Drug Releasing Characteristics of Thermo- and pH-Sensitive Interpenetrating Polymer Networks Based on Poly(*N*-isopropylacrylamide)

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ABSTRACT: Interpenetrating polymer networks (IPNs) of poly(*N*-isopropylacrylamide)/polyurethane (PNIPAAm/PU) and poly(*N*-isopropylacrylamide)/poly(acrylic acid) (PNIPAAm/PAA) were synthesized to investigate the swelling and drug releasing behavior. The presence of urethane network in PNIPAAm/PU IPNs improved the mechanical strength, but reduced the swelling and drug releasing rates because of its hydrophobic characteristics. The swelling transition temperatures of PNIPAAm gels were little affected by the incorporation of PU networks in IPN structures. The drug releasing process was analyzed with a simple exponential expression of time dependent fractional drug release. The swelling and drug releasing behavior of PNIPAAm/PAA IPNs was significantly affected by the variation of PAA compositions. The drug release process changed from anomalous to dual type via zero-order mode with increasing PAA concentration due to the competitive swelling rates between PNIPAAm and PAA during release process. The releasing rate decreased in the buffer solution of pH 7.4, but increased in that of pH 5.0 with increasing PAA concentration at both 28 and 37°C because the swelling power of PAA in pH 5.0 was much less than that in pH 7.4. © 1997 John Wiley & Sons, Inc. J Appl Polym Sci **64:** 2647–2655, 1997

INTRODUCTION

The polymers sensitive to the external stimuli are of significance in applications to the auto feedback delivery systems and self-regulating systems such as drug delivery, rate barriers, and sensors. Controlled drug delivery systems[1–3] applying the hydrogels activated by variation of temperature, electric and magnetic fields, and pH, have been widely studied in their materials performance and phenomenological analysis.

Poly(*N*-isopropylacrylamide) (PNIPAAm) is one of the widely studied hydrogels due to its unique properties, showing phase transition behavior at low critical solution temperature (LCST) of 32°C. To correct its drawback of mechanical strength,[4] some hydrophilic or hydrophobic components were copolymerized with pure components.[5–9]

Interpenetrating polymer networks (IPNs) are characterized that two chemically crosslinked polymers form physically interlocked structures so that they may induce more complete mixtures than classical polymer blends. Physical interlocking of two water-soluble crosslinked networks may provide macroscopically separated phases. Being different from the copolymer systems in which the swelling properties are controlled by copolymer compositions, those in IPN systems may be independently activated. Bae[10] et al. investigated the drug releasing behavior of vinyl polymer/polyurethane (PU) IPNs.

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PNIPAAm, a typical thermo-sensitive hydrogel, is a good candidate for an auto feedback drug delivery system. Body temperature change induced by the presence of pathogens may be an important stimulus to the effective release of anti-hyperpyretic drugs for cure and its effectiveness is mainly controlled by temperature sensitive swelling characteristics of drug incorporating PNIPAAm hydrogel. In this contribution, PNIPAAm/PU IPNs were simultaneously synthesized to improve mechanical strength of thermo-sensitive PNIPAAm hydrogel by incorporating small amount of the hydrophobic PU network. Their equilibrium swelling and dynamic drug releasing behavior, as well as their mechanical strength was investigated. Also, PNIPAAm/poly(acrylic acid) (PAA) IPNs were sequentially synthesized to observe the temperature and pH dependence of equilibrium swelling and dynamic drug releasing behavior, as PAA is sensitive to pH change. In this study indomethacine was used as a model drug as it is effective for cure in hyperpyretic symptoms.

EXPERIMENTAL

Raw Materials

N-isopropylacrylamide(NiPAAm) monomer (Eastman Kodak Co.) was recrystallized twice in *n*-hexane. 1,4-butadiene (1,4-BD) (Tokyo Kasei Chem. Co.), trimethylolpropane (TMP) (Celanese Chem. Co.) and poly(teramethylene oxide) (PTMO 1000) (DuPont De Nemours & Co.) were dehumidified at 60°C under vacuum for 6 h for purification. Acrylic acid (AA) (Junsei Chem. Co.) was vacuum-distilled to remove inhibitors. Other materials were used without further purification.

IPN Synthesis

PNIPAAm network was prepared by the radical polymerization method at 80°C for 3 days using benzoyl peroxide (BPO) (Polyscience Co.) as an initiator and ethylene glycol dimethylacrylate (EGDMA) (Fluka Chemie AG.) as a crosslinking agent. PNIPAAm/PU IPNs were synthesized by simultaneous polymerization technique. The reactants for the synthesis of PNIPAAm network and those for PU network, i.e., hexamethylene diisocyanate (HDI) (Fluka Chemie AG.) and ethylene glycol (EG) monomers with a crosslinking agent of EGDMA and a catalyst of dibuthyltin dilaurate (DBTL) (M&T Chem. Co.) were homogeneously mixed in dimethyl sulfoxide (DMSL) (Tatyama Chem. Co.) by agitation at 50°C for 20 min under N_2 environment, and then placed in a mold with silicone spacer of 1 mm thickness. Two polymerization reactions, the radical reaction for PNIPAAm and the condensation reaction for PU, were conducted simultaneously at 80°C for 3 days.

For the swelling and drug releasing experiments, PNIPAAm/PU IPN samples were separated from the mold and cut in disk types of 10 mm diameter. The unreacted monomers were extracted using water/ethanol (50/50, v/v %) solution. Disks were dried at room temperature for 1 day, and then at 50°C under vacuum for 3 days to remove residual solvents. The reactant compositions for the synthesis of P(NiPAAm/PU IPNs are summarized in Table I.

PNIPAAm/PAA IPNs were obtained by sequential polymerization technique. PNIPAAm films already synthesized were cut in disk types of 10 mm diameter. Unreacted reactants were extracted by placing disks in water/ethanol solution (50/50, v/v %) for a week and then in distilled water for another week. Other residual solvents were removed by drying in vacuum at room temperature for 1 day, and then at 50°C for 3 days. A mixture of acrylic acid monomer with a crosslinking agent of EGDMA and an initiator of BPO, respectively, was absorbed in PNIPAAm disk and left for 24 h to obtain uniform concentration. The radical reaction for the synthesis of PAA network was conducted at 60°C for 24 h, and then at 80°C for 24 h for completion. Disks were placed in distilled water to extract unreacted monomers, and then vacuum-dried at room temperature for 1 day, followed by 70°C for 3 days.

Measurement of Mechanical Strength

Stress–strain behavior of PNIPAAm/PU IPN samples swollen in water to equilibrium at 20, 23, 26, and 30°C were investigated using a tensile tester (Instron Model IB840099, Autograph S-100, Shimadzu). Each sample was cut in rectangular dimension of 10 mm (width) × 60 mm (length) × 1 mm (thickness). The measurements were performed in air at room temperature. The weight of the load cell was 5 kg.

Measurement of Swelling Transition Temperature

The swelling transition temperatures of PNIPAAm/PU IPNs swollen to equilibrium in water

Table I Feed Compositions of PNIPAAm/PU IPNs

Composition of IPN Component	PNIPAAm/PU Weight Ratio			
	100/0	95/5	90/10	75/25
NIPAAm (g)	5.00	4.75	4.50	3.75
EGDMA (g)	0.088	0.083	0.079	0.063
BPO (g)	0.015	0.015	0.015	0.015
PTMO (g)	0.00	0.25	0.50	1.25
HDI (g)	0.00	0.084	0.168	0.421
1,4BD + TMP (g)	0.00	0.022	0.045	0.112
DBTL (g)	0.00	3.34×10^{-6}	7.76×10^{-6}	1.67×10^{-5}
DMSO (mL)	5.00	5.00	5.00	5.00

at 28°C were measured using the differential scanning calorimetry (Du Pont 910 DSC). The scanning rate was 5°C/min in the experimental temperatures ranging from 15 to 50°C. The sample weight was 5 mg. Nitrogen was used as a sweep gas.

Drug Loading and Releasing Experiments

Indomethacine (Aldrich Chem. Co.), a model drug, was dissolved in ethanol/water (80/20, wt/wt %) solution. Drug was loaded at 25°C in PNIPAAm/PU and PNIPAAm/PAA IPN samples up to equilibrium by swelling each disk in the drug containing solution. Drug incorporated disks were dried under vacuum at room temperature for 3 days to remove residual ethanol/water solution. No presence of residual solution was assumed, as no weight change was observed in vacuum after this drying period.

The quantity of drug incorporated in each IPN disk was determined by measuring the weight of sample before and after drug load. PNIPAAm/PU and PNIPAAm/PAA IPN samples were placed in vials containing 10 mL of phosphate buffered saline (PBS) of pH 7.4. The content of drug released from each sample was measured using UV/VIS spectrophotometer (Unicam UV100) by detecting the characteristic peak of indomethacine at maximum absorption wavelength of 264 nm. The ratio of the absorption peak areas at its unique wavelength at different times represented the ratio of the drug concentrations in solution releasing from the bulk polymer samples. Each injection quantity was 1 μL. The same experiments were conducted for PNIPAAm/PAA IPN samples in buffer solutions of pH 5 and 3 to observe the pH effect. The selected buffer solutions having pH 5 and pH 3 were prepared by mixing 150 mg of NaOH, 1.2 g of citric acid, and 8.47 g of NaCl in 1000 cm^3 of water, and 271 mg of NaOH, 619 mg of citric acid, and 8.47 g of NaCl in 1000 cm^3 of water, respectively. Drug releasing experiments were carried out at least more than twice and only reproducible results were presented in this report.

RESULTS AND DISCUSSION

Thermal and Mechanical Properties of PNIPAAm/PU IPNs

Figure 1 represents the modulus of PNIPAAm/PU IPNs crosslinked with 2 mol % EGDMA swollen in

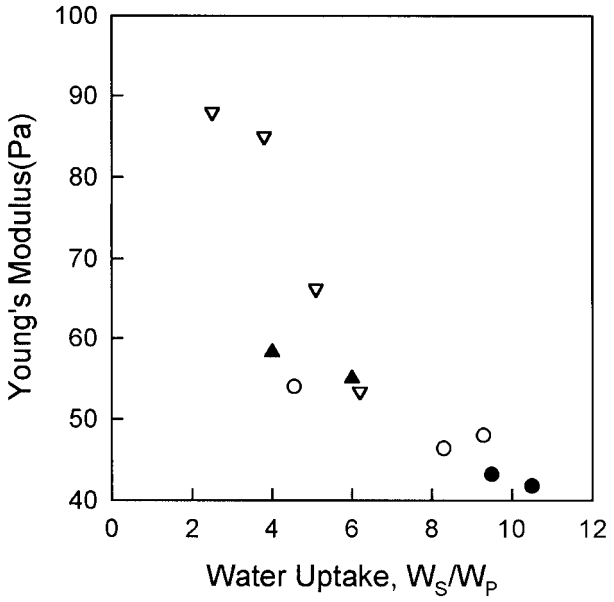


Figure 1 Effect of water uptake on the moduli of PNIPAAm/PU IPNs for varying PNIPAAm/PU weight ratios of 100/0 (●), 95/5 (○), 90/10 (△), and 80/20 (▽).

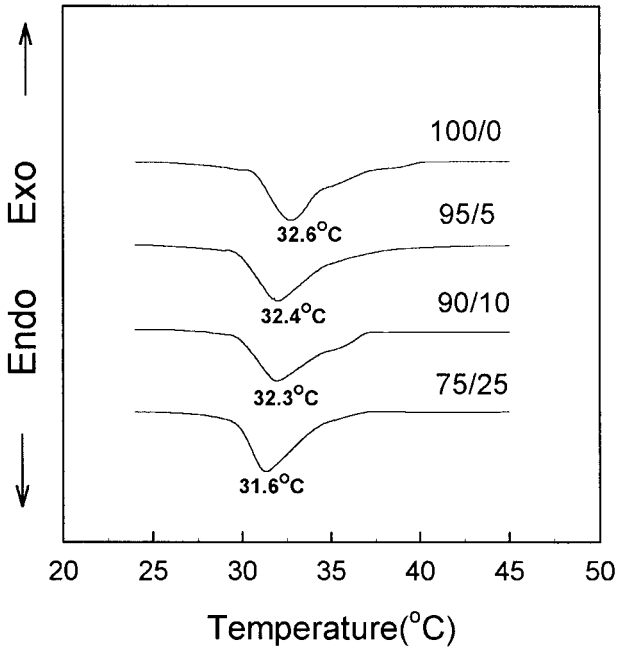


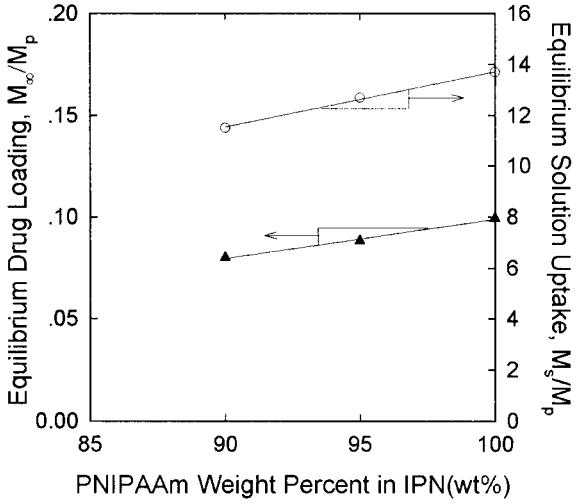
Figure 2 DSC thermograms for swollen PNIPAAm/PU IPNs for varying PNIPAAm/PU weight ratios of 100/0, 95/5, 90/10, and 75/25.

water to different degrees. The modulus in swollen state decreased with increasing water content at a fixed IPN composition, but increased with increasing PU concentration at a fixed water sorption amount. These results indicate that the hydrophobic PU segment in PNIPAAm/PU IPN systems decreased the water sorption amount, but increased the mechanical strength.

Figure 2 shows the DSC thermograms of water swollen PNIPAAm/PU IPNs. The thermogram showed endothermic peak in heating. As the swelling transition peaks of all IPNs are shown around LCST of PNIPAAm of 32°C, there was not significant PU concentration effect on the swelling transition in the present IPN composition ranges. Increasing concentrations of PU network from 0 to 25 wt % decreased the swelling transition temperatures very slightly.

Drug Loading Behavior

Figure 3 shows IPN concentration effect on the equilibrium drug loading and solvent sorption amount in PNIPAAm/PU and PNIPAAm/PAA IPNs. As PU was not compatible with water or ethanol, the equilibrium sorption amount of drug containing ethanol/water solution decreased linearly with increasing PU concentration in PNIPAAm/PU IPN systems. Also, the equilibrium drug loading content in IPN decreased linearly with PU concentration. It means that there is no chemical interaction between the drug and polymers. In case of PNIPAAm/PAA IPNs, both the equilibrium solvent sorption and drug loading content increased linearly with increasing PNIPAAm concentration, as the equilibrium swelling ratio of PNIPAAm was higher than that of PAA at the drug loading temperature of 25°C. Refer to Figure 4 in which the equilibrium and dynamic



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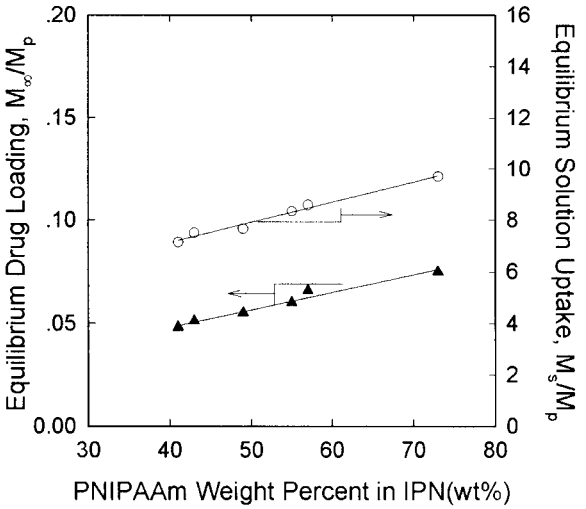

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Figure 3 Equilibrium solution uptake and drug loading content as a function of composition of (a) PNIPAAm/PU IPNs and (b) PNIPAAm/PAA IPNs at 25°C.

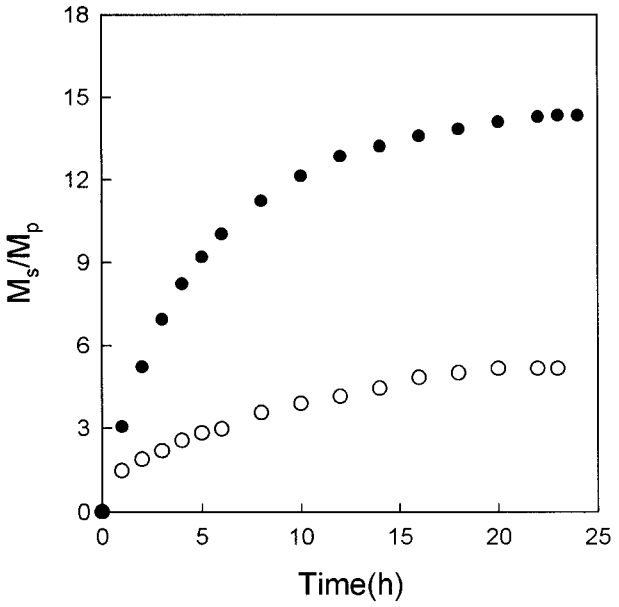


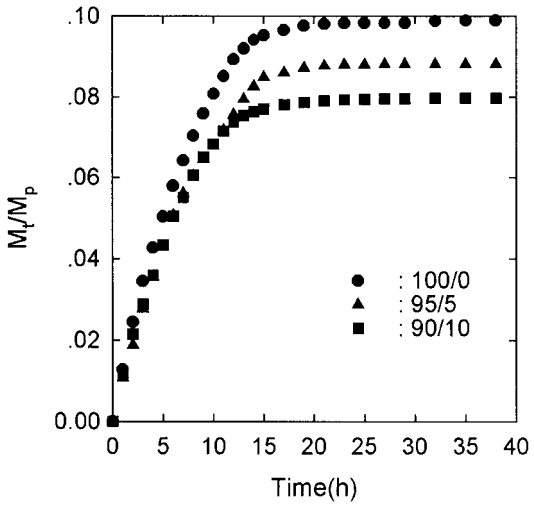
Figure 4 Weight swelling ratio of PNIPAAm (●) and PAA (○) in ethanol/water (80/20 wt/wt %) solution as a function of time at 25°C.

swelling behavior of pure PNIPAAm and PAA in drug solution is well illustrated. Figure 5 shows the relationship between the equilibrium drug loading and equilibrium solvent sorption amount for varying compositions of PNIPAAm/PU and PNIPAAm/PAA IPNs. The ratio of drug loading content to the equilibrium solvent sorption amount was constant, which implied that the drug loading content in IPN is proportional to the absorbed solution amount.

Drug Releasing Behavior

Figure 5 shows the time dependence of drug content releasing from a unit mass of PNIPAAm/PU IPN. At the constant temperature the releasing rate and equilibrium release content were significantly affected by the IPN compositions. As the hydrophobic PU concentration increased, the equilibrium drug release content decreased because of the decrease in both the equilibrium drug loading content and the equilibrium swelling ratio. For a fixed IPN composition, the drug releasing performance was mostly controlled by the PNIPAAm fraction as the increasing unswellable PU concentration reduced the overall swelling ratio, even it improved the mechanical strength. The releasing rate increased at the lower temperature of 25°C, as the swelling rate and the equilibrium swelling ratio of PNIPAAm increased with decreasing temperature in the temperature ranges below its LCST of 32°C.

Figure 6 shows the time dependence of fractional drug release for varying PNIPAAm/PU IPN compositions. The drug release process was similar to Fickian behavior and there were no significant kinetic changes for the PU compositions ranging from 0 to 10 wt %. The time to reach equilibrium drug release content decreased with increasing PU concentration and temperature, be-



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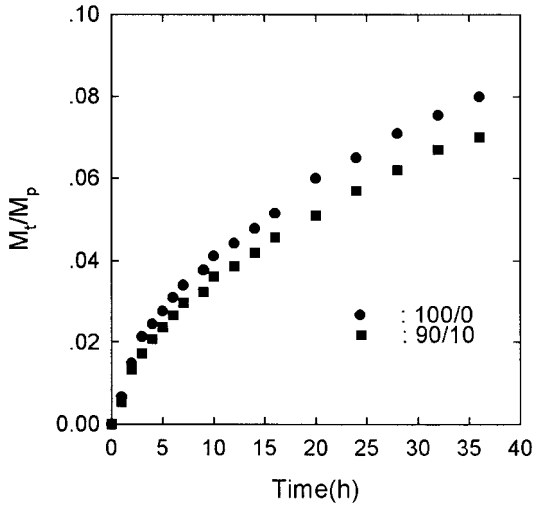

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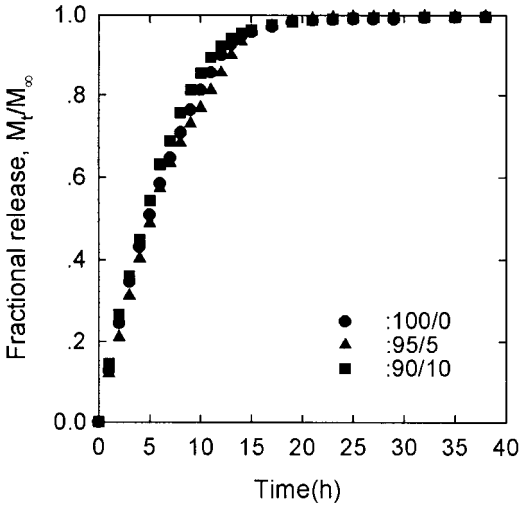
Figure 5 Time dependent drug releasing content per unit mass of PNIPAAm/PU IPN samples at (a) 25°C and (b) 28°C. The codes in each figure represent the weight ratios of PNIPAAm/PU in IPNs.



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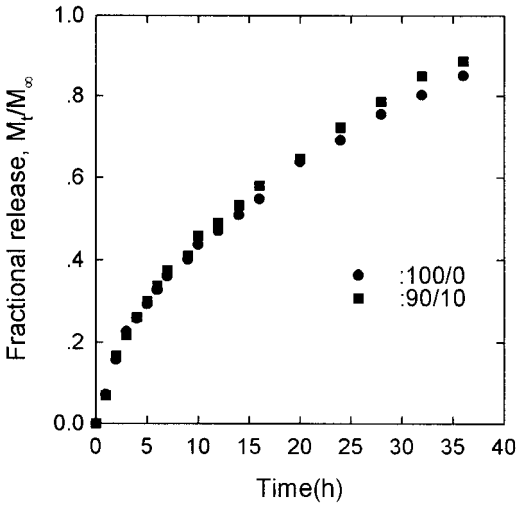
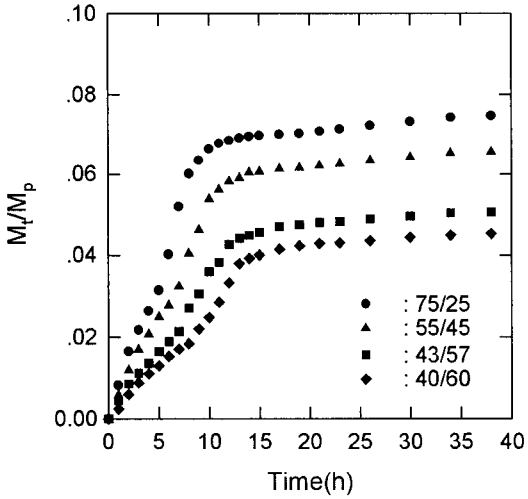


(b)

Figure 6 Time dependent fractional drug releasing behavior of PNIPAAm/PU IPNs at (a) 25°C and (b) 28°C. The codes in each figure represent the weight ratios of PNIPAAm/PU in IPNs.

cause the increasing PU concentration and temperature retarded the swelling rate of IPNs in the releasing medium. The swelling medium was more difficult to diffuse into PU concentrated IPNs due to the existence of more interlocked structures caused by hydrophobic network segments. The temperature effect was also significant upon the PNIPAAm swelling rate. The higher temperature induced more volume shrinkage of PNIPAAm networks, resulting in lower polymer swelling and drug releasing rate.

Figure 7 shows the time dependence of drug releasing content from a unit mass of PNIPAAm/PAA IPNs in buffer solution of pH 7.4. At the constant temperature of 28°C, the equilibrium drug release content increased with decreasing PAA concentration, because the equilibrium swelling ratio of IPNs decreased with decreasing PAA. Refer to Figure 4. At constant IPN composition, the equilibrium drug release content was af-



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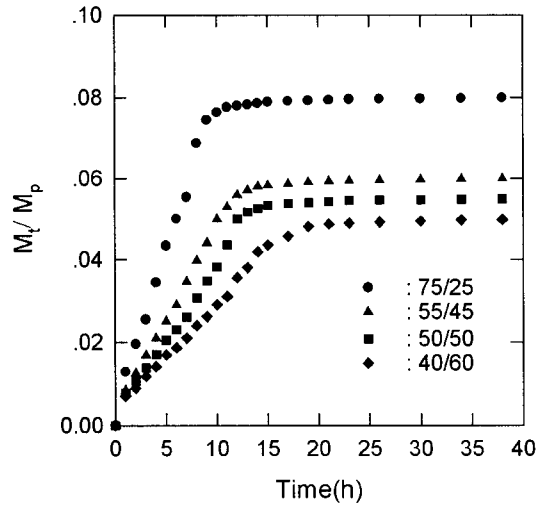
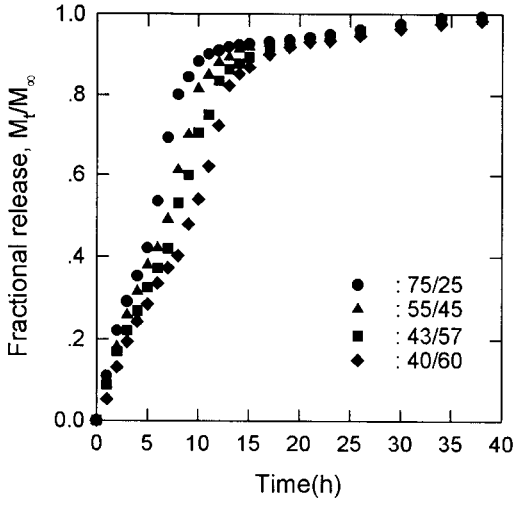


(b)

Figure 7 Time dependent drug releasing content per unit mass of PNIPAAm/PAA IPN samples in PBS buffer solution of pH 7.4 at (a) 28°C and (b) 37°C. The codes in each figure represent the weight ratios of PNIPAAm/PU in IPNs.

fected by experimental temperature. The increasing temperature led to decrease in the equilibrium release amount as the releasing performance was much more significantly controlled by the PNIPAAm component. At 28°C the drug releasing performance was controlled competitively by both PAA and PNIPAAm components, whereas at 37°C the releasing capacity was controlled mostly by the PAA because the PNIPAAm network was in a shrunken state, which inhibited the swelling ability of PAA network. This inclination is more easily explained with Figure 8, where the fractional drug releasing behavior as a function of time is described. At 28°C, the dual type releasing behavior was observed as the PAA content increased from 40 to 60 wt %. It was seemed to be caused by the initial release of drug from both PNIPAAm and PAA networks, followed by mostly from PNIPAAm network, as the swelling rate of PAA is higher than that of PNIPAAm at this condition. At 37°C, the PNIPAAm network is in a shrunken state, but the PAA is in a swollen state in buffer solution. The shrunken PNIPAAm network structure has an effect on the overall drug releasing behavior, even though its content is mostly from the swelling PNIPAAm network.

Figure 9 represents the dynamic drug releasing behavior of PNIPAAm/PAA IPNs in buffer solution of pH 5.0. Being very different from pH 7.4, the releasing rate increased with increasing PAA concentration at both 28 and 37°C. This results from no squeezing effect in pH 5.0 solution because the swelling power of PAA in pH 5.0 was much less than that in pH 7.4. For constant compositions of IPNs, the time to reach equilibrium release was observed even longer than at pH 7.4. These results are also caused by the pH effect on the swelling characteristics of PAA component in that the equilibrium swelling ratio of PAA was reported decreasing with decreasing pH values.[11] As shown in Figure 9(a) and (b) for constant compositions of IPNs, the time to reach equilibrium at 28°C was shorter than that at 37°C in the solution of pH 5.0. It is due to the negative temperature dependence of PNIPAAm component up to 37°C.



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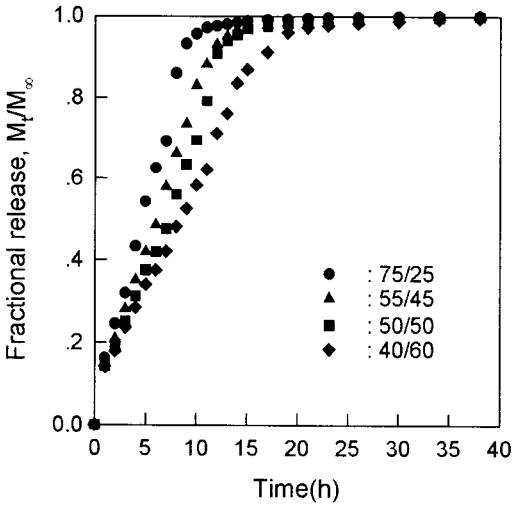


(b)

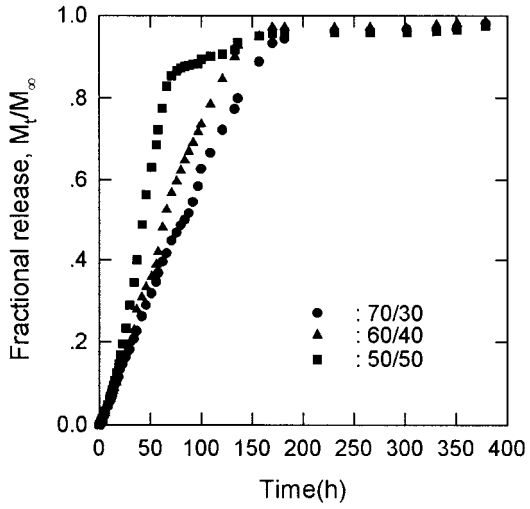
Figure 8 Time dependent fractional drug releasing behavior of PNIPAAm/PAA IPNs in PBS buffer solution of pH 7.4 at (a) 28°C and (b) 37°C. The codes in each figure represent the weight ratios of PNIPAAm/PU in IPNs.

Drug Releasing Kinetics of PNIPAAm/PAA IPNs

The kinetics implying the drug releasing mechanism is generally described by the following simple exponent equation[12,13]:

$$\frac{M_t}{M_\infty} = kt^n \qquad (1)$$

where t is the drug releasing time, k is the releasing kinetic constant, and the value of the exponent, n, is the indication of drug releasing characteristics. When the value of n is 0.5 or 1, the releasing mechanism is characterized as Fickian. An anomalous releasing mechanism is characterized by the value of n in the range between 0.5 and 1. Applying the logarithm to the both sides of equation (1) and plotting log versus log t provided the values of n and k from its slope and y



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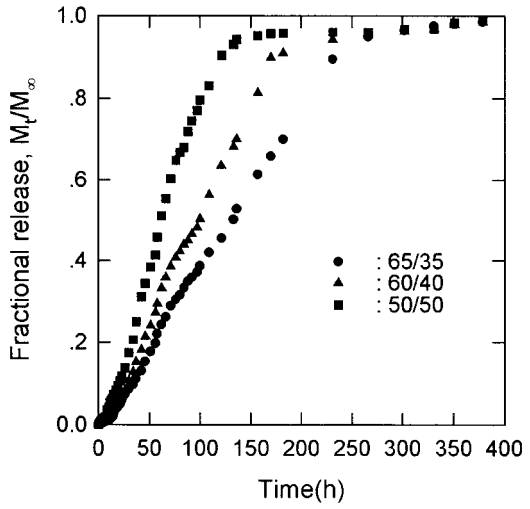

(b)

Figure 9 Time dependent fractional drug releasing behavior of PNIPAAm/PAA IPNs in buffer solution of pH 5.0 at (a) 28°C and (b) 37°C. The codes in each figure represent the weight ratios of PNIPAAm/PU in IPNs.

axis, respectively. The resulting values of n and k are summarized in Table II. At 37°C the values of n decreasing from 0.76 to 0.63 with increasing PAA concentrations from 25 to 60 wt % indicate the overall releasing kinetics follow the anomalous releasing behavior. It was postulated that this anomalous releasing kinetics, not an usual Fickian kinetics in hydrogels, was attributed from the swelling PAA network structure constrained by the shrinking PNIPAAm network structure. On the other hand, the increasing values of n from 0.86 to 0.95 with increasing PAA concentrations from 25 to 60 wt % at 28°C indicate that the drug releasing rate was affected by both (PAA) and PNIPAAm network structures, which were competitively swelling in buffer solution. The releasing kinetics changing from anomalous to dual releasing characteristics for increasing PAA concentration from 40 to 60% resulted from the difference in the swelling rate between two IPN components—fast swelling of PAA network followed by the relatively slow swelling PNIPAAm network. In other words, the drug released relatively faster from the PAA than from the PNIPAAm. This trend is more significant with increasing PAA concentration, resulting the varying releasing kinetics from anomalous to dual type via zero-order mechanism. This explanation is complemented by the result of the time to reach equilibrium drug release. At 28°C the drug was still releasing in the experimental time scale from the IPN, whereas at 37°C the drug release reached equilibrium in 15 h because the drug incorporated in PNIPAAm was locked to release at 37°C, but at 28°C the drug in PNIPAAm was free to release at 15 h from the start of experiment.

CONCLUSIONS

The increase of hydrophobic PU domain in PNIPAAm/PU IPNs increased the modulus but decreased the equilibrium swelling ratio. The quantity of drug loaded in PNIPAAm/PU and PNIPAAm/PAA IPNs was proportional to the equilibrium quantity of drug-containing solution absorbed. As the hydrophobic PU concentration increased, the equilibrium drug releasing content decreased because of the decrease of the drug loading and swelling ratio in equilibrium. Fractional drug releasing kinetics was similar to Fickian behavior for the PU compositions ranging from 0 to 10 wt %. The time to reach equilibrium drug release decreased with increasing PU concentration and temperature, because the increasing concentration of PU and temperature retarded the swelling rate of IPNs in releasing medium.

For the drug releasing behavior of PNIPAAm/PAA IPNs at 28°C, the drug releasing ability was controlled competitively by both PAA and PNIPAAm components, whereas at 37°C it was controlled mostly by the PAA because the PNIPAAm

Table II The Values of Exponent, *n*, Indicating the Drug Releasing Kinetics of PNIPAAm/PAA and PNIPAAm/PU IPNs

PNIPAAm/PAA IPNs			PNIPAAm/PU IPNs		
	n, Values of Exponent			*n*, Values of Exponent	
Weight Ratio	28°C	37°C	Weight Ratio	25°C	28°C
75/25	0.86	0.76	100/0	0.83	0.67
55/45	0.87	0.73	95/5	0.87	0.67
50/50		0.65	90/10	0.81	0.69
40/60	0.95	0.63			

network was in a shrunken state, which inhibited the swelling intent of PAA network. The releasing kinetics changing from anomalous to dual releasing characteristics was observed for increasing PAA concentration from 40 to 60%. It was due to the difference in the swelling rate between two polymer networks—fast swelling of the PAA network, followed by relatively slow swelling of the PNIPAAm network.

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