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Stimulus-Sensitive Drug Delivery Systems

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1. INTRODUCTION

The aim of conventional drug delivery system is the delivery of drug with a constant rate to maintain blood levels within the therapeutic ranges, avoiding peaks where toxic effect may occur and troughs where the drug is ineffective. In many cases, however, the constant blood level of drug may result in tolerance to pharmacologic effect. From this perspectives, the drug release with a constant rate is not acceptable in all cases and a proper dose of the drug should be released depending on physiological time cycles or certain metabolite concentration. For an ideal drug delivery in this case, stimulus-sensitive drug delivery system has been designed using polymer gels.

A gel is a crosslinked polymer network and it has been used widely in a variety of biomedical and chemical systems. Recently, much interest has been focused on the charged gel (polyelectrolyte gel) and a number of polyelectrolyte gels have been found to show the reversible changes in their structure and functions in response to external stimuli such as pH,[1-3] temperature,[4,5] electric current[6-12] and the concentration of added salts.[13] These properties of polyelectrolyte gel can be explained in terms of phase transition and critical phenomena which attract much attention because of their scientific interest and technological importance. In particular, stimulus-sensitive polyelectrolyte gel have a potential application in the area of controlled drug delivery system because these polyelectrolyte gels not only respond to external stimulus but also control the release rate of solute dispersed in the polyelectrolyte gel network.

In this paper, modulated drug release based on pH-sensitive and electric current-sensitive polyelectrolyte gels, under study in our research group, are presented. Three types of polyelectrolyte gel network (random copolymer network (RCN), semi-interpenetrating network (semi-IPNs), and polymer complex network (PCN)) were prepared as model polymer networks in an attempt to investigate the pH-dependent swelling behaviors of polyelectrolyte gel networks depending on their structure and application as a stimulus-sensitive drug delivery system. RCN was prepared by random copolymerization of 2-acrylamido-2-methyl-1-propanesulfonic acid (AMPSA) and butyl methacrylate (BMA). Semi-IPNs composed of acrylamide (AAm) and AMPSA [or poly acrylic acid (AA)] were prepared by the polymerization of AAm in the presence of poly AMPSA (or poly AA). With the initiation of polymerization, crosslinked poly AAm gel network was formed and non-crosslinked poly AMPSA (or poly AA) entangled through the poly AAm gel network resulting in semi-IPNs. Semi-IPNs composed of sodium alginate (SA) and poly AA were prepared by the gelation using calcium chloride aqueous solution. SA is easily converted to a gel matrix (calcium alginate) in the presence of divalent ions. Based on this property of SA, the solution mixture of SA and poly AA was treated with calcium chloride

aqueous solution to form calcium alginate gel matrix and poly AA chains entangled through the gel matrix resulting in semi-IPNs. PCN were prepared by immersing semi-IPNs in poly ethylenimine (EI) aqueous solution. Ion complex between poly AMPSA (or poly AA) in semi-IPNs and poly EI was formed in the crosslinked poly AAm gel network. Different pH-dependent swelling behaviors of gel network were observed depending on their structures and thermal characterization of swollen gel was conducted with differential scanning calorimeter for the explanation of swelling behaviors of gel network. Different release pattern of hydrocortisone (model drug) from the prepared gel networks was also observed depending on the structure of gel network in which hydrocortisone was dispersed.

2. MATERIALS AND METHODS

2-1. Materials

SA and AAm monomer were purchased from Junsei Chemical Co. (Japan). N,N'-Methylenebisacrylamide (NMBAAm), ammonium persulfate (APS), sodium pyrosulfite (SPS), ethyleneglycol dimethacrylate (EGDMA), AMPSA, BMA, and poly AMPSA aqueous solution (10 wt %) were purchased from Aldrich Chemical Co. (USA). Poly AA aqueous solution (25 weight %, M.W. 90,000), poly EI aqueous solution (50 wt %), azobisisobutyronitrile (AIBN) and hydrocortisone were purchased from Sigma Chemical Co. (USA). BMA was purified by distillation as reduced pressure under nitrogen and all other chemicals were used without further purification.

2-2. Preparation of Hydrocortisone-Dispersed Gel Network

RCN was synthesized using EGDMA as a crosslinker and AIBN as an initiator. AMPSA was dissolved in DMF followed by the addition of BMA, EGDMA and AIBN. Polymerization was performed between two Mylar® sheets separated by a silicone rubber gasket and backed by glass plates at 60℃ for 24 hours. After purification, the polymer was removed from the mold and soaked in a water/acetone (50/50 volume %) solvent mixture. The solvent mixture was replaced daily for 1 week to extract the unreacted compounds. After extraction, the polymer was immersed in distilled-deionized water until use.

Semi-IPNs composed of AAm and poly AMPSA (or poly AA) were prepared by free radical polymerization using redox initiators. For the preparation of hydrocortisone-dispersed gel network, AAm, NMBAAm as a crosslinker, hydrocortisone, and poly AMPSA (or Poly AA) were dissolved in distilled water, to which redox initiators were added to initiate the polymerization. Polymerization was performed between the two Mylar® sheet separated by a silicone rubber gasket and backed by glass plates at room temperature for 12 hours. After polymerization, the gel network was removed from the mold and immersed in distilled water for 3 hours to remove the unreacted compound.

Semi-IPNs composed of SA and poly AA were prepared by the gelation of polymer solution mixture of SA and poly AA in the presence of divalent ion. The known amounts of 2 wt % SA aqueous solution and 25 wt % polyacrylic acid aqueous solution were mixed throughly with hydrocortisone using homogenizer (Bodline Electronic Co., USA). Four compositions (10/0, 9/1, 7/3, and 5/5 (w/w) SA/poly AA) were prepared for semi-IPNs composed of SA and poly AA. 5 wt % calcium chloride solution was poured gently onto the surface of polymer solution mixture. The volume of calcium chloride solution used was twice larger than that of the polymer solution mixture. The gel network was formed from the surface. The solution mixture of SA and poly AA was completely converted to the gel matrix within 1 hour. The gel matrix was immersed in distilled water for 3 hours to

remove unreacted calcium chloride.

PCN were prepared by immersing semi-IPNs in poly EI aqueous solution (2 wt %) for 6 hours. Ion complex between poly AMPSA (or poly AA) in semi-IPNs and poly EI was formed in poly AAm gel network. Semi-IPNs composed of SA and poly AA were not used for the formation of PCN because the severe disruption was observed during the formation of ion complex. For the preparation of hydrocortisone-dispersed PCN, hydrocortisone-dispersed semi-IPNs before purification was immersed in poly EI aqueous solution. To prevent hydrocortisone release from the gel network during the formation of ion complex, the saturation of hydrocortisone in poly EI aqueous solution was maintained. After the formation of ion complex, the gel network was removed from poly EI solution and was then immersed in distilled water for 3 hours. It was impossible to prepare PCN using AAm/AMPSA (II) with poly EI. During the formation of ion complex, the severe disruption was observed especially at the surface of gel network.

Although hydrocortisone was released from the gel network during the purification, the release amount was within the range of 10 wt % of the total dispersed hydrocortisone. The swollen gel was cut into disk (diameter: 2.5 cm and thickness: 0.5 cm) or hexahedron ($2\times2\times2$ and $2\times4\times2$ cm^3) and stored in the bottles after sealing to maintain the swollen state of gel network until use. The drug loading amount was approximately 25 wt % after purification.

The feed composition for the gel network used in this study is shown in Table I. The aqueous solutions of SPS (3.5 g/25 m*l*) and APS (10 g/25 m*l*) were used as redox initiators and 0.25 m*l* of each component of redox initiators was added to solution mixture.

2-3. Swelling Measurement

The water uptakes (swelling) of gel network were measured at 37.5℃ with the pH change of aqueous media. The water uptake of gel network was measured by first wiping the excess surface water and weighing. The swelling is defined as the weight of water uptake per unit weight of dried gel network. The pH of aqueous solution was controlled by the addition of HCl and NaOH.

For the measurement of reversible swelling kinetics of gel matrix composed of SA and poly AA, the swelling was measured in 0.9% NaCl solution at two pH points (pH 2 and 6). To simulate the experimental condition under electric stimulus, the pH of 0.9% NaCl solution was controlled by the addition of 0.1 N HCl.

2-4. Differential Scanning Calorimetry

Thermal characterization of swollen gels

Table I—Feed Composition for Polyelectrolyte Gel Networks (unit: g)

Category	Sample Code	Composition								
		AAm	poly AMPSA	AMPSA	poly AA	BMA	NMBAAm	EGDMA	AIBN	WATER
Homopolymer	poly AAm	3.88	–	–	–	–	0.12	–	–	40
RCN	AMPSA/BMA	–	–	1.46	–	3.94	–	0.01	0.01	40
Semi-IPNs	AAm/AMPSA (I)	3.88	0.39	–	–	–	0.12	–	–	40
	AAm/AMPSA (II)	3.88	1.16	–	–	–	0.12	–	–	40
	AAm/AA	3.88	–	–	0.39	–	0.12	–	–	40
PCN*	AAm/AMPSA/PEI									
	AAm/AA/PEI									

*PCN were prepared by immersing AAm/AMPSA (I) and AAm/AA in poly EI aqueous solution (2 weight %).

(ca. 10 mg) was conducted with a differential scanning calorimeter (DSC) (Du Pont DSC-9900 computer/thermal analyzer). The heating rate was 10℃/min. and nitrogen was used as the sweep gas (30 ml/min).

2-5. Release Experiment

Hydrocortisone release experiments were performed at two pH conditions (pH 3 and 7) (temperature: 37.5℃). The pH of release media was controlled by the addition of HCl. The amount of released drug was measured by taking 1 ml of the release media at specific time points, replacing total release media (20 ml) with fresh release media to maintain sink condition and assaying the drug concentration at 248 nm using UV spectrophotometer (Shimadzu, Japan).

Two kinds of apparatus were designed for the electric current-sensitive release experiment of hydrocortisone as presented in Fig. 1.

In the case of non-contacting device, the hexahedron-type gel network was placed between positive and negative electrodes is 0.9 % NaCl solution. The distance between two electrodes was 3 cm and the voltage between the electrodes was 9 V. The applied electric current was 32 mA as measured by Volt-Ohm-Milliammeter (Shimpson Electric Co., USA).

In the case of contacting device, the gel network was placed in 0.9% NaCl aqueous solution and the electrodes were inserted into polymer matrix directly. The distance between two electrodes was 3 cm and the voltage between the electrodes was 9 V. The applied electric current was 6 mA. The electric currents used in both cases were almost constant during the experiments. The amount of released drug was measured by taking 1 ml of the release media at specific time points, replacing the total release media (50 ml) with fresh NaCl aqueous solution to maintain sink condition and assaying the drug concentration at 248 nm using a UV spectrophotometer (Shimadzu, Japan).

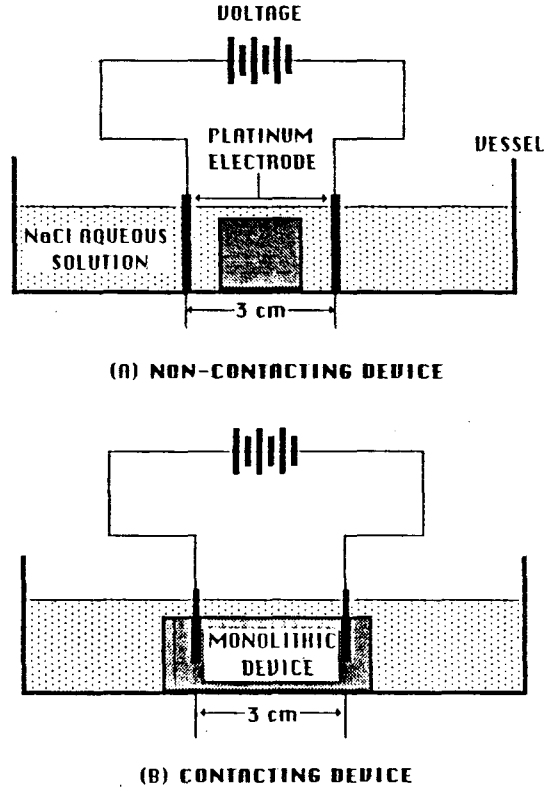

Figure 1—Schmatic diagram for apparatus used in electric current-sensitive drug release experiment. (A) Non-contacting device, (B) Contacting device

The pH change of release media caused by the application of electric current was measured by taking 1 ml release media under the application of electric current for 10 minutes. The sampled release media was 10 times diluted with fresh NaCl solution to obtain sufficient volume for pH measurement and assayed by pH meter 245 (Corning, USA). In the case of the contacting device, the release media was directly taken from the gel matrix-electrode interface using syringe. In the case of the non-contacting device, the release media was taken from three different points in the release experimental vessel (i.e., points near the positive and negative electrode and point between these two). The pH profiles in the release experimental vessel were reproducible.

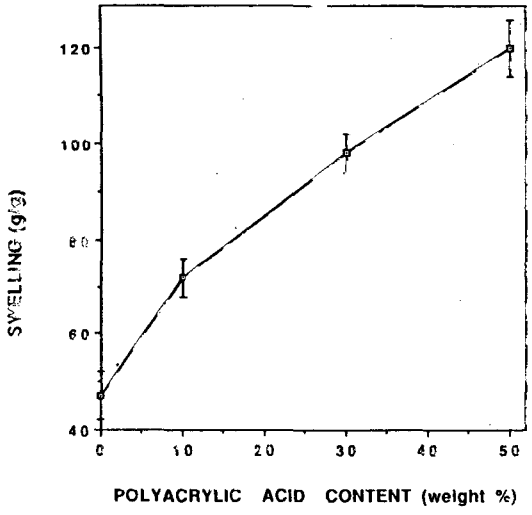

Figure 2—Swelling behavior of SA/poly AA network as a function of poly AA content in the gel network.

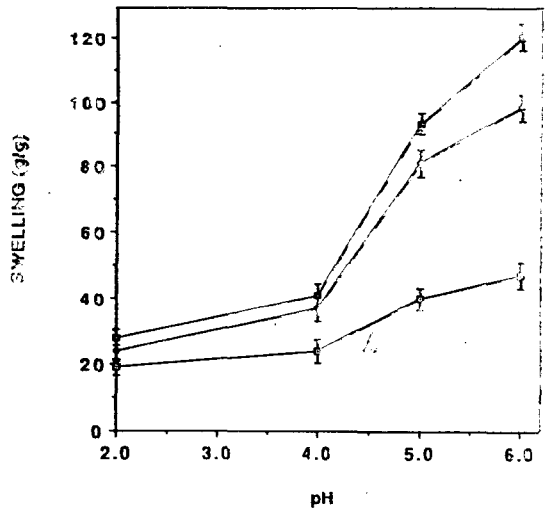

Figure 3—Swelling behavior of SA/poly AA network as a function of environmental pH.

3. RESULTS AND DISCUSSION

Firstly, the swelling behaviors of polyelectrolyte gel network depending on their structure were observed in response to the environmental pH change. Three types of gel network (RCN: AMPSA/BMA, Semi-IPNs: AAm/AA, AAm/AMPSA (I) and (II), and SA/AA, PCN: AAm/AMPSA/EI and AAm/AA/EI, and poly AAm as a control) were prepared as model gel networks.

Fig. 2 shows the swelling behaviors of semi-IPNs composed of SA and poly AA as a function of their composition. SA is easily converted to a gel network in the presence of divalent at the concentration of >0.1 w/w %.[14] Based on this property of SA, the solution mixture of SA and poly AA was treated with calcium chloride solution to form a gel network. It could be expected that SA formed a gel network (calcium alginate) and poly AA chains entangled through the calcium alginate gel matrix resulting in semi-IPNs. One of the prepared gel networks, (5/5) (w/w) calcium alginate/poly AA composite, was stored in distilled water for one month and the pH change of aqueous media was measured to observe poly AA leaking from the gel network. The pH change of aqueous media was not observed. This indicated the minimal leaking of poly AA from the gel network (pH of 0.5 w/w % aqueous solution of poly AA was 3.22). The swelling of gel network composed of SA and poly AA increased as the content of poly AA in the gel network increased. This swelling increase reflected the high swelling capacity of poly AA.

To investigate pH-sensitivity of gel network composed of SA and poly AA, the swelling behaviors of gel network was observed as a function of environmental pH. Fig. 3 shows that these gels exhibit sharp swelling change around pH 4 indicating the ionization of carboxylic groups in poly AA. At acidic condition (pH 2), carboxylic groups were protonated and the protonated carboxylic groups lost their swelling power. As the pH of aqueous media was increased from pH 2, the increasing concentration of negatively charged carboxylic group in the CPC network was accompanied by a drastic increase in swelling. This phenomena was reversible and the range of swelling change increased with the increase of poly AA content in the gel matrix as shown in Fig. 4. As the content of poly AA in the gel network increased, the

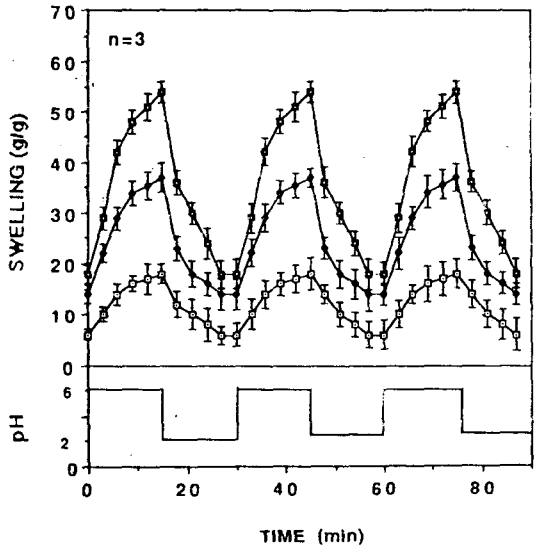

Figure 4—Reversible swelling change of SA/poly AA network in response to the pulsatile pH change. (▣) 10/0 (w/w) SA/poly AA network, (◆) 7/3 (w/w) SA/poly AA network, (□) 5/5 (w/w) SA/poly AA network

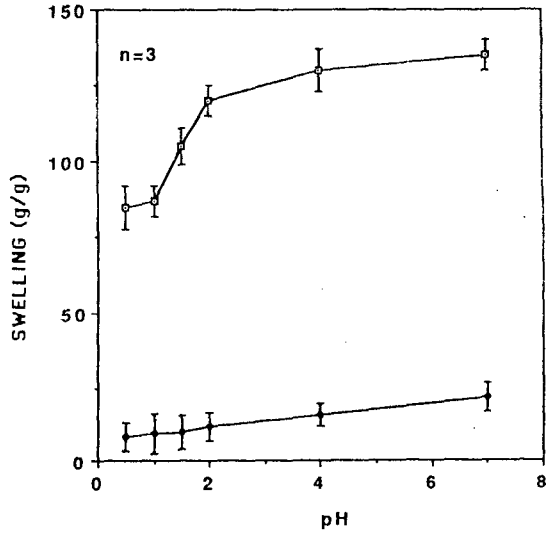

Figure 5—Swelling behaviors of poly AAm and AMPSA/BMA as a function of environmental pH. (◆) Poly AAm, (▣) AMPSA/BMA

range of swelling change inreased indicating the feasibility of regulation of swelling range by the control of the content of poly AA in the gel network. Note that specific intermolecular co-operative interaction occurs between calcium ion and G blocks owing to the buckled ribbon structure of the polyguluronic acid moiety in SA leaving free carboxylic groups in the gel formatiion of SA in calcium chloride solution.[14] The pH-dependent swelling of 100% sodium alginate matrix were attributed to these free carboxylic groups in the gel network.

Fig. 5 shows the swelling behaviors of AMPSA/BMA and poly AAm as a function of the environmental pH. In AMPSA/BMA, AMPSA provided the charged groups into the gel network and the improved mechanical strength was obtained by the introduction of BMA. The maximum swelling increase of AMPSA/BMA with the increase of environmental pH occurred at pH 1.0-1.5 (the inflection point) indicating the ionization of the sulfonic groups in AMPSA.

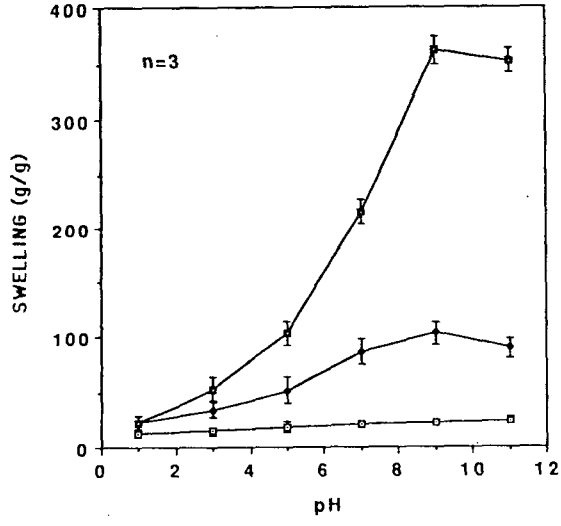

Figure 6—Swelling behaviors of semi-IPNs as a function of environmental pH. (▣) AAm/AA, (◆) AAm/AMPSA (I), (□) AAm/AMPSA (II)

Fig. 6 shows the swelling behaviors of semi-IPNs composed of AAm and poly AMPSA (or poly AA). It could be expected that AAm formed a crosslinked gel network and non-crosslinked poly AMPSA (or poly AA) chains entagled through poly AAm gel net-

work resulting in semi-IPNs. To observe the leakage of poly AMPSA (or poly AA) from semi-IPNs, AAm/AMPSA(II) and AAm/AA were stored in distilled water for 1 month and the pH change of aqueous media was measured. In the case of AAm/AA, noticeable pH change of aqueous media was not found indicating the minimal leakage of poly AA from the gel network. In the case of AAm /AMPSA(II), the pH of aqueous media decreased from 7.0 to 3.1 during the storage of gel network in distilled water for 1 week and minimal pH change was observed during the first day of 1 week. This indicated the leakage of poly AMPSA from the gel network (pH of 0.2 wt % of aqueous solution of poly AMPSA was 2.54.). But noticeable swelling decrease was not observed during one month replacing the distilled water with fresh one every three days. Comparing with the swelling behavior of poly AAm in Fig. 5, AAm /AMPSA (I) and (II) showed the increased swelling capacity. Although sulfonic groups in AMPSA played a major role in the pH-dependent swelling behaviors of AMPSA/BMA and AAm/AMPSA (I) and (II), the inflection points were observed at different pH points depending on their structures. The inflection point of AMPSA/BMA was observed at pH 1.0-1.5 and those of AAm/AMPSA (I) and (II) were observed at pH 3.5-4.0. The increased swelling capacity of AAm/AMPAS (I) and (II) was due to the high swelling capacity of non-crosslinked poly AMPSA and the shift of inflection point might be caused by the intermolecular interaction between sulfonic groups in poly AMPSA and amide groups in poly AAm.

Although the increased swelling of AAm/AA was expected due to the high swelling as shown in Fig. 5. This might be explained in terms of hydrogen bonding between carboxylic groups in poly AA and amide groups in poly AAm.

Fig. 7, 8 and 9 show the calorimetric thermograms of swollen gels and polymer aqueous solutions. As shown in Fig. 7, poly AAm did not exhibit any noticeable peaks in the temperature range between 25℃ and

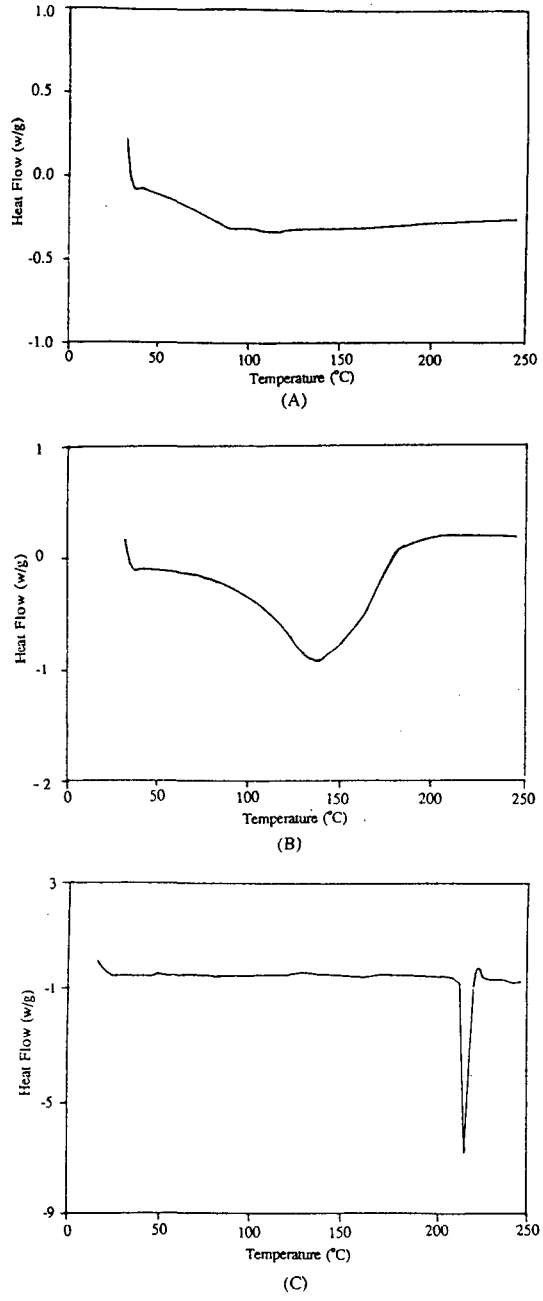

Figure 7—Calorimetric thermogram
(A) swollen poly AAm gel, (B) 10 wt % of poly AMPSA aqueous solution, (C) 50 wt % of poly AA aqueous solution

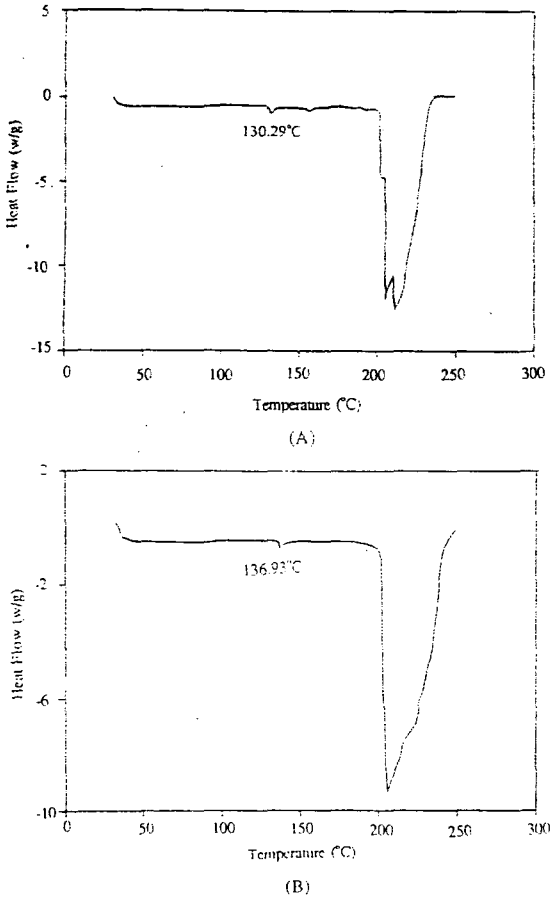

Figure 8—Calorimetric thermogram (swollen gel) (A) AAm/AMPSA (I), (B) AAm/AMPSA/EI

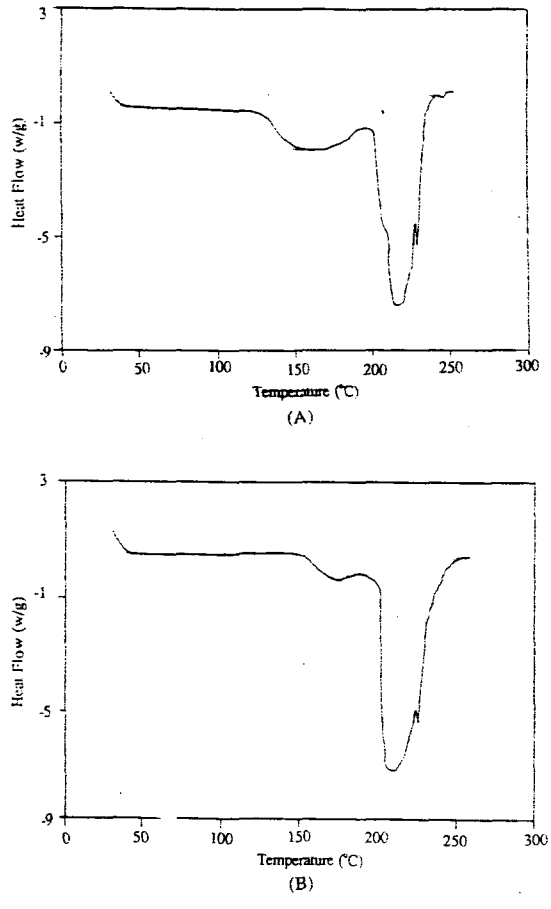

Figure 9—Calorimetric thermogram (swollen gel) (A) AAm/AA, (B) AAm/AA/EI

250℃. Poly AMPSA aqueous solution and poly AA aqueous solution exhibited the characteristic endothermic peaks at 136.5℃ and 209.7℃, respectively. With the formation of semi-IPNs, the endothermic peak was observed at 210℃ in both case of AAm/AMPSA (I) and AAm/AA as shown in Fig. 8 and 9, respectively. Particularly, the thermal characterization was conducted using AAm/AMPSA (I) and AAm/AA which were equilibrated with distilled water for one month. The presence of poly AMPSA in the gel network was confirmed by the endothermic peak at 136℃.

Fig. 10 shows the swelling behaviors of PCN. With the formation of ion complex, the concentration of sulfonic groups in the gel

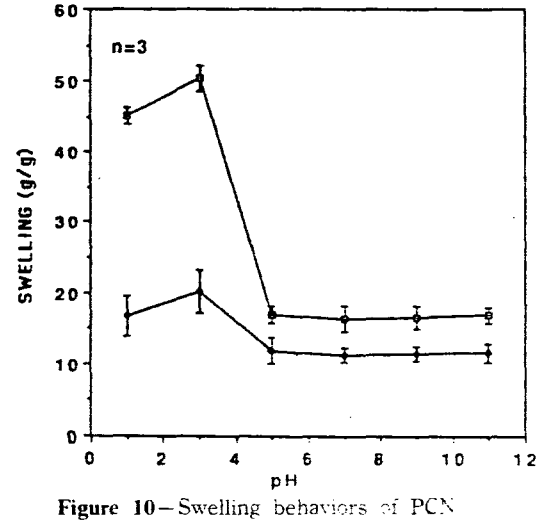

Figure 10—Swelling behaviors of PCN (●) AAm/AMPSA/EI, (◆) AAm/AA/EI

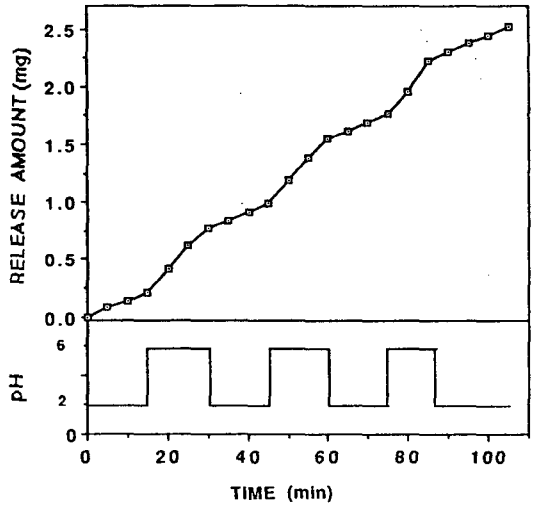

Figure 11—Hydrocortisone release pattern from (7/3) (w/w) SA/poly AA network.

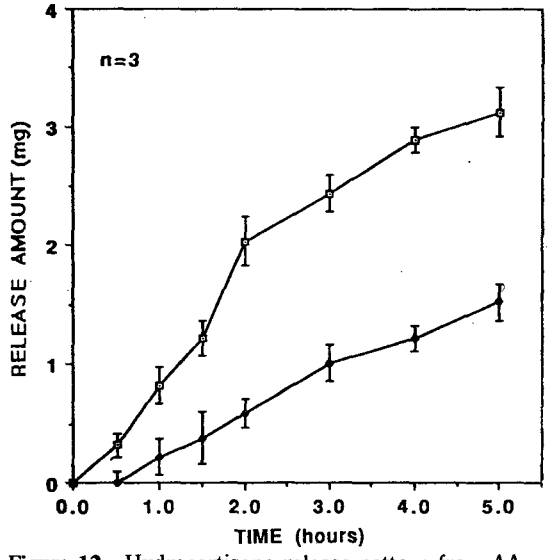

Figure 12—Hydrocortisone release pattern from AAm /AMPSA (I).
(■) at pH 3, (◆) at pH 7

network was diminished resulting in the swelling decrease of AAm/AMPSA/EI in the pH range between 5 and 11. In the case of AAm/AA/EI, the swelling decrease caused by the ion complex was not observed but the pattern of pH-dependent swelling was changed. In both cases of AAm/AMPSA/EI and AAm/AA/EI, the maximum swelling decreases with the increase of environmental pH were observed at pH 3.5-4.0 (the reverse inflection point). From this result, it might be expected that there were some imine groups which were not participated in the formation of ion complex and the ionization of these imine groups played a major role in the swelling behaviors of PCN. No change was found between calorimetric thermograms for semi-IPNs and for PCN.

In the external stimulus-sensitive drug delivery system, the swelling, change in the drug delivery devices caused by external stimulus can be represented as surface swelling and bulk swelling changes (squeezing effect). For examples, the major factor to control the drug release from the device was the bulk swelling change[2] or the surface swelling change[3] in the case of thermo-sensitive drug delivery system. The release pattern from model polymer networks was explained in terms of these two phenomena. The release kinetics of loaded hydrocortisone from the gel network composed of SA and poly AA (The content of polyacrylic acid is 30 wt %) at two pH conditions (pH 2 and 6) was measured as shown in Fig. 11. The release rate increased with the increase of environmental pH. The protonation of carboxylic groups in the gel network at pH 2 caused the surface deswelling, which resulted in blocking the release of hydrocortisone from the gel network. As the environmental pH was increased from pH 2, the concentration of negatively charged carboxylic groups in the gel network increased with the drastic increase in swelling. Therefore, the block at the surface of gel network was diminished and hydrocortisone can diffuse out more easily from the gel network.

The pulsatile drug release kinetics depending on pH variation of surrounding aqueous media was measured as shown in Fig. 11. The release amount of hydrocortisone increases drastically with the increase of environmental pH. This pulsatile release under

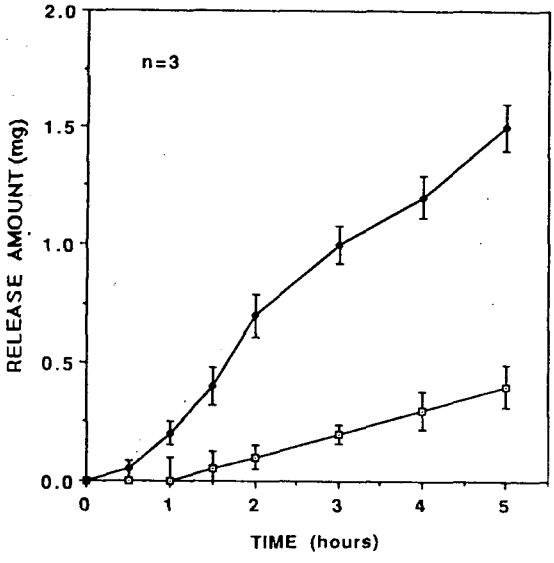

Figure 13—Hydrocortisone release pattern from AAm /AMPSA/EI
(▣) at pH 3, (◆) at pH 7

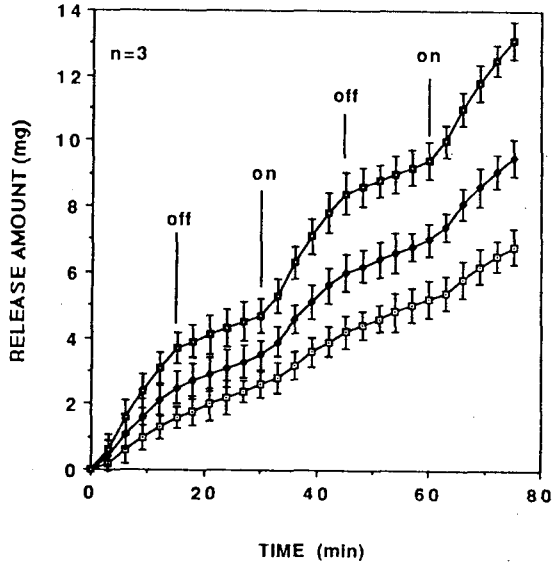

Figure 14—Hydrocortisone release pattern using contacting device.
(▣) 10/0 (w/w) SA/poly AA network, (◆) 7/3 (w/w) SA/poly AA network, (□) 5/5 (w/w) SA/poly AA network

pH variation of surrounding aqueous media is attributed to the reversible swelling change caused by pH variation.

Fig. 12 shows hydrocortisone release pattern from AAm/AMPSA (I) at two pH conditions (pH 3 and 7). The overall release rate increased with pH decrease of release media. Since hydrocortisone was physically entrapped inside the gel network, the release pattern was closely releated to the swelling behaviors of gel network. As described previously, the swelling of AAm/AMPSA (I) decreased with the pH change of release from pH 7 to 3. Therefore, the increase of release rate in response to pH change could be explained in terms of the bulk squeezing effect caused by the deswelling of gel network.

Fig. 13 shows hydrocortisone release pattern from AAm/AA/EI at two pH conditions (pH 3 and 7). The overall release rate decreased with the decrease of pH change contrary to the results in Fig. 12. Considering the relation between the swelling behavior of gel network and the release pattern of drug, this phenomena could be explained in terms of the bulk squeezing effect caused by the deswelling of gel network.

Under the same pH change, the drug release from gel network composed of SA and poly AA was regulated by the surface swelling change and that from gel composed of AAm and poly AMPSA was regulated by bulk swelling change. From the results of hydrocortisone release pattern in response to the environmental pH change, it was strongly dependent on the character of polymer networks used as drug carriers.

In the observation of electric current-sensitive drug release, two kinds of apparatus (contacting and non-contacting devices) were designed for our purpose. Semi-IPNs composed of SA and poly AA was used as a model gel network in electric current-sensitive drug release experiment. The other gel networks used in this study were excluded because of slow pH-sensitivity of gel network. In the contacting device, the bulk swelling change was induced by inserting (contacting) the electrodes into gel network. The release rate was increased by the application of electric

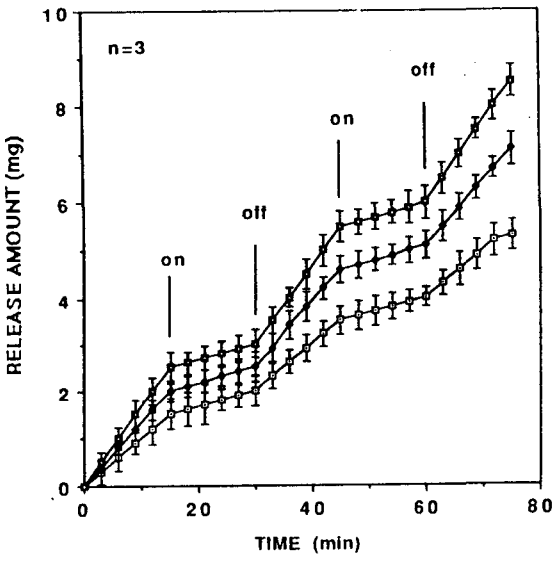

Figure 15—Hydrocortisone release pattern using non-contacting device.
(▣) 10/0 (w/w) SA/poly AA network, (◆) 7/3 (w/w) SA/poly AA network, (□) 5/5 (w/w) SA/poly AA network

current and it was posible to obtain a pulsatile drug release pattern as shown in Fig. 14. Under the application of electric current, the NaCl solution at the gel network-positive electrode interface became acidic (pH 2), therefore, the protonation of the carboxylic groups led to the irreversible shrinkage (collapse) of gel network (bulk squeezing). The shrinkage of gel network around the positive electrode could be observed visually, while no shrinkage was found around the negative electrode. The release pattern was observed as a function of poly AA content in the gel network. As the content of poly AA increased, the pulsatile release pattern became more apparent due to the increase of the magnitude of swelling change as shown in Fig. 14. In non-contacting device, the surface swelling change played a major role in regulating pulsatile drug release pattern as shown in Fig. 15. The pH of release media under electric stimulus was measured at three different points in the release experimental vessel. The pH of release media was approximately 2.1 around the positive electrode, 7.9 around the negative electrode, and 3.8 between two electrodes. H^+ ions generated around the positive electrode protonated the carboxylic groups at the most part of the surface of the gel network and the surface deswelling caused by protonation retarded the solute release from the gel network. With the application of electric current, the amount of solute released decreased due to the surface deswelling; this is contrary to the results in the case of the contacting device. The change in drug release rate was also observed with the variation of polyacrylic acid content in CPC gel matrix and the results showed the similar trend in the case of the contacting device.

From Figs. 14 and 15, the release rate from the non-contacting device without electric current, even though its size was smaller than the contacting device, was faster. In contacting device, the collapse of gel network occurred with the application of electric current as mentioned previously. The release rate of hydrocortisone from the contacting device might be hindered by the formation of collapsed gel network.

4. CONCLUSION

In this study, pH-dependent swelling behaviors of polyelectrolyte gel networks were observed depending on their structures and the feasibility for the application of polyelectrolyte gel networks as a pH-sensitive drug delivery system was examined. Three different types of polyelectrolyte gel network were prepared as model polymer networks in an attempt to perform the purpose of this study. The variation of pH-dependent swelling behaviors was observed depending on the structure of gel network and pH-dependent drug release pattern was closely related to the swelling behaviors of gel net work.

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