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Preparation and Swelling Behaviors of Hydrogel Composed of Alginate, Poly(N-isopropylacrylamide) and Polyaniline

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Abstract: Comb-type graft hydrogels composed of alginate and poly(N-isopropylacrylamide) (PNIPAAm) were prepared to manifest rapid temperature and pH sensitivity. To appear the electro-sensitivity, the polyaniline, conducting polymer, was added into the matrix. The swelling kinetics and ratios were compared under the various compositions of polyaniline. The swelling behaviors revealed that conducting polymer/hydrogel composites could control the swelling ratio and kinetics. The addition of polyaniline in the matrix improved the thermal stability in comparison with that of the hydrogel without polyaniline. In temperature sensitivity, the adding the polyaniline into the matrix decreased the degree of change in the swelling ratio. The swelling ratios continuously increased with increasing pH values. The drug release rate from the hydrogel increased with the adding the polyaniline and the applying the direct voltage to the hydrogels.

Keywords: *hydrogels, polyaniline, conducting polymer, electric stimulus alginate*

1. Introduction

Stimuli-sensitive membranes have the capability to change their swelling behavior, permeability, or mechanical strength in response to external stimuli, such as small changes in pH, ionic strength, temperature and electromagnetic radiation[1-4], indicating that the stimuli may be either chemical signals, such as pH, metabolites, and ionic factors, or physical signals, such as temperature or electrical potential. Among these stimuli, pH/temperature-responsive systems have been extensively studied because these two factors are important environments inside the human body.

In our previous reports[1,4], we synthesized alginate/poly(N-isopropylacrylamide) (PNIPAAm) comb-type graft hydrogels which were able to respond rapidly to temperature and pH changes. Alginate has several unique properties[5-6] and has been much used in medical applications such as wound dressing, scaffolds and delivery matrices. The PNIPAAm exhibits large swelling changes in aqueous media in response to small changes in temperature. This is manifested in aqueous solutions of PNIPAAm as a lower critical solution temperature (LCST) near 32°C[7-9]. PNIPAAm chains hydrate to form expanded structures in water when the solution temperature is below its LCST but becomes compact structures by dehydration when heated up above the LCST. In addition, comb-type graft membranes show rapid swelling behaviors compared to semi-interpenetrating network (IPN) hydrogels[1,4].

Thus, we were interested in the mixing the conducting polymer in the pH and temperature sensitive hydrogels, because the hydrogel composed of conducting polymer have the potential application as electrically stimulated controlled release devices[10-11] or artificial muscles. Several groups have performed their studies on controlled release from conducting polymer-hydrogels

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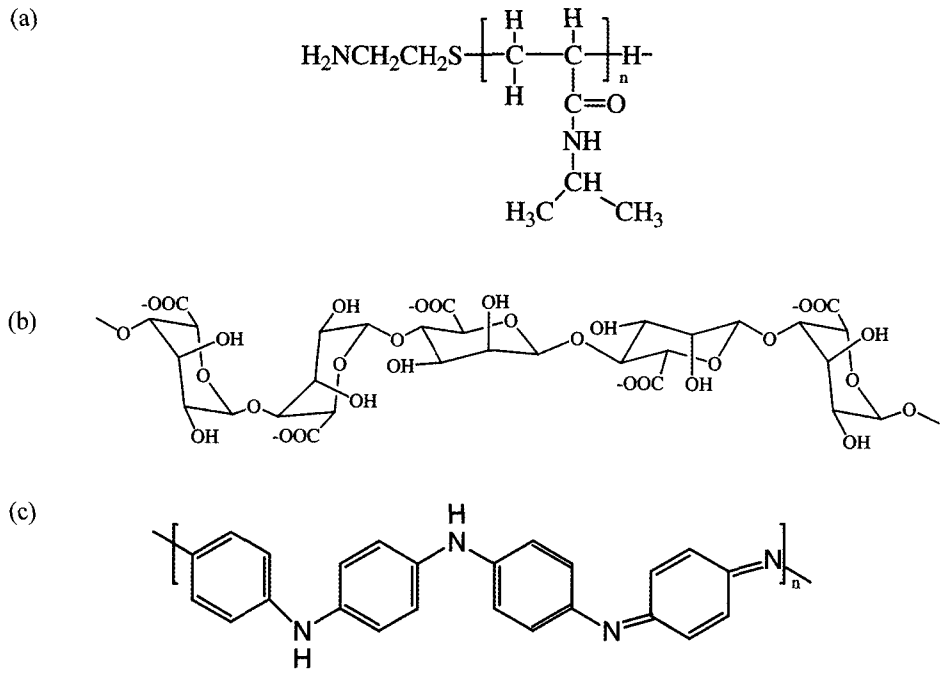

Fig. 1. Molecular structures of (a) telechelic PNIPAAm-NH_2, (b) alginate and (c) polyaniline.

composites. Wallace et al. suggested that there were various dimensions to be formed and showed spatial distribution of conducting polymer throughout the gels [10]. They performed controlled release experiments under applying a constant potential. Massoumi et al. showed that polyaniline monolayer as inner film or outer film was made of four methods to compare the release rate[11]. In addition, our previous research revealed that electric-release system using poly(vinylalcohol)/poly(acrylic acid) IPN hydrogels showed the possibility to be used for drug delivery actuated by electric signal and sensor in feedback controlled system[12].

The purposes of this study are to prepare the pH, temperature and electro-active hydrogels composed of alginate, PNIPAAm and polyaniline (see Figure 1), to investigate the swelling behaviors under various stimuli and to evaluate the controlled release of indomethacin (IMC) from the hydrogel under electric stimulus.

2. Experimental

2.1. Materials

N-isopropylacrylamide (NIPAAm) (Aldrich Chem. Co.) was purified by recrystallization from n-hexane/toluene. Sodium alginate and 2-aminoethanethiol hydrochloride (AESH) were purchased from Aldrich Chemical Co. (Milwaukee, WI). Polyaniline in emerald base was purchased from Aldrich Chemical Co. N,N'-Azobisisobutyronitrile (AIBN) (Aldrich Chem. Co.) was recrystallized from methanol. N,N-Dimethylformamide (DMF) (Duksan Pure Chemical Co., LTD, Korea) was purified by distillation. 1-Ethyl-(3-3-dimethylaminopropyl) carbondiimide hydrochloride (EDC) and N-hydroxysuccinimide (NHS) were purchased from Sigma Chemicals. Indomethacin was purchase from Aldrich Chem. Co. Calcium chloride ($CaCl_2$) and ethyl ether (Duksan Pure Chemical. Co., LTD, Korea) were used without further purification. Water was first treated with a reverse osmosis system (Sambo Glove Co., Ansan, Korea) and further purified with a Milli-Q Plus system (Waters, Millipore, MA, USA).

2.2. Preparation of Hydrogels Composed of Alginate, PNIPAAm and Aniline

The semi-telechelic PNIPAAm were synthesized by the method reported in our previous study[1,4]. Instead

Table 1. Designation and Composition of the Hydrogels

Hydrogel Type	Sample code	Weight Parts		
		Alginate	PNIPAAm-NH_2	Polyaniline
Comb-type graft hydrogels	Comb	50	50	0
	Comb-10	50	50	10
	Comb-20	50	50	20
	Comb-30	50	50	30

of directly grafting the NIPAAm monomer onto the alginate chain, semi-telechelic PNIPAAm with amino end group was synthesized by radical polymerization using 2-aminoethanethiol hydrochloride as the chain transfer agent, and was grafted onto alginate having carboxyl groups. To prepare the comb-type grafted polymer chains composed of PNIPAAm and alginate, the aqueous solution of alginate (1 wt%), NHS, EDC and PNIPAAm- NH_2 (5 wt%) were dissolved in water at room temperature. Each solution had a molar ratio of alginate: EDC:NHS of 2:2:1 on the basis of carboxyl group in alginate. The solution mixture was continuously stirred at room temperature. The reactant was precipitated into THF-hexane (4:1) and then dialysis for 3 days and dried in vacuum oven.

As shown in Table 1, the product (3 g) was dissolved in water to prepare 5 wt% solution then polyaniline powder (0, 10, 20, 30 weight parts, respectively) was dispersed homogeneously in it and poured into a petri- dish and dried to constant weight at room temperature in a vacuum oven. Crosslinking of alginate was done with $CaCl_2$ by the same method as that for the above prepared hydrogels. To cross link the hydrogels, the dry film was immersed in 20 mL of $CaCl_2$ aqueous solution (0.5 wt%) and cut into the size of 1.0 $\times$1.0 cm^2. After 30 min at room temperature, the hydrogels were washed in water and dried at room temperature in a vacuum oven.

2.3. Thermogravimetric Analysis

TGA was done using Perkin-Elmer System 7 (Connecticut, USA) to investigate the thermal stability of the polymer. Decomposition profiles of TGA were recorded with a heating rate of 10°C/min in nitrogen between 10°C and 600°C.

2.4. Determination of Swelling Property

A swelling study was conducted on the hydrogels to observe the behavior as functions of the temperature, pH and direct voltage in the swelling medium. To measure the swelling behaviors, pre-weighed dry samples were immersed in water. After wiping off the excessive water on the samples' surface, the weight of the swollen samples was measured at various time intervals. The swelling ratio was calculated using the following formulae:

$$\text{Swelling ratio} = (W_s - W_d)/W_d$$

where, W_s is the weight of hydrogel in the swollen state, and W_d is the dry weight of the hydrogel after drying the gels in a vacuum oven for two days.

2.5. Loading of Indomethacin (IMC) Into Hydrogels

IMC (1-[p-chlorobenzoyl]-5-methnowl-2-methylindole-3-acetic acid) which had a hydrophobic property was used as a model drug. The 0.4 g of IMC was dissolved in 23 mL of ethyl alcohol and stirred at room temperature. The IMC was loaded into dried comb-type graft hydrogels by swelling-loaded technique. Each of samples (1 cm by 1 cm) soaked into aqueous drug solution for 2 days at 25°C and allowed to swell to an equilibrium to achieve a high loading content in the hydrogels. The fully swollen sample removed from drug solution were blotted with filter paper to eliminate the surface water and dried at a room temperature.

2.6. Drug Release Behaviors Under Electric Stimulus

Drug-loaded comb-type graft hydrogels were placed

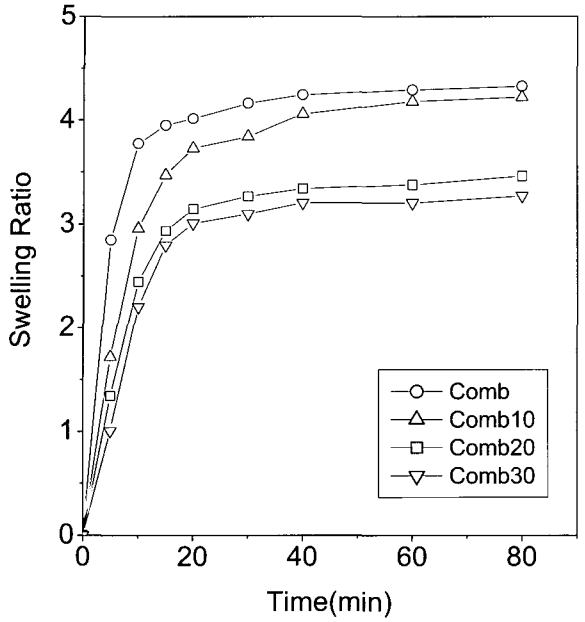

Fig. 2. Swelling kinetics of the hydrogels in deionized water (pH=5.4) at 25°C.

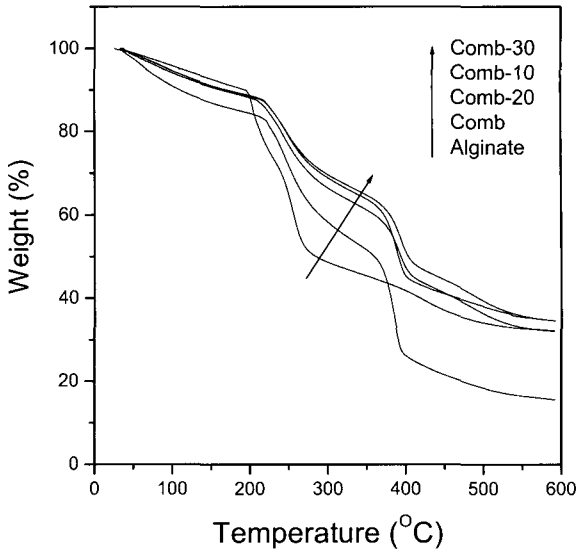

Fig. 3. Thermogravimetric analysis of alginate and comb-type hydrogel series.

and fixed in the middle of two carbon electrodes, whose width is about 1 cm, in distilled water under gentle stirring to remove the boundary layer of drug. Appropriate voltage was altered at desired time interval to investigate the electrically stimulated released behaviors. Then, the 3 mL aliquots sampled periodically from the release medium were analyzed by using a ultraviolet (UV) spectrophotometer (Shimatzu, Model UV-2101PC). The UV absorbance of IMC was measured at λ_{max} = 320 nm, which agreed with the literature. Samples were taken from the 8 mL solution at regular intervals for analysis and subsequently returned to the franz cell. Solutions with known concentrations of IMC in distilled water were used to make a calibration curve, which was liner above the absorbance of 0.01551. The concentration of IMC was calculated using a previously prepared calibration curve.

3. Results and Discussion

3.1 Swelling Kinetics of Hydrogels

Figure 2 shows the time-dependence of the swelling kinetics of comb-type graft hydrogels for polyaniline content of 0, 10, 20 and 30 weight parts. The swelling ratio of comb-type graft hydrogels reached an equilibrium state within 15 min. In our previous study, we already concluded that the fast rate of swelling and deswelling was affected by the freely mobile chain in comb-type graft hydrogels.

The swelling ratio of comb-type graft hydrogels decreased with increasing the ratio of polyaniline in hydrogels because the polyaniline powders were acted as filler. Thus, the degree of the swelling ratio of the hydrogels tended to depend on the composition of polyaniline.

3.2 Thermal Stability

Thermal stabilities of the composite hydrogels were measured using TGA analysis. Figure 3 shows the weight loss curves recorded with a heating rate of 10°C/min in nitrogen between 30 and 600°C. The thermal degradation profile of comb-type grafted hydrogel without polyaniline is relatively lower thermal stability in comparison with alginate alone due to the introducing the PNIPAAm chain of low thermal stability.

However, the polyaniline-added hydrogels show a slower thermal decomposition in comparison with that of alginate alone, because the introduction of the

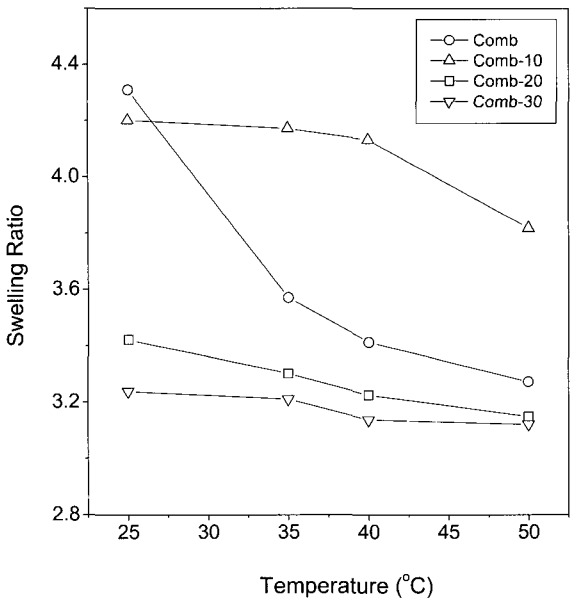

Fig. 4. Temperature-dependent swelling behaviors of the hydrogels in deionized water (pH=5.4)

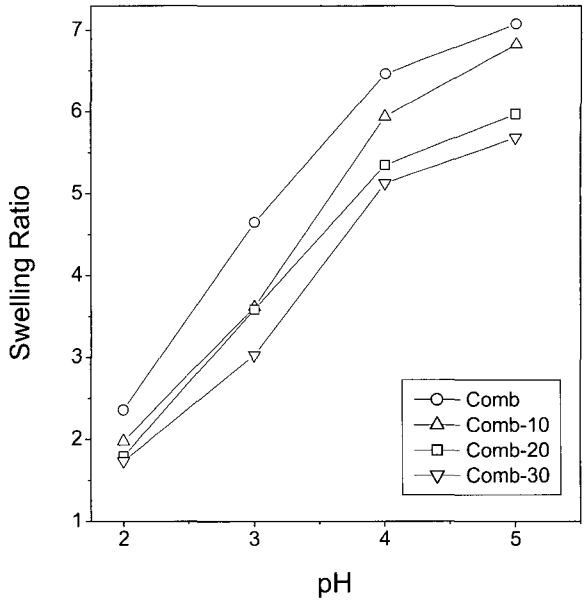

Fig. 5. pH-dependent swelling behaviors of the hydrogels at 25°C.

polyaniline powders inside the matrix increased thermal stability caused by the interaction with the carboxyl groups of alginate. The amine groups of polyaniline might be interacted with the opposite charged alginate, in the results of forming the polyelectrolyte and improving thermal stability.

3.3. Stimuli-response Swelling Behaviors of Hydrogels

Temperature dependence of equilibrium swelling of hydrogels is shown in Figure 4. All hydrogels had significant changes in swelling ratio over the temperature range between 30 and 35°C. It could be expected that the temperature-sensitivity of PNIPAAm was due to the dissociation of water molecules surrounding hydrophobic N-isopropyl groups in PNIPAAm. The adding the polyaniline into the matrix decreased the degree of change in the swelling ratio because the polyaniline is not temperature-sensitive polymer.

Figure 5 shows that pH-responsive properties of hydrogels at 25°C with changes in pH whose range was between 2 and 5. The swelling ratio of comb-type graft series continuously increased with increasing pH values. This is because comb-type grafted hydrogels have carboxylic acid in alginate. At low pH region, most carboxylic acid groups in alginate are in the form of COOH, indicating the hydrogel is shrunk[13-15]. The carboxylic acid of guluronic acid in alginate becomes the carboxylate ion (COO^-) at pH >3.2, the number of ammonium ion exceeds that of carboxylate ion. As the pH of the medium increases, the carboxylic acid groups become ionized, and the resulting electrostatic repulsion in the network causes the hydrogels to swell.

3.4. Drug Release Behaviors of Comb-type Graft Hydrogles Under Electric Stimulus

To investigate the electric stimulus release behaviors of drug to conductive polymer, we measured the amount of released drug from the hydrogels into release medium at 25°C by UV-spectrophotometer.

Figure 6 shows drug release results from the hydrogels under applied voltage. When the voltage was applied to the matrix, the release rate was faster than not applied matrix both containing polyaniline and not. In addition, the addition of polyaniline improved the drug release rate. As shown in Figure 6-(b), over the first 10 min, the release rate was very fast and majority of

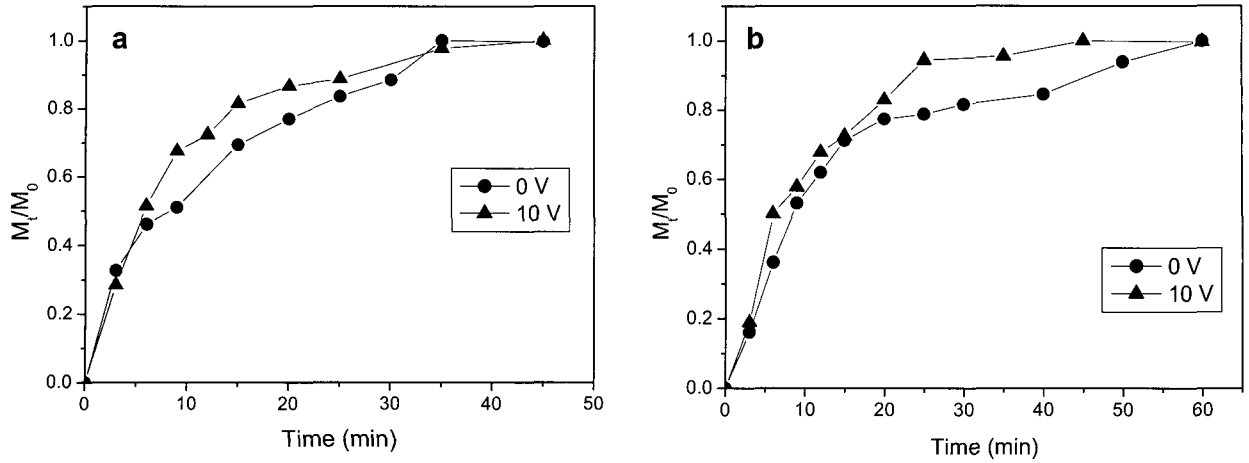

Fig. 6. IMC release profiles of (a) comb and (b) comb-30 hydrogels under direct voltage in in deionized water (pH=5.4).

the drug was released. When electric stimulus was not applied, it took about 25 min for comb to reach 80% of release equilibrium amount. But it took about 10 min to reach the same ratio under 10 V.

4. Conclusions

The swelling ratio of comb-type graft hydrogels decreased with increasing the ratio of polyaniline in hydrogels. The thermal degradation profile of comb-type grafted hydrogel without polyaniline is relatively lower thermal stability in comparison with alginate alone, whereas the polyaniline-added hydrogels show a slower thermal decomposition in comparison with that of alginate alone. In temperature sensitivity, the adding the polyaniline into the matrix decreased the degree of change in the swelling ratio. The swelling ratios continuously increased with increasing pH values. When the voltage was applied to the matrix, the release rate was faster than not applied matrix both containing polyaniline and not. In addition, the addition of polyaniline improved the drug release rate.

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