-HA Hydrogel Membranes

Water contents of PVA-HA membranes were measured using following method. The sorption capacity of the membrane was measured by immersing the membrane samples in the pure component at 25 and 37°C and also various pH conditions. After being wiped with the cleansing tissue, the membranes were weighed as quickly as possible. This procedure was repeated about 10 times until satisfactory reproducibility was obtained. Then the samples were dried in a vacuum oven at room temperature to a constant weight. Water content (W) was calculated as follows:

$$Water\ content = \frac{W_{wet} - W_{dry}}{W_{dry}} = \frac{g\,H_2O}{g\ dry\ membrane} \quad (1)$$

2.4. Permeation Measurement

The permeation of indomethacin through hydrogels was measured by using the diffusion cell as illustrated in Figure 1. The permeated drug was filled in a chamber A and pH buffer solution in a chamber B, respectively. PVA-HA hydrogel membrane was placed

in between two chambers. The used effective membrane area was 7.06 cm^2. Each chamber was stirred to minimize the concentration gradient. The diffusion cell was put into the constant water bath to maintain the temperature. The permeated concentration of indomethacin was obtained through the sampling the chamber B at constant time interval followed by the measurement of the concentration using UV spectrophotometer (SMART PLUS SP-1900PC). Then, the permeability coefficient was determined from the following equation:

$$P=\frac{-d}{A(1/V_A+1/V_B)}\ln\left[\left(1+\frac{V_A}{V_B}\right)\frac{C_t}{C_0}-\frac{V_A}{V_B}\right] \quad (2)$$

where P : permeability coefficient (cm^2/s), V_A: volume of chamber A (mL), V_B: volume of chamber B (mL, reservoir chamber), C_0: indomethacin concentration at time 0 (mg/L), C_t: indomethacin concentration at time t (mg/L), d: membrane thickness (μm), A: effective membrane area (cm^2)

3. Results and Discussion

It is reported that HA could be crosslinked with GA in acetone-water mixtures[10]. When the blended PVA and HA film is placed in the crosslinking medium, both polymers are separately crosslinked and, as a result, forms the interpenetrating polymer network (IPN) since it is well known that PVA is crosslinked with GA[11]. Therefore, it is considered that the crosslinking polyelectrolyte captured the hydrophilic group and produced a tight and ionic bonded structure and also the crosslinking degree influenced on the water content[12].

Figure 2 shows the water content for the hydrogel membrane, HA=10 wt% of PVA at 25 and 37°C in the low pH region, pH=3 to 7. As pH value increases, the water content gradually increases. To determine the characterization of the response of PVA-HA hydrogels to the change in external pH conditions, PVA-HA hydrogels were allowed to swell to equilibrium in an aqueous swelling medium of pH 3-7 at 25 and 37°C. It is clear that the hydrogels in question are more labile

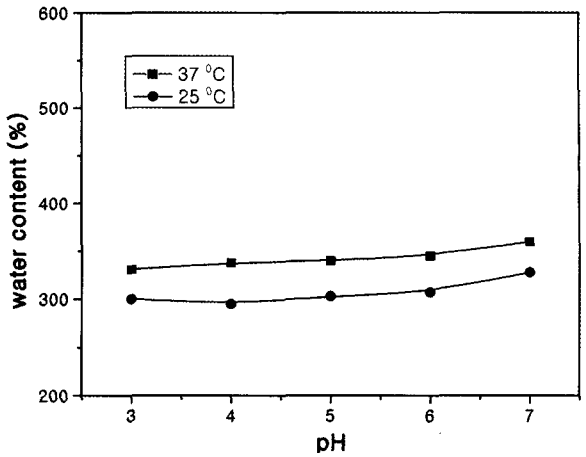

Fig. 2. Water content of PVA-HA hydrogel at various pH values (HA 10 wt%).

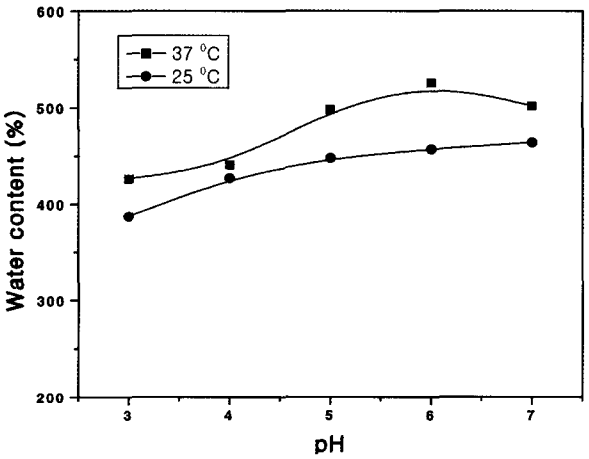

Fig. 3. Water content of PVA-HA hydrogel at various pH values (HA 30 wt%).

in acidic conditions than in near neutrality and basic conditions. The water content increases when the pH is below 4 (pK_a value of HA is 2.9)[12], which is caused by the dissociation of ionic bonds in the hydrogels. In this case, the pH brings about the dissociation of ionic bonds because most carboxyl groups are charged and change into a protonated form. Under extremely low pH conditions, most HA carboxyl groups are part of COOH. On the other hand, at higher pH levels, most carboxyl groups of HA are -COO^- form. This trend shows same in higher HA composition of PVA as illustrated in Figures 3 and 4, which HA contents are 30 and 50 wt%, respectively.

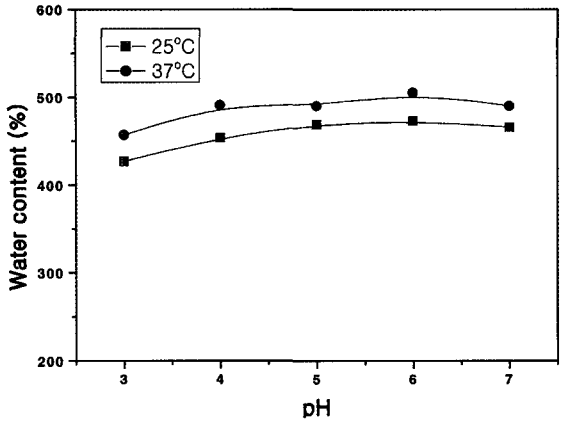

Fig. 4. Water content of PVA-HA hydrogel at various pH values (HA 50 wt%).

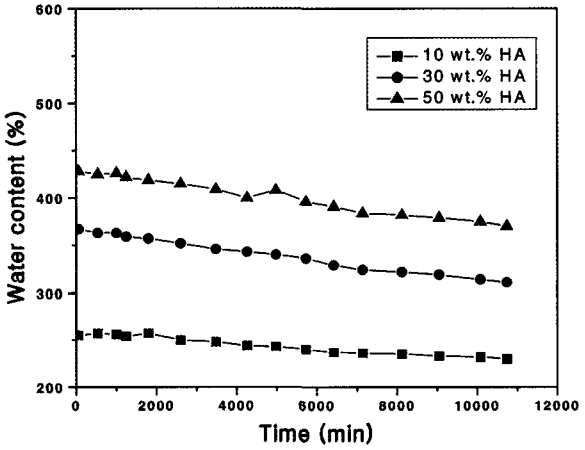

Fig. 5. Water content of PVA-HA hydrogel with various HA contents as a function of time (pH 2, 25°C).

And also the HA fraction in PVA-HA hydrogels led to an increase in the water content as shown in Figures 2 to 4. This is simply attributed to the fact HA has a large hydrophilic content. This behavior may be due not only to the crosslinking degree of the PVA-HA network but also to the amount of HA, having a large number of water-bonding site.

Figure 5 shows the change of the water content at 25°C and pH 2 as the time passes. The gradual weight loss can be observed with time passing. This may be due to the loss of unreacted polymers, PVA and HA, during the swelling measurement. It is also observed that the weight loss of HA=50 wt% membrane is more than that of HA=10 wt% membrane. It is reported that

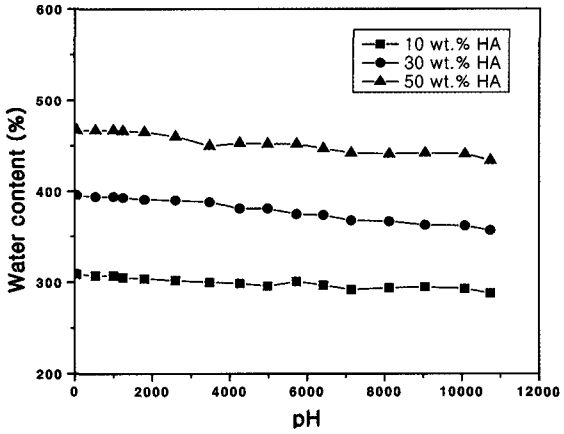

Fig. 6. Water content of PVA-HA hydrogel with various HA contents as a function of time (pH 2, 37°C).

the hemiacetalization rather than the full acetalization is more probable when the aldehyde group of GA is reacted with the hydroxyl group of HA since the reaction proceeds so slowly[10]. However, PVA is a well-known polyol which undergoes quickly full acetalization with aldehyde (6-membered ring upon reaction of 1,3-glycol of PVA with GA) in an acidic medium. In other words, when both PVA and HA exist in the crosslinking medium of GA and water, PVA crosslinking reaction may proceed more than HA crosslinking reaction at same desired reaction time. Therefore, the weight loss becomes more severe as HA portion in PVA-HA hydrogels increases. At elevated temperature, 37°C, same phenomena can be observed as illustrated in Figure 6.

Figures 7 and 8 show the results carried out under the same experimental conditions except for pH=7. As expected, the same trend is obtained as the previous Figures 5 and 6.

Next Figure 9 illustrates the permeation of indomethacin through several hydrogel membranes as a function of HA contents at various pH conditions in terms of the permeability coefficient. The permeability coefficient increases with increasing HA contents at each pH value. As mentioned above, the resulting structure of HA may be more loosen than that of PVA since HA has the hemiacetalization whereas PVA undergoes the full acetalization with GA. And as the

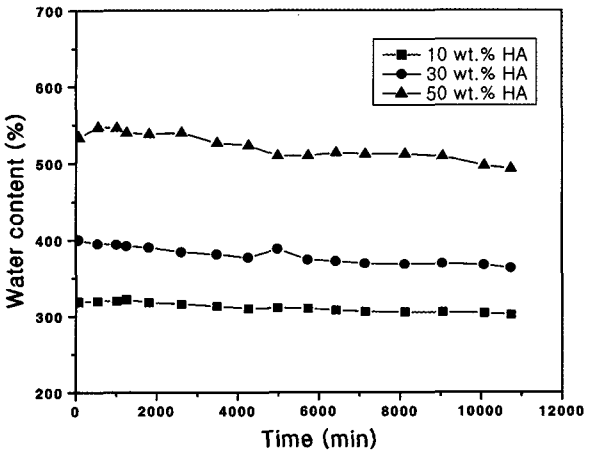

Fig. 7. Water content of PVA-HA hydrogel with various HA contents as a function of time (pH 7, 25°C).

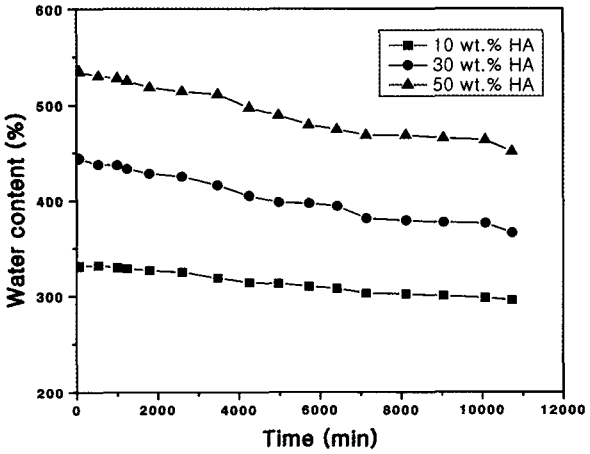

Fig. 8. Water content of PVA-HA hydrogel with various HA contents as a function of time (pH 7, 37°C).

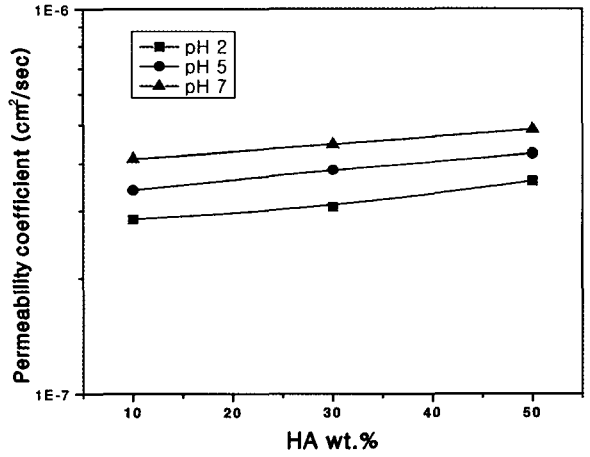

Fig. 9. Indomethacin permeability coefficient for PVA-HA hydrogel membranes at various pH conditions and 37°C.

pH value increases, the permeation of indomethacin also increases. The more water content in a hydrogel can leads the more permeation of indomethacin out of the gel as described in Figure 1 through Figure 3.

4. Conclusion

Poly(vinyl alcohol)(PVA) and hyaluronic acid (HA) hydrogel membranes were prepared with varying HA contents, 10, 30 and 50 wt% of PVA. The water contents of the PVA-HA hydrogel membranes in various pH buffer solutions were measured at 25 and 37°C. And the permeation coefficient of indomethacin was determined using several PVA-HA hydrogel membranes at various pH conditions and also 37°C. It was observed that the water contents increased with increasing pH value and HA contents, respectively. The weight loss of HA=50 wt% membrane was more than that of HA=10 wt% membrane due to the hemiacetalization HA caused by the slow reaction. The permeability coefficient increases with increasing HA contents at each pH value.

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