Drug Release Behavior of Electrical Responsive Poly(vinyl Alcohol)/Poly(acrylic Acid) IPN Hydrogels under an Electric Stimulus

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ABSTRACT: The electrically modulated properties of interpenetrating polymer networks (IPN) composed of poly(vinyl alcohol) (PVA) and poly(acrylic acid) (PAAc) under electric field were investigated for drug delivery systems. PVA/PAAc IPNs with various compositions were synthesized by a sequential method, that is, ultraviolet polymerization of AAc in the mixture of PVA and aqueous AAc monomer solution, followed by a freeze-thawing process to prepare elastic hydrogels. The amount of loaded drug significantly increased with the content of PAAc containing ionizable groups in IPN. The amount of introduced ionic drug (cefazoline) was greater than that of the nonionic drug (theophylline). Release behaviors of drug molecules from negatively charged PVA/PAAc IPN were switched on and off in a pulsatile pattern depending on the applied electric stimulus. The released amount and the release rate of drug were influenced significantly by the applied voltage, ionic group contents in IPN, ionic properties of drug solute, and the ionic strength of release medium. In addition, the ionic properties of drug molecules dramatically affected release behaviors, thus the release of ionic drug was much more enhanced than that of the nonionic drug. © 1999 John Wiley & Sons, Inc. J Appl Polym Sci 74: 1752–1761, 1999

Key words: poly(vinyl alcohol); poly(acrylic acid); IPN; hydrogel; electric stimulus

INTRODUCTION

There has been a variety of concepts in drug delivery system to get a maximum therapeutic effect of drug and minimum side effect.[1–4] As the meaning of "drug delivery" expands to the targeting drug at specific body site or releasing drugs when needed as well as the controlling release rate of drug, the stimuli-sensitive drug delivery has been required depending on the changes of physiological signal in the body. The stimuli-sensitive system using polymer can change volume and shape reversibly according to the various external physicochemical factors.[2–4] For example, chemical signals, such as pH, metabolites, and ionic factors, will alter the molecular interactions between polymer chains or between polymer chain and solutes being present in a system. The physical stimuli, such as temperature or electrical potential, may provide various energy sources for molecular motions and altering molecular interactions. These interactions will change properties of polymer materials such as swelling, solubility, configuration or conformational change, redox states, and crystalline/amorphous transition.[5–12]

Among them, electric current sensitive hydrogels composed of polymeric material actuated by electric stimulus seem to be particularly interesting in connection with the fact that the mechan-

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ical energy is triggered by an electric signal.[13–25] Electric-current sensitive hydrogels are usually made of polyelectrolytes and insoluble, but swellable polymer networks which carry cations or anions. This system can transform chemical free energy directly into mechanical work to give isothermal energy conversion and can be used as actuators, electromechanical engines, artificial muscle, chemical valve, and drug delivery system.[13–25]

Grodzinsky et al.[19,20] reported that collagen fibers immersed in an electrolyte bath could deform and thereby perform mechanical work under an external electric stimulus. They also altered the restricted diffusion of sucrose through collagen membranes via electrodiffusion, producing flux changes of up to 25%. Tanaka et al.[21] showed that the partially hydrolyzed polyacrylamide gel underwent phase transition upon application of an electric field, and collapsed if the gel was placed in a solvent such as 50% acetone-water binary mixture. Osada et al.[23–25] reported that the hydrogel made of weakly crosslinked poly(2-acrylamido-2-methylpropanesulfonic acid) possessed motility in water by the contraction and curvature of a strip of gel. They also observed both mechanical deformation and changes in the hydraulic permeability of polyelectrolyte gels subjected to DC electric fields. They showed bioactive materials, such as pilocarpine hydrochloride, glucose and insulin, were successfully released from the gel by switching the electric field alternately on and off.[23–25]

Electrically controlled drug delivery may particularly offer unique advantages for providing on-demand release of drug molecules from implantable or transdermal reservoirs. In addition, electrical control is advantageous for coupling to sensors and microelectronics in feedback controlled systems.[4,19]

In our previous studies,[26–29] we already prepared the novel interpenetrating polymer network (IPN) hydrogels composed of poly(vinyl alcohol) (PVA) and poly(acrylic acid) (PAAc) by a unique sequential method through ultraviolet (UV) irradiation and a repetitive freezing-thawing process. To investigate the feasibility as a stimuli-responsive drug delivery system, we characterized pH- and temperature-dependent swelling properties of PVA/PAAc IPN in buffer solution at various pH and temperature ranges.[26] The swelling ratios of all PVA/PAAc IPNs were relatively high, and they showed reasonable sensitivity to both pH and temperature. In addition, we loaded the model drug into PVA/PAAc IPN hydrogels by a swelling-loading method and examined their release behavior from drug-loaded IPN.[27] The release of drug incorporated into IPN hydrogels showed pulsatile patterns in response to both pH and temperature. The release mechanism of drug was dominated by the magnitude of swelling in the PVA/PAAc IPN hydrogels. Furthermore, to look for a potential application as a stimuli-sensitive drug delivery system, the solute permeation through swollen PVA/PAAc IPN hydrogel membrane was investigated by varying several environmental factors and compared using the solutes having different characteristics such as size, molecular weight, and pKa values.[28] Recently, we focused on the electric responses of these PVA/PAAc IPN hydrogels.[29] The bending behavior of these IPN hydrogels under an electric field and factors affecting electric sensitivity were investigated. When a swollen PVA/PAAc IPN was placed between a pair of electrodes, the IPN exhibited the bending behaviors upon applied electric field.[29] Electric responsive behavior was driven as a function of applied voltage, charge density of ionic group within IPN, and electrolyte concentration of external solution.

In the present study, we concentrated on the release behaviors of drug from PVA/PAAc IPN hydrogels depending on the electric stimulus to apply as an electrically modulated drug delivery system. We examined the release behavior of drug by varying influencing factors such as applied voltage, content of charge group within PVA/PAAc IPN, ionic properties of drug, and ionic strength of release medium.

EXPERIMENTAL

Materials

Acrylic acid (AAc) monomer obtained from Junsei Chemical Co. (Tokyo, Japan) was used after purification with inhibitor removal column (Aldrich Chemical Co., Milwaukee, WI) to eliminate hydroquinone inhibitor. PVA [DP (degree of polymerization) = 2500, degree of deacetylation = 99%] was purchased from Shinetsu Chemical Co., Ltd. (Tokyo, Japan). Methylenebisacrylamide (MBAAm) and 2,2-dimethoxy-2-phenylacetophenone (DMPAP), purchased from Aldrich, were used as a crosslinking agent and photoinitiator, respectively. All

Table I Composition and Designation of PVA/PAAc IPNs

Sample[a]	Feed Composition PVA : PAAc (mol %)	Mass of Acrylic Acid (g)	Mass of MBAAm[b] (g)	Mass of DMPAP[c] (g)
IPN64	60 : 40	2.16	0.023	0.0043
IPN55	50 : 50	3.26	0.035	0.0065
IPN46	40 : 60	4.89	0.052	0.0098
IPN37	30 : 70	5.70	0.061	0.0114

[a] Each sample was prepared using 10 wt % PVA aqueous solution.
[b] 0.5 mol % of MBAAm was dissolved in acrylic acid.
[c] 0.2 wt % of DMPAP was also dissolved in acrylic acid.

other chemicals used were reagent grade and used as purchased without further purification. Theophylline was purchased from Aldrich and cefazoline was kindly donated from Chongkeundang R&D Center in Seoul, Korea.

Preparation of PVA/PAAc IPN Hydrogels

The IPN hydrogels composed of PVA and PAAc were prepared by the unique sequential method reported in our previous studies.[26–29] PAAc as an initial network was synthesized inside of PVA solution by using UV irradiation, then PVA networks as a secondary network were formed by a repetitive freeze-thawing process. PVA was dissolved in deionized water and heated at 80°C for 2 h to make the 10 wt % aqueous solution. Acrylic acid monomer solution containing 0.2 wt % photoinitiator, DMPAP, and 0.5 wt % crosslinking agent, MBAAm, was mixed with PVA aqueous solution in which the weight ratios of the equivalent amount of vinyl alcohol residue in PVA to AAc monomer became 6:4, 5:5, 4:6, and 3:7. The mixture solutions were poured onto petri-dishes and exposed to radiation from a 450 W UV lamp (Ace Glass Co.) for 1 h under N_2 atmosphere. The irradiated samples were frozen at −50°C for 6 h and thawed at room temperature for 2 h. These freezing-thawing cycles were repeated eight times. The synthesized gels were removed from the petri-dishes, cut into a rod or disk shape, and washed by deionized water to remove any residual AAc monomer. The swollen gels were dried, first at 25°C for 1 day, and then at 45°C *in vacuo* for an additional 2 days and finally at 25°C for 1 day. Feed composition and designation of each PVA/PAAc IPN sample are listed in Table I.

Swelling Properties of PVA/PAAc IPN Hydrogels

To measure the swelling ratio of IPN, the dried PVA/PAAc IPN was placed in buffer medium of different pH value and ionic strength at 25°C until hydrated weight reached a constant value. From our previous experiments,[26] it was confirmed that the swelling of these PVA/PAAc IPN disks was enough to reach an equilibrium state within 24 h. After excessive water on the surface of IPN disk was removed using filter paper, the hydrated weight of swollen gel was measured. The swelling ratio of each sample was evaluated as swelling ratio = $(W_s - W_d)/W_d$ where W_s and W_d were fully swollen and dry weight of each sample, respectively.

Electrically Modulated Properties of PVA/PAAc IPN

The PVA/PAAc IPNs hydrogels were swollen in NaCl aqueous solution at room temperature and cut into a 50 × 2 × 2 mm rectangular column. After the one end of the sample column was fixed and placed vertically between two carbon electrodes in NaCl aqueous solution, its bending behavior was investigated under electric field. The bending degree of PVA/PAAc IPNs hydrogels from vertical position was measured by varying the applied electric potential, the contents of ionic group within IPN, and the ionic strength of medium.

We also examined the deswelling of these IPN hydrogels in contact with electrode under aerobic condition. PVA/PAAc IPN was swollen to equilibrium condition in distilled-deionized water at room temperature. The swollen IPN was placed between two 15 × 15 mm platinum plates. To prevent from changing the area of contact between the surface of PVA/PAAc IPN and platinum plates, we applied the constant dead weight on platinum plate. The released water from IPN was continually removed using filter paper and the weight change of swollen PVA-PAAc IPN was checked periodically under electric field. The de-

swelling water ratio of each IPN was evaluated as W_t/W_{t0} where W_{t0} and W_t were the initial weight of fully swollen IPN and the weight of IPN at deswelling time t, respectively.

Loading of Drug into PVA/PAAc IPN

In this experiment, cefazoline as an ionic drug and theophylline as a nonionic drug were respectively adopted. These two model drugs were loaded into each PVA/PAAc IPN sample by the swelling-loading technique. That is, dried PVA/PAAc IPN disks were soaked into each aqueous drug solution for 3 days at 25°C, and allowed to swell to an equilibrium to achieve a high loading content in the IPN. The fully swollen IPN hydrogels removed from the drug solution were blotted with filter paper to eliminate the surface water and dried as already mentioned in the synthesis procedure of IPN.

The amount of drug loaded into PVA/PAAc IPN was determined from the weight difference of IPN between the fully swollen state in drug aqueous solution and completely dried state.

Drug Release Experiment under Electric Field

To investigate the release behaviors of drug from PVA/PAAc IPN hydrogel according to electric stimulus, release experiment of two model drugs (cefazoline and theophylline) was conducted in various conditions. Drug-loaded PVA/PAAc IPN was placed in the middle of two carbon electrodes in a desired release medium under gentle stirring to remove the boundary layer of drug. Then, the amount of drug released into medium was monitored by varying factors such as applied electric potential, charge density due to ionic group within IPN, ionic strength of medium, and ionic properties of drug. The 3-mL aliquots sampled periodically from the release medium were analyzed by using a UV spectrophotometer (Shimatzu, Model UV-2101PC). The UV absorbances of cefazoline and theophylline were measured at λ_{max} = 274 and 270 nm, respectively.

RESULTS AND DISCUSSION

Drug Release Mechanism from Polyelectrolyte Gel under Electric Stimulus

In general, the physicochemical properties or redox states of the polymeric system are influenced by the various mechanisms induced under electric field or current. Such a change of these properties could induce an electric-sensitive release behavior of a drug from polymer gel matrix or permeation of solute through the polymer membrane.

Particularly, electrical-release system using polyelectrolyte gel was controlled by several electrokinetic phenomena, such as electrodiffusion processes, electroosmotic or electrophoretic augmentation of solute flux, and electrostatic partitioning of charged solutes into the charged gels. These electrokinetic phenomena are based on the following fundamental factors. For the determination of an equilibrium condition of a gel, there are three competing forces acting on the gel polymer network such as rubber elasticity, the polymer–polymer affinity and the ionic pressure. These forces were collectively called the osmotic pressure.[14,25] Namely, the osmotic pressure π is given as the sum of π_1, π_2, and π_3 which corresponds to the osmotic pressure due to the rubber elasticity, the solubility of the solvent in the polymer chain, and the difference in ionic concentration between the inside and outside of the gel, respectively. Therefore,

$$\pi = [\ln(1 - v) + v + xv^2]RT/V_1 + (v^{1/3} - v/2)RTv_e/V_0 + (\sum C_i - \sum C_j)RT \quad (1)$$

where v is the volume fraction of the polymer network, x is the solubility parameter, V_0 is the volume of the polymer network under the dry condition, v_e is the number of chains, V_1 is the molar volume of the gel, respectively, R is the gas constant, and T is the temperature. Therefore, the changing balance of these forces induces the volume change of a gel polymer network. At equilibrium, osmotic pressure π of the gel is equal to that of the surrounding aqueous solution, π_0, and thus π_1, π_2, and π_3 have the definite values, respectively. When an electric field is applied on the negatively charged gel in an aqueous solution, the counterion of polyion which is an ionic group in polymer network moves toward the negative electrode, while the polyion remains immobile. Also, the free ions in the surrounding solution move toward their counter electrode and come into a gel. Thus, the osmotic pressure of the gel polymer network near the positive electrode increases and becomes larger than that of the negative electrode side. Consequently, the osmotic pressure difference occurs within the gel, and it is the driving force for releasing of solute entrapped in a gel.

Table II Loading Content of Drug within the PVA/PAAc IPNs

Sample[a]	Feed Composition PVA : PAAc (mol %)	Model Drug (Ionic/Nonionic)[b]	Loading Content of Drug (mg)[c]
IPN64C	60 : 40	Cefazoline	0.9579 ± 0.063
IPN55C	50 : 50	Cefazoline	1.2965 ± 0.030
IPN46C	40 : 60	Cefazoline	1.5382 ± 0.163
IPN37C	30 : 70	Cefazoline	1.6803 ± 0.095
IPN64T	60 : 40	Theophylline	0.5081 ± 0.027
IPN55T	50 : 50	Theophylline	0.6938 ± 0.054
IPN46T	40 : 60	Theophylline	0.7400 ± 0.016
IPN37T	30 : 70	Theophylline	0.8633 ± 0.026

[a] Two model drugs were loaded within each PVA/PAAc IPN sample by swelling loading technique in aqueous drug solution at 25°C.
[b] Cefazoline, ionic drug; theophylline, nonionic drug.
[c] Mean ± standard deviation ($n = 3$ for each sample).

Another factor that influences the release of loaded drug from polyelectrolyte gel may be the local pH gradient attributed to water electrolysis. Several researchers reported that ions produced by electrochemical reactions and the movement of ions toward the counter electrodes induced the pH gradient inside the gel matrix under the flow of electric current.[19,22] When an electric field was applied to the gel immersed in NaCl electrolyte solution, electrochemical reactions (positive electrode ; $2\ Cl^- \rightarrow 2\ Cl_2 + 2\ e^-$, negative electrode ; $2\ H_2O + 2\ e^- \rightarrow 2\ OH^- + H_2$) occurred. Then, the movement of produced ions toward their counter electrode by electroattractive force caused a local pH gradient inside the gel, and it could influence the release of drug molecules from the drug-loaded polyelectrolyte gel.

Loading Efficiency of Drug into PVA/PAAc IPN

In this experiment, we loaded cefazoline as an ionic drug and theophylline as a nonionic drug into each PVA/PAAc IPN sample by the swelling-loading technique. The amount of drug introduced into PVA/PAAc IPN was determined and is listed in Table II. The amount of loaded drug significantly increased with the content of PAAc containing ionizable groups in IPN composed of PVA and PAAc as shown in Table II. Particularly, IPN37C where the feed composition of PVA:PAAc (mol %) was 30:70 showed the largest loading amount of cefazoline. Because the swelling-loading technique through solvent sorption was used to incorporate the drug, swelling ratio of IPN could affect the loading of a drug. Thus, the more the content of PAAc network containing ionizable groups in the IPN, the higher the swelling ratio, as already reported in our previous articles.[26–29] As a result, it could induce the higher loading amount of drug.

In addition, the amount of drug loaded into PVA/PAAc IPN depended on the ionic property of a drug. Theophylline (nonionic drug) loaded PVA/PAAc IPN also exhibited an increase of loading content according to the ratio of PAAc to PVA in IPN, but their loading amount was smaller than that the of ionic drug, cefazoline. It was expected that loading of the ionic drug was much influenced by ionic binding via interaction between the ionic groups in IPN and ionizable drug as well as swelling through diffusion.

Drug Release Behavior under Electric Fields

To investigate the electrically induced release behaviors of drug, we determined the amount of released drug from PVA/PAAc IPN into release medium under various conditions by UV-spectrophotometer. The drug-loaded IPN disk was placed between two carbon electrodes in a release chamber filled with a release medium. Then, applied voltage was altered at every 30 min time interval.

Figure 1 exhibits the release behaviors of drugs from IPN37 as a function of time and the voltage of applied electric field in 0.9 wt % NaCl solution at 37°C. Release behaviors of drugs from IPN37 as a function of time and the voltage of applied electric field in 0.9 wt % NaCl solution at 37°C were investigated. Figure 1 shows the plot of $M_t/M\infty$ vs. time (min) while altering electric stim-

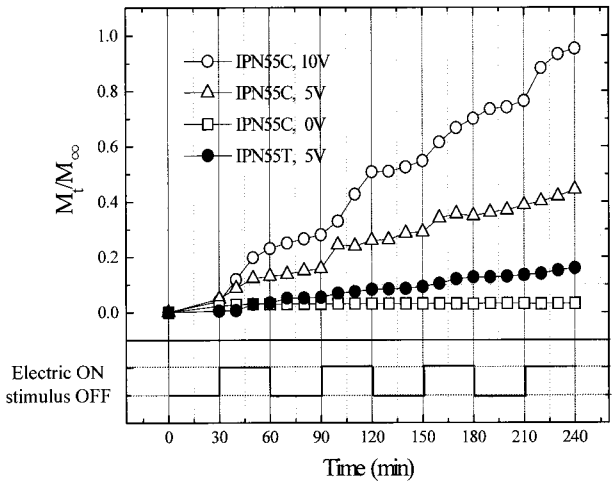

Figure 1 Release behaviors of cefazoline and theophylline from PVA/PAAc IPN55 as a function of applied voltage in 0.9% NaCl solution at 37°C. Electric potential was altered at 30-min time intervals.

ulus. Here, M_t is the amount of drug released up to time t, $M\infty$ is the amount of drug present in the IPN at time $t = 0$. Depending on the electric stimulus turned on and off, the release of drug molecules loaded within PVA/PAAc IPN was switched on and off in a pulsatile fashion. Note that their release rate gradually increases with an applied voltage. The rapid release behaviors of cefazoline were observed when an electric stimulus was at "ON" state, whereas they showed a relatively slow release rate during the "OFF" state. The possible reason for switching pattern of the release of drug molecules was that the electrically induced changes in osmotic pressure within the gel and local pH gradient attributed to water electrolysis could affect the swelling of IPN with charged groups. As a result, the change of swelling of IPN hydrogel could enhance the release of drug from the negatively charged PVA/PAAc IPN.

In the case of theophylline (nonionic solute), however, the magnitude of their "ON-OFF" release pattern induced by electrical stimulus was not so large as that of cefazoline (ionic solute). Particularly, the release rate of theophylline from IPN55T (theophylline-loaded IPN55) under 5 voltage of electric potential was even smaller than that of cefazoline from IPN55C (cefazoline-loaded IPN55) without electric stimulus. This fact confirmed that electrically induced release of ionizable drug, cefazoline, from negatively charged PVA/PAAc IPN was modulated not only by the change of local pH due to electrolysis or electroosmotic pressure within IPN but also by electrophoresis of the charged drug.

In Figure 2, the swelling ratio is measured as a function of time in 0.9 wt % NaCl solution at 37°C under various electric potentials. The swelling ratio of PVA/PAAc IPN gradually increased with an applied potential. After 150 min, the swelling ratio $[(W_s - W_d)/W_d]$ of IPN37 at 10 V was 2.45

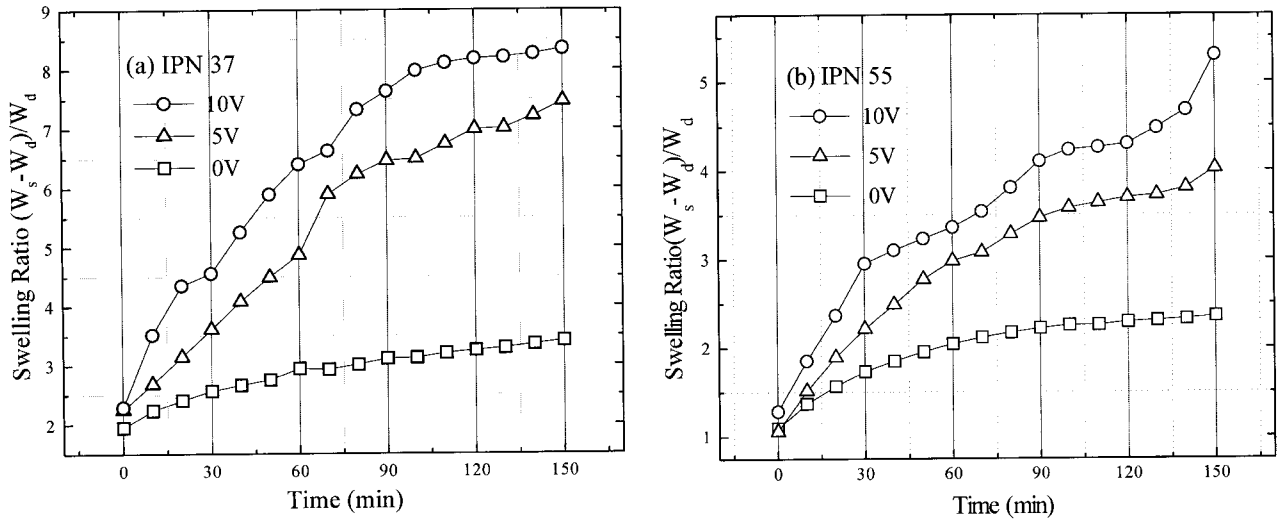

Figure 2 Swelling behaviors of PVA/PAAc IPN depending on the applied voltage and the content of ionic group in NaCl 0.9% NaCl solution at 37°C; swelling ratio = $(W_s - W_d)/W_d$; (a) IPN37, (b) IPN55.

times greater than that without electrical stimulus [see Fig. 2(a)]. Note that IPN37 (composition ratio of PVA : PAAc = 30 : 70) shows the larger swelling ratio than the IPN55 (composition ratio of PVA : PAAc = 50 : 50) at the same electrical potential. When electrical stimulus was not applied, the swelling ratio of IPN37 was 1.45 times greater than that of IPN55, but IPN37 showed 1.58 times larger swelling ratio than IPN55 under 10 V of applied voltage. It indicated that the amount of ionic group showed more intensive influence on the swelling of charged IPN hydrogel under higher applied voltage. The swelling of IPN may enhance the release of drug from IPN through diffusion.

We measured the deswelling of IPN in contact with electrodes under aerobic condition. Figure 3 exhibits the deswelling water ratio as a function of time depending on the applied voltage and the content of PAAc having ionic groups in IPN. When PVA/PAAc IPN swollen until equilibrated state was in direct contact with a pair of electrode under aerobic condition, we could observe the deswelling of IPN as shown in Figure 3. Therefore, the "squeezing" effect of PVA/PAAc IPN hydrogel by deswelling could also enhance the release of drug. Several researchers reported on anisotropic deswelling of electrolyte gel which was attributed to the electroosmosis inside the gel, combined with local pH changes around the electrodes resulting from electrochemical reactions.[25,30,31]

As shown in Figure 3, the deswelling of PVA/PAAc IPN was enhanced in proportion to the applied voltage. Particularly, fully swollen IPN37 showed about 50% weight reduction of its original weight within 10 min under 15 V of applied voltage.

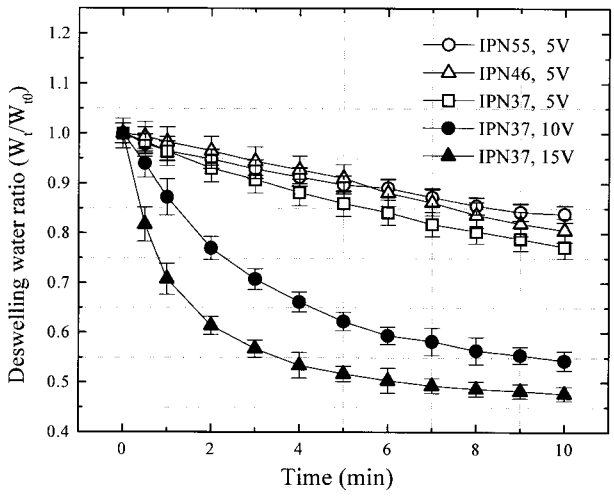

Figure 3 Deswelling behavior of PVA/PAAc IPN in direct contact with a pair of electrodes under aerobic condition.

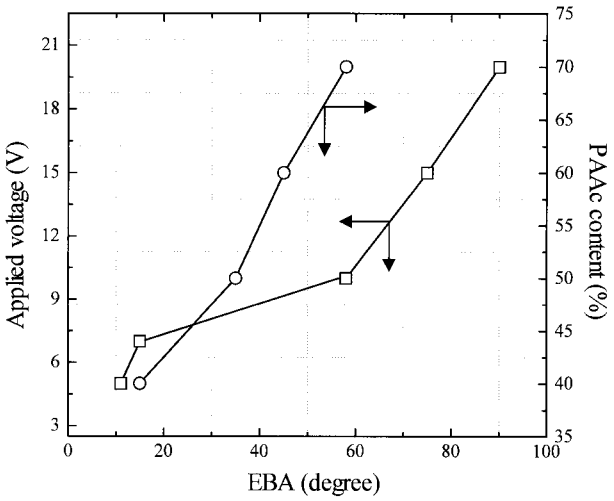

Figure 4 Equilibrium bending angle (EBA) of PVA/PAAc IPN as a function of applied voltage and PAAc content within IPN in 0.1*M* NaCl solution; ○, EBA of IPN37 sample; □, EBA of IPN with various PAAC content under 10 V of applied voltage.

In addition, we observed the similar effect of applied voltage on the bending behaviors of PVA/PAAc IPN hydrogel under electric field (see Fig. 4). Equilibrium bending angle (EBA) increased with an applied voltage as shown in Figure 4. Gradient slope in the plot of bending angle vs. time became steeper with increasing applied voltage, and then leveled off at a steady state. This could be explained by the fact that there was an enhancement in transfer rate of counter ions of immobile carboxylate groups of PAAc within PVA/PAAc IPN to external solution and that of free ion moved from external solution into IPN, as potential gradient in electric field increased.

Releasing behavior of drug depending on the amount of negatively charged ionic group within PVA/PAAc IPN was also measured as shown in Figure 5. We examined the release pattern of cefazoline from PVA/PAAc IPN with different composition ratios in 0.9 wt % NaCl releasing medium at 37°C under constant applied voltage of 5 V. As the content of PAAc network having ionic group increased, the release rate of cefazoline increased. This fact confirmed the effect of ionic group in IPN on the swelling ratio under electric field as shown in Figure 2. Also, note the effect of

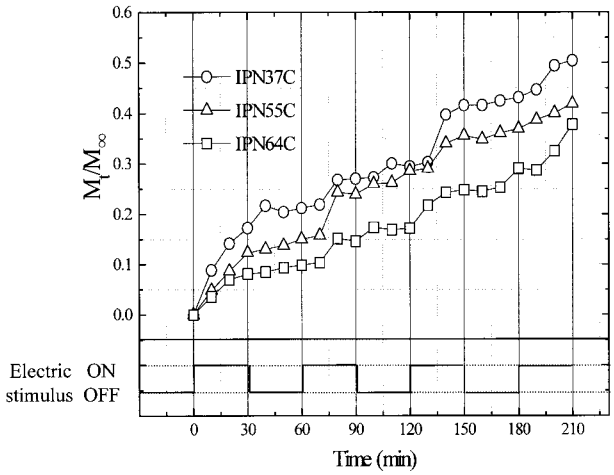

Figure 5 Effect of ionic group content within PVA/PAAc IPN on release behaviors of cefazoline from IPN in 0.9% NaCl solution at 37°C under 5 V applied voltage. The "ON-OFF" state of electric stimulus was altered every 30 min.

ionic group on the deswelling water ratio and the bending behaviors of IPN as shown in Figures 3 and 4, respectively. Figure 3 show the deswelling of IPNs with different compositions, IPN55, IPN46, and IPN37. It exhibits that the deswelling water ratio of PVA/PAAc IPN increased with the content of ionic group in IPN. As the content of PAAc network having negatively charged ionic groups within IPN increased, EBA increased linearly, as shown in Figure 4.

It is well known that the ionic strength of medium affects the swelling of charged gel. In our previous articles,[26–29] we already reported that the swelling ratio decreased with increasing the ionic strength of the medium because the presence of ions in the surrounding solution counteracted the mutual repulsion of fixed ions on the network itself. In addition, under the electric field, electrically induced movement of PVA/PAAc IPN gel was significantly influenced by the ionic strength of surrounding medium. Therefore, we conducted the release experiment of drug from cefazoline- or theophylline-loaded IPN46 in NaCl solution with different ionic strengths to examine the effect of ionic strength on release medium. Figure 6 shows the release behaviors of cefazoline and theophylline as a function of ionic strength in release medium at 5 V. In the case of IPN46C, the release rate of cefazoline increased inversely proportional to the ionic strength of release medium. Therefore, an increase of electrolyte concentration in solution induces the movement of free ion from surrounding solution toward their counter electrode or into IPN, resulting in an increase in release rate of cefazoline from charged PVA/PAAc IPN.

If we compare the swelling results depending on the ionic strength of solution as shown in Figure 6, the change of swelling in PVA/PAAc IPN due to ionic strength of surrounding medium does not significantly affect the release behaviors of drug. It rather indicates that electrically induced changes of osmotic pressure within the gel, local pH gradient attributed to water electrolysis, and squeezing effect of IPN gel are more important than the decrease of swelling ratio due to ionic strength of release medium.

However, in view of the ionic property of drugs, we can see that the release rate of the ionic drug is much faster than that of the nonionic drug as shown in Figure 6. The IPN46T sample containing the nonionic drug, theophylline, exhibited the slower release rate in 0.1*M* NaCl at 5 V than that of the ionic drug, cefazoline, in 0.01*M* NaCl. This could be attributed to the enhancement of release by electrophoresis of charged drug molecules.

Therefore, the release behavior of drug molecules from the present PVA/PAAc IPN system under electric field could be effectively controlled by such factors as applied voltage, content of charge groups within IPN, ionic properties of drug, and ionic strength of release medium.

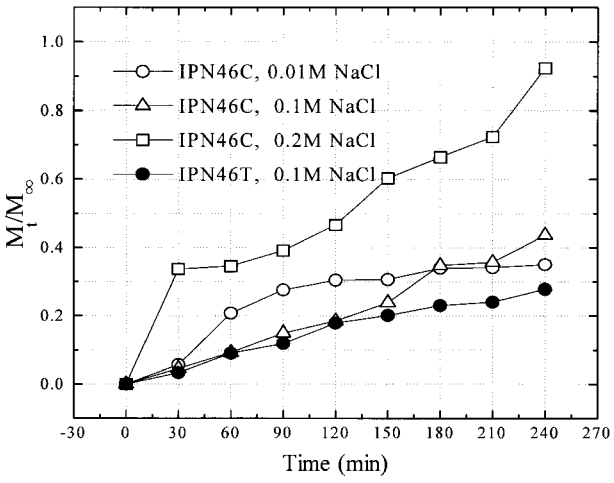

Figure 6 Effect of ionic strength in release medium on release behaviors of cefazoline and theophylline from IPN46 under 5 V applied voltage.

CONCLUSIONS

PVA/PAAc IPNs composed of PVA networks formed inside of crosslinked PAAc chains were prepared by the UV irradiation and repetitive freezing-thawing process for electric-responsive drug delivery system. In the present study, we examined the electrically modulated properties of PVA/PAAc IPN and release behaviors of drug molecules from IPN hydrogel by varying factors, such as applied voltage, content of charge group within PVA/PAAc IPN, ionic properties of drug, and ionic strength of release medium. We loaded cefazoline as an ionic drug and theophylline as a nonionic drug into each PVA/PAAc IPN sample by the swelling-loading technique. The amount of loaded drug increased significantly with the content of PAAc containing ionizable groups in IPN composed of PVA and PAAc. Particularly, IPN37C where the feed composition of PVA : PAAc (mol %) was 30 : 70 showed the largest loading amount of cefazoline. In addition, the introduced amount of cefazoline (ionic drug) was greater than that of theophylline (nonionic drug) because the loading of ionic drug was influenced by ionic binding via interaction between the ionic group fixed IPN and ionizable drug as well as swelling through diffusion. As an electric stimulus was turned on and off, the release of drug molecules loaded within PVA/PAAc IPN was switched on and off in a pulsatile pattern. The rapid release behaviors of cefazoline were observed when an electric stimulus was at "ON" state, whereas they showed relatively slow release during the "OFF" state. The electrically induced changes in the osmotic pressure within the gel and local pH gradient attributed to water electrolysis could affect the swelling of IPN with charged group. Finally, the change of swelling in IPN hydrogel could enhance the release of drug from the negatively charged PVA/PAAc IPN. When PVA/PAAc IPN swollen until equilibrated state was in a direct contact with a pair of electrode under aerobic condition, we could observe the deswelling of IPN. The "squeezing" effect of PVA/PAAc IPN hydrogel by deswelling could also enhance the release of drug. As the content of PAAc network having ionic group increased, the release rate of cefazoline increased. An increase of electrolyte concentration in solution induces the movement of free ion from surrounding solution toward their counter electrode or into IPN. As a result, the release rate of cefazoline from charged PVA/PAAc IPN became faster. Applied voltage and the PAAc content containing ionic group also affected the bending angle, the swelling ratio of PVA/PAAc IPN, and the deswelling in a direct contact with electrode under aerobic condition.

Therefore, the present PVA/PAAc IPN system can be useful for drug delivery system actuated by electric signal, which will then provide the advantage of on-demand release of drug molecules and sensor in feedback controlled systems.

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