Indomethacin Release Behaviors from pH and Thermoresponsive Poly(vinyl alcohol) and Poly(acrylic acid) IPN Hydrogels for Site-Specific Drug Delivery

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ABSTRACT: A temperature- and pH-responsive drug delivery system was studied by using interpenetrating polymer network (IPN) hydrogels constructed with poly(acrylic acid) (PAAc) and poly(vinyl alcohol) (PVA). The release of indomethacin incorporated into these hydrogels showed pulsatile patterns in response to both pH and temperature. Indomethacin diffused from the polymer matrices through the swelling and deswelling mechanism. The release amount increased at higher temperature because of the swelling caused by the dissociation of hydrogen bonding. The drastic change of drug release was achieved by alternating pH of the buffer solution and was attributed to the change of states of ionic groups within IPN hydrogels. The free water contents were calculated by using differential scanning calorimetry (DSC), and were proved to be the main factor in the swelling. These results demonstrated that the drug release could be controlled by the swelling/deswelling degree of IPN hydrogels as functions of pH and/or temperature.
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INTRODUCTION

Our previous studies reported on pH- and temperature-sensitive hydrogels[1] and membranes,[2] and we synthesized novel pH/temperature-sensitive poly(vinyl alcohol) (PVA)/poly(acrylic acid) (PAAc) interpenetrating polymer network (IPN) hydrogels and investigated their swelling kinetics.[3] PVA/PAAc IPNs prepared by using ultraviolet (UV) irradiation and the freezing–thawing method showed wide changes of swelling ratios as a function of pH and/or temperature. Oscillatory swelling/deswelling behaviors were obtained by alternating pH between 4 and 7, or temperature between 25 and 45°C.

Recently, there have been many investigations on pulsatile and self-regulated drug delivery systems, which release proper amounts of drugs at suitable timing and period in response to various stimuli (e.g., electric field,[4,5] pH,[6–10] temperature,[11,12] ionic strength,[13] or other chemicals[14,15]). These systems offer major advantages such as reduction in side effect and effective bioavailability over conventional delivery forms. Among these, pH and/or temperature responsive systems have been potential candidates because these factors could be the most available environment in the human body.

Temperature-sensitive drug delivery systems have been extensively studied. Katono et al.[16] investigated thermal collapse from IPNs composed of poly(acrylamide-*co*-butylmethacrylate) and PAAc, and obtained on–off release profiles as a function of temperature. Poly(*n*-isopropylacrylamide) (PNIPAAm) hydrogels demonstrated negative temperature sensitivity with lower critical solution temperature (LCST) in aqueous solution, which showed the decrease of swelling by increasing the temperature above 30–32°C.[17] LCST results from the influence of temperature on polymer–polymer interaction and polymer–water interaction such as hydrogen bonding and hydrophobic/hydrophilic interaction.

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By utilizing PNIPAAm hydrogels, Okano, Bae, and Kim[18] achieved a temperature controlled on–off drug delivery system for indomethacin.

On the other hand, positive temperature-dependent drug delivery has been reported.[19–21] The hydrogel composed of polyacrylamide (PAAm) and PAAc showed positive swelling which formed an attractive interaction at lower temperature that dissociated at higher temperature.[19,20] Aoki et al.[21] observed positive temperature sensitivity and the release of ketoprofen from IPNs constructed with PAAc and poly(*N,N*-dimethylacrylamide) reflected "on" state at higher temperature and "off" state at lower temperature.

In the case of pH-dependent drug delivery systems, much research has focused on swelling properties of hydrogels. The acidic or basic components in the hydrogels led to reversible swelling/deswelling because they changed from the neutral state to the ionized state, and vice versa, in response to the change of pH. Peppas and Peppas[22] reported pH-sensitive drug release systems composed of copolymer of hydroxyethyl methacrylate (HEMA) and methacrylic acid (MAAc) or maleic anhydride. Poly(NIPAAm-*co*-vinyl terminated polydimethyl siloxane-*co*-AAc) hydrogel synthesized by Hoffman and Dong[23] permitted release of drugs at pH 7.4, and showed release–off at pH 1.4, and was proved to be a suitable carrier for indomethacin through the gastrointestinal (GI) tract. Furthermore, Narayani and Rao[24] investigated two different types of pH-responsive delivery systems for methotrexate from gelatin microspheres coated with chitosan and/or alginate.

pH/temperature dual responsive materials are polymer networks which contain both pH- and temperature-sensitive components in their structure. Feil et al.[25] studied pH/temperature influence on the swelling of hydrogel from poly(NIPAm-*co*-butyl methacrylate-*co*-dimethylaminoethylmethacrylate), and investigated the optimal loading and release of human calcitonin[26] from statistical terpolymer of PNIPAAm, butylmethacrylate, and acrylic acid. Chen and Hoffman[27] prepared dual responsive copolymer composed of NIPAAm and 4-pentenoic acid for possible use in protein conjugation.

In the present article, the pH/temperature sensitive release of indomethacin, as a model drug, from IPN hydrogels composed of PVA and PAAc is reported on the basis of the idea that swelling of IPN is attributed mainly to the drug release kinetics. In addition, differential scanning calorimeter (DSC) studies for the swollen gel were performed to understand the state of water in IPN hydrogels, which is an important factor in the drug release control.

EXPERIMENTAL

Materials

Acrylic acid monomer (AAc), obtained from Junsei Chemical Co., was purified by an inhibitor removal column (Aldrich Chem. Co.). Poly(vinyl alcohol) (PVA; DP = 2500, degree of deacetylation = 99%) was purchased from Shinetsu Co. Methylenebisacrylamide (MBAAm) as a crosslinking agent and 2,2-dimethoxy-2-phenylacetophenone (DMPAP) as a photoinitiator were purchased from Aldrich Chem. Co. Indomethacin (Anhydrous, M_w = 357.8), used as a model drug, was obtained from Sigma Chem. Co.

Synthesis of IPN Hydrogels

Interpenetrating polymer networks were prepared by the unique method reported in a previous paper.[3] 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 freezing–thawing process. PVA was dissolved in deionized water and heated at 80°C for 2 h to make 10 wt % aqueous solution. AAc monomer was mixed with 0.2 wt % DMPAP as a photoinitiator and 0.5 mol % MBAAm as a crosslinking agent. The mixture was combined with PVA solution to yield PVA-PAAc molar ratios of 4 : 6, 5 : 5, and 6 : 4. These solution mixtures were poured into Petri dishes and irradiated using a 450 W UV lamp (Ace Glass Co.) for 1 h under N_2 atmosphere. The Petri dishes were placed at −50°C for 6 h and at room temperature for 2 h. These freezing–thawing cycles were repeated eight times. The synthesized gels were removed from the Petri dishes, punched into 23-mm diameter disks, and washed by deionized water to remove the unreacted AAc monomers. 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.

Characterization

Fourier transform infrared (FTIR) spectroscopy (Nicolet Model Magna IR550) was used to confirm the structure of the IPNs. Equilibrium water con-

tent (EWC) was measured in pH 4 and 7 buffer solutions. Preweighed, dry IPN disks were immersed in pH 4 or 7 buffer solution until they swelled to equilibrium. It was confirmed that 24-h equilibration was enough to reach the equilibrium swelling of disks from our previous experiments.[3] After excessive surface water was removed by filter paper, the hydrated weights of swollen gels were measured. The EWC was calculated from the following equation[28]:

$$\mathrm{EWC}(\%) = \frac{(W_s - W_d)}{W_s} \times 100$$

where W_s and W_d represent the weight of swollen and dry disks, respectively. The melting endotherm of dry disks and the state of waters in the IPN hydrogels were investigated by differential scanning calorimetry (DSC, Du Pont Instruments DSC 910). The IPN disks equilibrated in pH 4 or 7 buffer solution were cooled down to −20°C and then rescanned up to 20°C at a heating rate of 5°C/min under N_2 flow. The amount of free water and bound water was calculated from the melting enthalpies.[29,30] The following equation assumes that the heat of fusion of free water in the hydrogel was the same as that of the ice.[31]

$$W_b(\%) = W_t - (W_f + W_{fb}) = W_t - (Q_{\mathrm{endo}}/Q_f) \times 100$$

Here, W_t was the equilibrium water content (EWC)(%); W_b, the amount of the bound water (%); W_f and W_{fb}, the amount of free water and the freezing bound water, respectively. Q_{endo} and Q_f were the heat of fusion of free water in IPN hydrogel and that of the ice (79.7 cal/g), respectively.[32]

Drug Loading and Releasing

Indomethacin, as a model drug, was loaded into IPN disks by the solvent sorption method. The dry IPN disks were soaked into a saturated ethanol solution of indomethacin at 25°C, and allowed to swell to equilibrium in order to get a high loading in the disks. The fully swollen hydrogels removed from the drug solution were blotted with filter paper to eliminate the surface water and dried as mentioned above.

Indomethacin release experiments were conducted in various conditions changing pH and/or temperature of the release medium. The IPN disks loaded with indomethacin were placed in the desired release medium under stirring to remove the boundary layer. Three-mL aliquots sampled periodically from the medium were analyzed by using a UV spectrophotometer (Shimatzu, Model UV-2101PC) at 320 nm, and then returned back into the medium solution.

To investigate the temperature effect on the release behavior, the pulsatile changes in the absorbance of the samples were monitored in pH 7 buffer solution at 25 and 45°C, respectively. The temperature-dependent stepwise release experiment was performed by fluctuating the temperature between 25 and 45°C. The release behavior as a function of pH was determined at 25°C in pH 4 and 7 buffer solutions, and the oscillatory release by pH was studied between pH 4 and 7 as mentioned above.

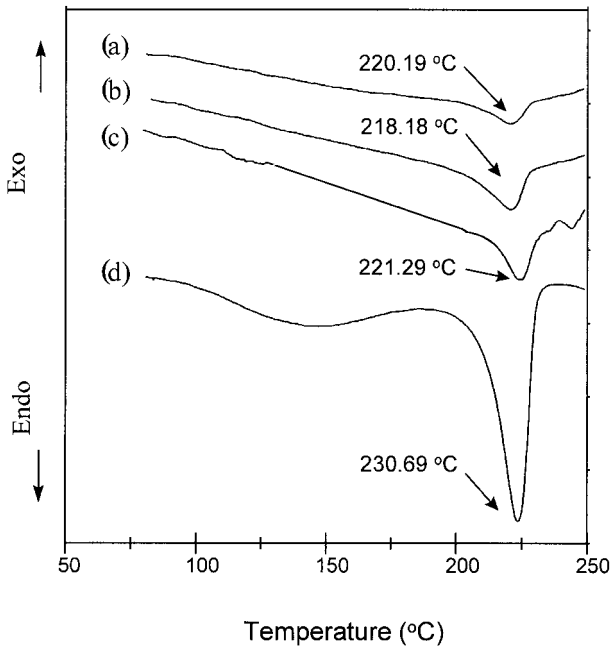


Figure 1 DSC thermogram of dry IPNs and PVA: (a) IPN46; (b) IPN55; (c) IPN64; (d) PVA.

RESULTS AND DISCUSSION

Characterization

The structure of IPN samples prepared was confirmed by FTIR spectra shown in our previous paper.[3] It was found that there existed hydrogen bonds between PVA and PAAc.

Figure 1 exhibits the DSC melting endotherms of dry IPN disks and a PVA sample. PAAc has an amorphous structure, and we cannot detect any

Table I Water States of IPN Hydrogels Calculated by Using DSC

States	Samples[a]	EWC (%)	Free Water (%)	Bound Water (%)
pH 4, 25°C	IPN46	73.89	54.0	19.5
	IPN55	71.27	50.0	21.27
	IPN64	70.34	48.0	22.34
pH 7, 25°C	IPN46	94.0	80.5	13.5
	IPN55	94.2	78.0	16.2
	IPN64	90.3	63.2	27.1
pH 7, 45°C	IPN46	94.6	85.0	9.6
	IPN55	93.4	79.2	14.2
	IPN64	94.6	68.0	26.6

[a] All samples were fully swollen at respective states for 24 h.

noticeable transition in the DSC thermogram. On the other hand, PVA gives a sharp endothermic peak at 224°C and IPN disks showed melting peaks close to this point. As the molar ratio of PVA to PAAc increased from 4 : 6 to 6 : 4, the integration of the peaks of IPN disks became more intensive (Fig. 1). It is evident that the crystallinity was remarkably reduced as a result of photocrosslinking and physical crosslinking and the decrease was mainly affected by PAAc composition.

Swelling kinetics of IPN hydrogels were investigated in our previous paper.[23] All IPNs reached their equilibrium after 20 h, and the more PAAc in the IPNs, the higher the swelling ratio.

In the present study, the equilibrium water content (EWC) was calculated both at pH 4 and 7 buffer solutions (see Table I). EWC, determined at pH 7, was >90%. Since IPN46 possesses more hydrophilic and ionizable groups examined within its structure, the swelling degree may be the highest among the other IPN, resulting in the highest total water content at all conditions of experiments. Moreover, at pH 7, the drastic increments of EWCs from all IPN samples were due to the ionization of carboxylic acid group in IPN. The ionic repulsion, caused by the formation of carboxylation, dominated the swelling behavior. In Scheme 1, we depict the diagrams of swelling/deswelling behaviors of IPN hydrogels in response to pH change.

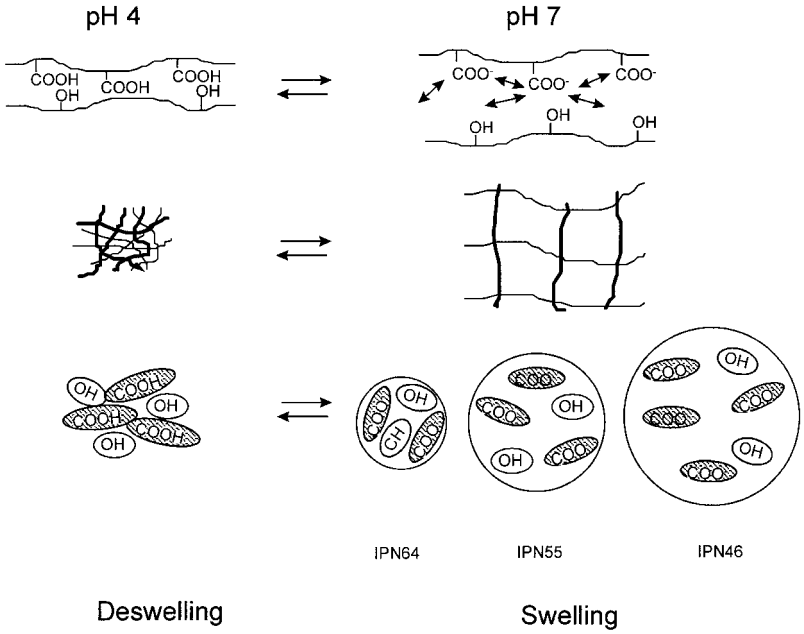
Since the structure of water in the swollen polymer matrix may play a significant role in the release of model drug in response to the swelling mechanism, the melting endotherms of swollen gels were investigated in order to calculate the free water and bound water content in the IPN hydrogels.

There have been studies concerning the water state of the polymer matrix by using DSC.[29–31] Figure 2 shows the DSC thermogram of fully swollen IPN hydrogels. The free water has good mobility, since it has no interaction with polymer chains. However, the bound water is involved in the hydrogen bonding with polymer. The endothermic peak of swollen gel appears between 0 and 10°C. The fraction of free water is approximately estimated by the ratio of endothermic peak, integrated between these ranges, to the melting endothermic peak of heat of fusion for pure water. The DSC measurement was conducted under various conditions in order to study the temperature and pH effect on the change of water state in IPN hydrogels. EWC values, free water contents, and bound water contents, respectively, are listed in Table I. The free water contents of IPN46, IPN55, and IPN64 were, at pH 4, 0.54, 0.50, and 0.48, respectively. However, the bound water remained almost constant.

The free water contents in IPN hydrogels at various conditions are shown in Figure 3. At pH 4, the PAAc, which existed as a hydrated state, formed strong hydrogen bonds with water and hydroxyl groups of PVA, and the free water contents were lower compared with those at pH 7. In addition, the water contents calculated at higher temperature were higher than those at lower temperature. It is clear that the increase of swelling at pH 7, and at higher temperature, is attributed mainly to the free water contents, and the ionic repulsion of carboxylic ions, and thus dissociation of hydrogen bonding, also induces the decrease of bound water in hydrogels.

Drug Releasing

A solvent sorption method was adopted to load the indomethacin into the polymer gels. This



Scheme 1. Schematic diagrams of swelling/deswelling behaviors of IPN hydrogels dependent on pH change.

method has advantages over the simultaneous method in which the drug is incorporated during polymerization, that is, the unreacted materials can be removed before drug loading and the loading amount of the gel can be adjusted by controlling the concentration of drug solution and/or degree of swelling.

Figures 4–6 show the temperature-sensitive indomethacin release profiles from drug-loaded hydrogels by putting them into pH 7 buffer solutions at 25 and 45°C, respectively. All the samples shown in Figures 4–6 exhibit high release rate at higher temperature. These results are in correspondence with the previous study[26] about the temperature-dependent swelling behaviors of IPN

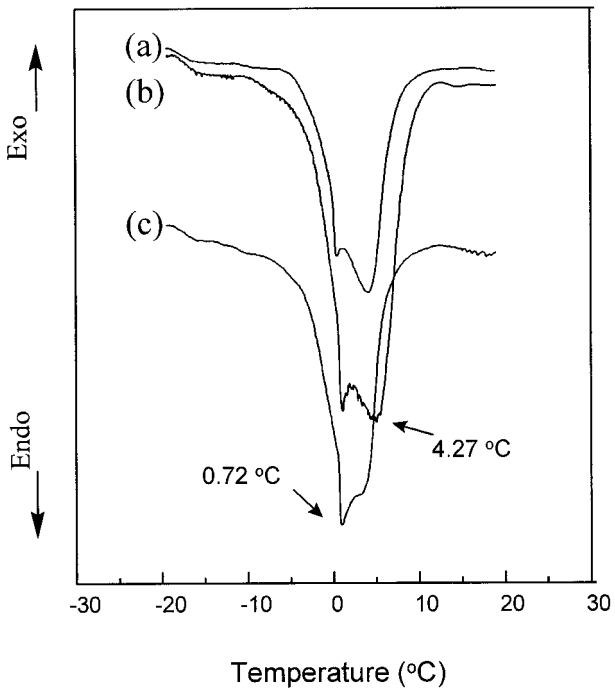


Figure 2 DSC thermograms of IPN hydrogels which were fully swollen in pH 7 buffer solution: (a) IPN46; (b) IPN55; (c) IPN64.

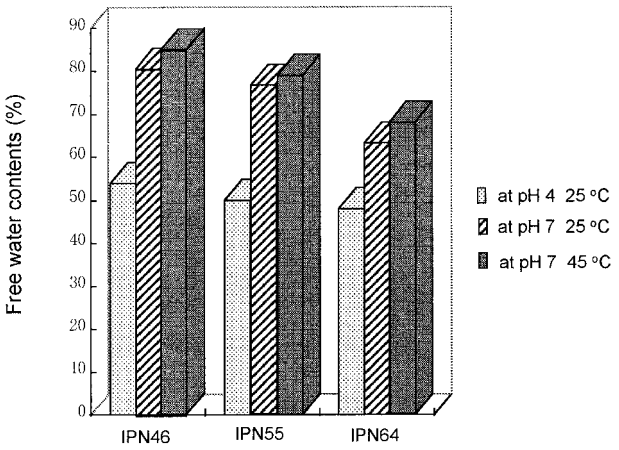


Figure 3 Free water contents in IPN hydrogels at various conditions.

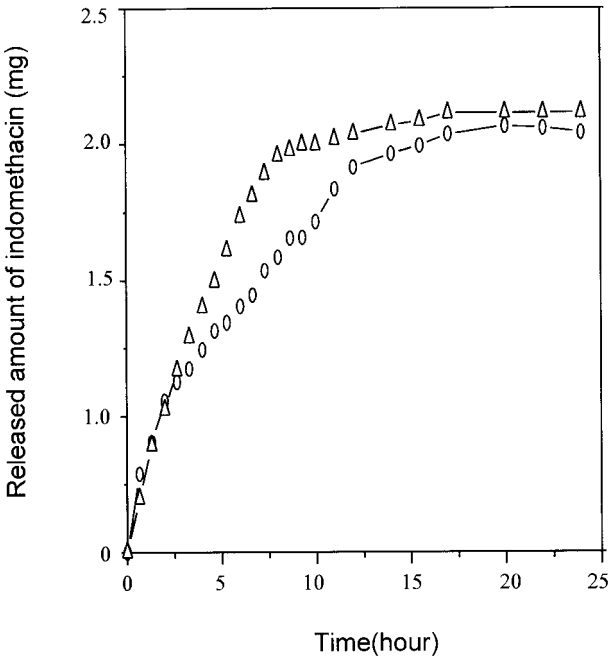


Figure 4 Temperature-dependent release profiles at pH 7 from IPN46 hydrogel measured at 25 (○) and 45°C (△).

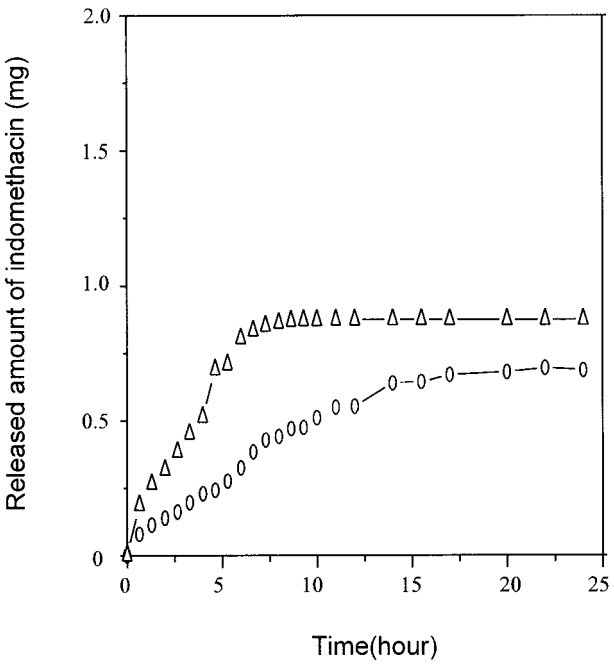


Figure 6 Temperature-dependent release profiles at pH 7 from IPN64 hydrogel measured at 25 (○) and 45°C (△).

hydrogels. We obtained swelling kinetics with changing temperature and reported that the swelling changes in IPN samples must be related to the hydrogen bonding between polymers and ionic repulsions due to the cleavage of hydrogen bonding with increasing temperature. IPN hydrogels show different kinds of thermosensitivity. All IPN samples show a positive temperature-sensitive system before they reach their equilibrated state. IPN64 and IPN55 exhibit negative swelling after equilibrium swelling. This is mainly due to the negative temperature sensitivity of PVA homopolymer, and thus IPN64 and IPN55, which have more PVA groups because of the removal of residual acrylic acid groups during the synthesis, have a different swelling tendency. However, the release of incorporated drugs within IPN hydrogels was delayed for ~10–15 h, which was not enough time for all the samples to be fully equilibrated. So all IPN samples showed higher release rate at higher temperature, and thus the composition of IPN was not significant in the temperature-dependent release system.

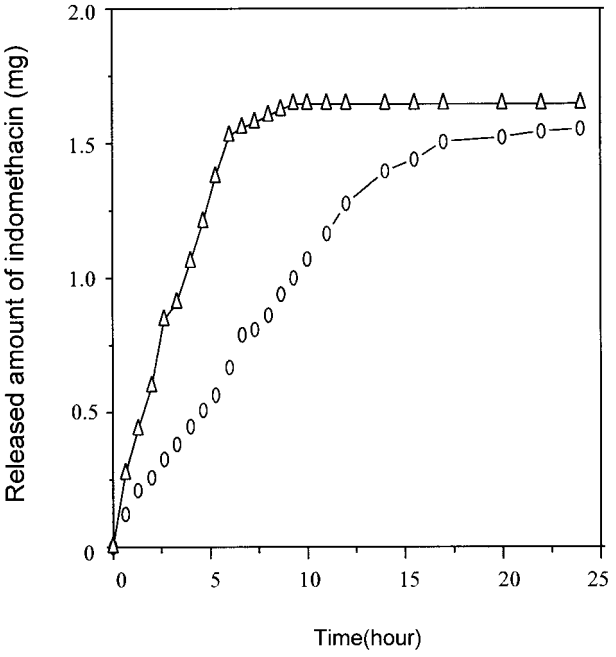


Figure 5 Temperature-dependent release profiles at pH 7 from IPN55 hydrogel measured at 25 (○) and 45°C (△).

Changes of release rate for IPN46, IPN55, and IPN64 hydrogels in response to stepwise temperature changes between 25 and 45°C are shown in Figure 7. High release rates are obtained at 45°C, while low release rates are observed during the lower temperature period, as mentioned above. The released amounts from IPN46 and IPN55 are almost the same, while the released amount from

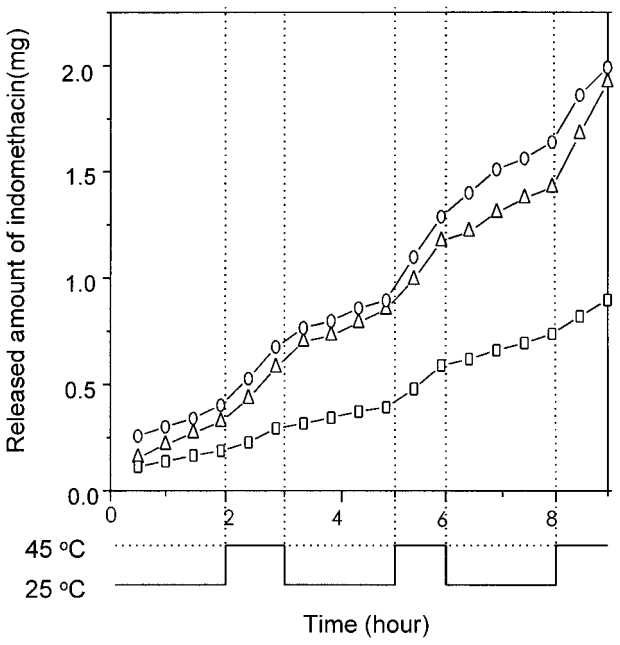


Figure 7 Release change of indomethacin from IPN hydrogels in response to stepwise temperature change between 25 and 45°C: (○) IPN46; (△) IPN55; (□) IPN64.

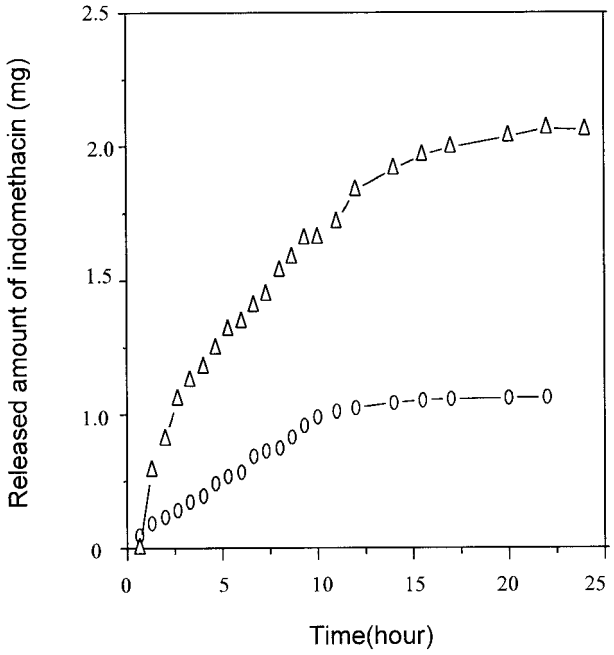


Figure 8 pH-dependent release profiles at 25°C from IPN46 hydrogel measured at pH 4 (○) and pH 7 (△).

IPN64 is small due to the limited swelling. In the case of IPN64, the fact that the hydroxyl groups in PVA formed hydrogen bonding, and had little chance to experience ionic repulsion from carboxylate groups, was proved.

pH-sensitive release behaviors of indomethacin were observed at 25°C with change in pH. In this system, the major factor for controlling the released amount is the swelling of the hydrogel affected by the surrounding pH. Indomethacin is expected to diffuse through the water swelling region in the polymer gel. Release profiles of indomethacin shown in Figure 8–10 are achieved at two pH conditions at 25°C for 25 h. The time is enough for the complete release from the hydrogels. Figure 8 represents the release profile of IPN46 containing the more PAAc component. Figures 9 and 10 show release profiles of IPN55 and IPN64, respectively. Since the pKa value of PAAc is 4.28, at pH 4, PAAc is in the form of carboxylic acid, which produces hydrogen bonding with the hydroxyl group of PVA, resulting in the decrease of drug release. However, at pH 7, carboxylate ions formed in PAAc induced a drastic increase in swelling and resulted in a high release rate. At pH 4, the release amounts from IPN46 and IPN55 were almost identical, and IPN64 gave lower values due to significantly lower swelling compared to the others. It is considered that the release rate from IPN hydrogels is nearly independent of the composition of samples at pH 4.

In the case of drug release experiments at pH

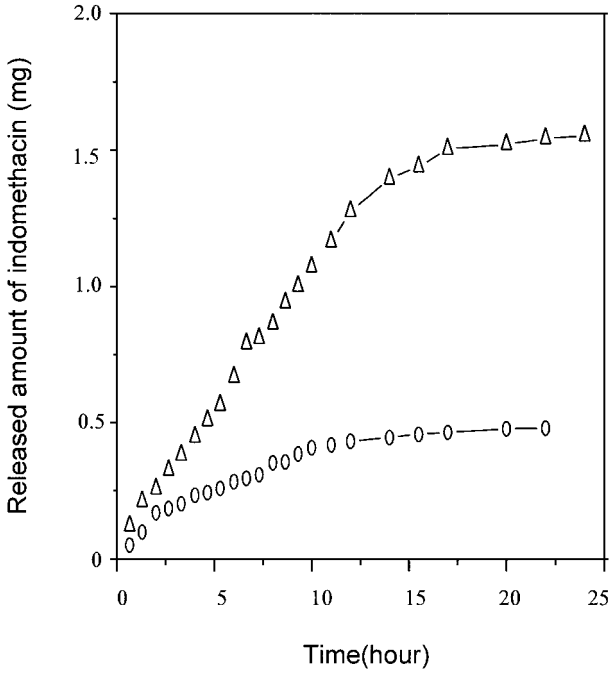


Figure 9 pH-dependent release profiles at 25°C from IPN55 hydrogel measured at pH 4 (○) and pH 7 (△).

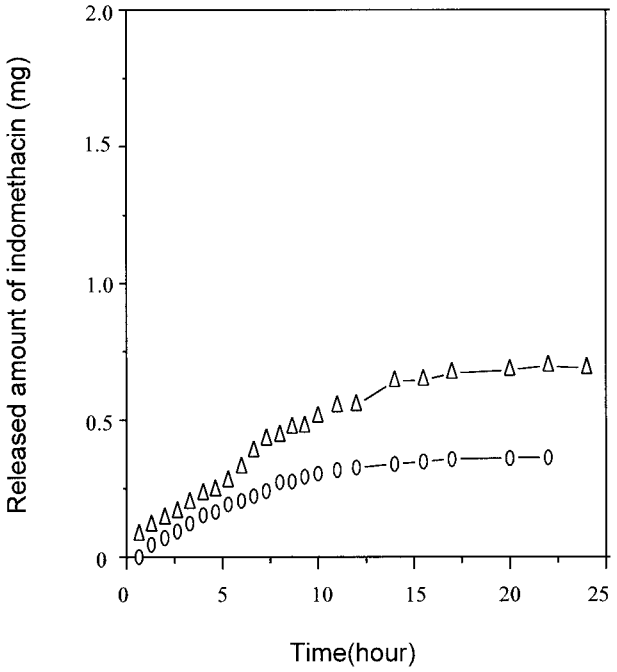


Figure 10 pH-dependent release profiles at 25°C from IPN64 hydrogel measured at pH 4 (○) and pH 7 (△).

7, more PAAc contents in IPN contributed to the higher release amount. This was in a good agreement with previous results that increasing PAAc contents caused an increase of swelling ratio. Furthermore, the pH-dependent release of indomethacin may be influenced by the free water contents reported in the previous section. From DSC data, the free water, attributed to the swelling, changes in response to the variation of pH. Therefore, the high amount of free water in hydrogels contributed to the high release rate, and it is expected that we may regulate the drug release rate by controlling the free water contents in the polymer.

Oscillatory release profiles at 25°C with changing pH between 4 and 7 are shown in Figure 11. The plot shows a reversible change of release rate with pH change. IPN46 and IPN55 showed lower release at pH 4 and higher at pH 7, and continued their reversible behavior during the experiment. However, IPN64 did not show a sharp reversible change because it did not have enough carboxylic groups.

CONCLUSION

A new pH/temperature-sensitive drug delivery system, based on IPN hydrogels composed of PAAc and PVA, was proposed. Dual sensitive release behavior from indomethacin-loaded IPNs, prepared by the solvent sorption method, was obtained with the changes in pH and/or temperature. The release mechanism of indomethacin was dominated by the magnitude of swelling in the IPN hydrogels.

In the temperature-sensitive system, positive release of drug caused by the hydrogen bonding between PVA and PAAc was observed, showing the increase of release amount with higher temperature. Temperature-sensitive stepwise release experiments showed that all the IPNs were reversible systems between 25 and 45°C.

In the case of pH-dependent release, the release rate being controlled by changing the pH, at pH 7 a higher release amount was observed since the water contents from the swelling increased significantly. However, the monomer composition in the polymer is not dependent on the release change at pH 4. From DSC experiments, the free water contents within the hydrogels were calculated, and were proved to have a dominant effect on the swelling changes as a function of temperature and pH.

In conclusion, the IPN system developed was an effective pH/temperature responsive drug delivery system and the release rate of a drug may be controlled by simultaneously changing stimuli depending on various biomedical applications. We

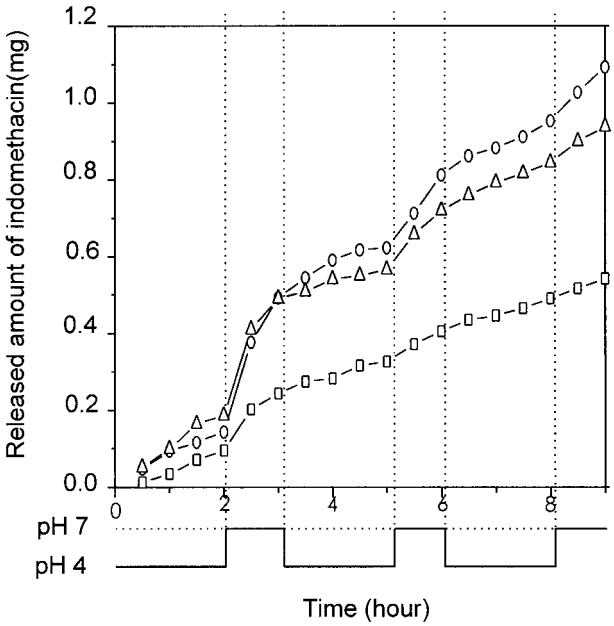


Figure 11 Release change of indomethacin from IPN hydrogels in response to stepwise pH change between pH 4 and 7: (○) IPN46; (△) IPN55; (□) IPN64.

evaluated the feasibility of these dual stimuli-sensitive hydrogels as drug carrier and will continue our study on other applications, such as permeability of various solutes through a hydrogel membrane by using these novel materials.

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