Synthesis and Characterization of pH- and Temperature-Sensitive Poly(methacrylic acid)/Poly(*N*-isopropylacrylamide) Interpenetrating Polymeric Networks

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ABSTRACT: Hydrogels of an interpenetrating polymeric network (IPN) composed of the temperature-sensitive poly(*N*-isopropylacrylamide) (PNIPAAm) and the pH-sensitive poly(methacrylic acid) (PMAA) were prepared by a sequential UV polymerization method. The IPN hydrogels were characterized for their temperature- and pH-responsive behavior by equilibrium swelling studies, oscillatory swelling studies, and differential scanning calorimetry. The permeability of these IPNs has been investigated under various pH and temperature conditions. The results showed that these hydrogels exhibited a combined pH- and temperature-sensitivity at a temperature range of 31−32 °C and a pH value of approximately 5.5. Permeation study results indicate a significant size exclusion behavior while model drugs with different sizes permeate through the IPN membranes. The permeability of the IPN membrane can be significantly affected by varying the pH and temperature conditions.

Introduction

In recent years, considerable research attention has been focused on hydrogels that are able to alter their volume and properties in response to environmental stimuli such as pH, temperature, ionic strength, and electric field. Because of their drastic swelling and syneresis in response to environmental stimuli, these polymeric hydrogels have been investigated for many biomedical and pharmaceutical applications, including controlled drug delivery,[1−6] molecular separation,[7] tissue culture substrates,[8] enzyme activity controlling systems,[9] and materials for improved biocompatibility.[10] Among these "intelligent" polymers, pH-[11−14] and temperature-sensitive[3,15−17] hydrogels are the most widely investigated.

More recently, work has been done to combine the pH and temperature sensitivities by copolymerizing two monomers[5,18−23] or forming interpenetrating polymer networks (IPNs)[24−27] of these pH-sensitive and temperature-sensitive materials. By chain interpenetration, we may attain combination of properties from these two polymer networks.[28,29] Since there is no chemical bonding between the two component networks, each network may retain its own property while the proportion of each network can be varied independently. Interpenetration of the two networks may also lead to a much higher mechanical strength with respect to the homopolymer network.

Poly(methacrylic acid) (PMAA) is an ionizable hydrophilic polymer. Cross-linked PMAA is able to swell in water. Its swelling behavior is greatly pH-dependent due to the ionization/deionization of the carboxylic acid groups. At low pH, usually pH value less than 5.5, the −COOH groups are not ionized and keep the PMAA network at its collapsed state. At high pH values, the −COOH groups are ionized, and the charged COO− groups repel each other, leading to PMAA swelling.

Poly(*N*-isopropylacrylamide) (PNIPAAm) is a temperature-sensitive polymer which has the sharpest transition of the class of thermosensitive alkylacrylamide polymers.[30] Cross-linked PNIPAAm exhibits drastic swelling transition at its lower critical solution temperature (LCST) of 32 °C. At temperatures lower than 32 °C, the gel is swollen whereas at temperatures higher than 32 °C, the gel dehydrates to the collapsed state due to the break down of the delicate hydrophilic/hydrophobic balance in the network structure.

The objective of this work is to synthesize the pH- and temperature-sensitive PMAA/PNIPAAm interpenetrating polymer networks, to investigate the swelling behavior of IPNs with respect to pH, temperature, and ionic strength, and to study to permeation behaviors of these IPNs under various pH and temperature conditions. An IPN hydrogel, which is sensitive to both pH and temperature, would be able to respond to conditions where both phenomena are coupled.

Experimental Section

Hydrogel Synthesis. A sequential UV solution polymerization was used to prepare the IPN samples of MAA and NIPAAm. Prior to the reaction, both monomers were purified of reaction inhibitors: NIPAAm (Fisher Scientific, Pittsburgh, PA) was recrystallized in benzene/hexane, and MAA (Aldrich, Milwaukee, WI) was distilled under vacuum to remove *p*-methoxyphenol.

The purified MAA was dissolved in methanol (40/60 vol) with 1 mol % of cross-linking agent, tetraethylene glycol dimethyl acrylate (TEGDMA) (Polysciences, Warrington, PA), and 1 wt % of the initiator, 2,2-dimethoxy-2-phenylacetophenone (DMPA) (Aldrich, Milwaukee, WI). Nitrogen was bubbled through the monomer/solvent mixture for 20 min to remove oxygen dissolved in the reaction mixture. The solution was cast on glass plates equipped with spacers and reacted under an UV source with an intensity of 1 mW/cm^2 for 30 min. The polymer was then removed from the plates and immersed in deionized water to remove the unreacted monomers. The gel was taken out and placed in fresh deionized water three times a day for 5 days before it was dried first in air and then dried in a vacuum oven. To incorporate the second network, the dried polymer network of PMAA was swollen in NIPAAm and methanol solution with the same cross-linking agent and initiator concentration until equilibrium.

The swollen gel was placed under the same UV source and polymerized for 10 min to form the IPN. The reaction time for

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the second polymerization was shorter than the first one. This was due to the higher conversion of the second polymerization. The IPN was subsequently washed as mentioned previously to remove the unreacted monomers. The IPNs can also be synthesized using PNIPAAm as the first network. However, the results showed that it was easier to prepare a PNIPAAm-rich IPN system using PMAA as the first network.

IPN Characterization. The compositions of the formed IPNs were determined by elemental analysis for nitrogen (model 240C elemental analyzer, Perkin-Elmer).

Equilibrium and oscillatory swelling studies were conducted on these IPN hydrogels as functions of environmental pH, temperature, and ionic strength to examine the behavior of the IPN hydrogels upon swelling in water or pH buffer solutions. The IPN hydrogels were cut into thin disks of 10 mm diameter using a cork borer and dried. In the equilibrium swelling experiments, dried IPN disks were placed in a pH buffer solution with a specific pH value and allowed to swell to equilibrium before it was transferred to another buffer solution with a different pH value or ionic strength. In the oscillatory swelling studies, either temperature or pH was kept constant. The IPN samples were swollen in buffer solutions for an equal period of time before they were replaced into a solution with higher pH value or higher temperature. Swelling has been evaluated in terms of the volume swelling ratio, Q, which was calculated as the ratio of hydrated volume to dry volume. Volume measurement of the gels was made by a buoyancy technique. The gels were weighed in air and heptane separately. The volume of the gel could be determined by dividing the density of heptane from the weight difference.

Differential scanning calorimetry (DSC) was used to determine the LCSTs of the IPNs. DSC (model DSC 2910, TA Instruments, New Castle, DE) experiments were performed on swollen hydrogel specimens of 15 mg by heating from 15 to 60 °C at 2 °C/min. The temperature-sensitive collapse of the hydrogels was identified as an endotherm in the thermograms. The onset of the thermogram corresponded to the LCST transition.

Permeation studies were performed using side-by-side diffusion cells (Crown Glass Co., Somerville, NJ). Preswollen IPN membranes with were mounted between the two half-cells of the donor cell and receptor cell. A solution with a specific model drug concentration was added to the donor cell, and fresh buffer solution was added to the receptor cell. The entire content of the receptor cell was removed at regular time intervals and replaced with fresh buffer solution. To ensure constant temperature of the solution, water with constant temperature was pumped through the outer half-cells. An ultraviolet−visible light spectrophotometer (Lambda 900, Perkin-Elmer, Norwalk, CT) was used to measure the absorbance of the samples taken from the receptor half-cell. The solute concentration of each sample could be determined using a calibration curve derived from the absorbance of the known concentrations of the solute. Theophylline (MW = 180, r_h = 0.13 nm) (Aldrich, Milwaukee, WI), proxyphylline (MW = 238, r_h = 0.23 nm) (Aldrich, Milwaukee, WI), oxprenolol HCl (MW = 302, r_h = 0.26 nm) (Aldrich, Milwaukee, WI), and FITC-dextran (MW = 4400, r_h = 4.9 nm) (Aldrich, Milwaukee, WI) were used as model drugs. The size of each model drug was indicated by r_h, the hydrodynamic radius. The drug concentration was determined by UV−vis spectroscopy (Lambda 900, Perkin-Elmer, Norwalk, CT).

Results and Discussion

Swelling Studies. Elemental analysis experiments indicated that the IPNs prepared under the above-mentioned synthesis conditions have a PNIPAAm concentration of 70 mol %. IPNs with various PNIPAAm concentrations were prepared. The result showed that a PNIPAAm-rich system was needed to achieve the temperature sensitivity. An IPN with PNIPAAm concentration of 70% was used as a model IPN in the following studies.

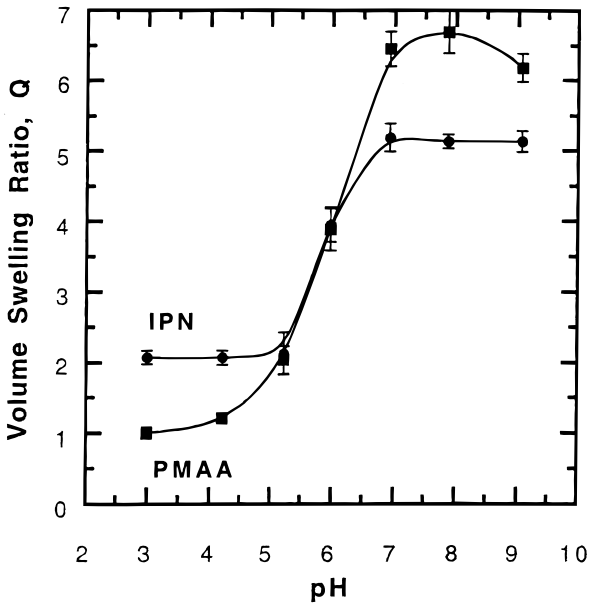

Figure 1. Equilibrium swelling behavior as a function pH at 22 °C in pH buffer solution for PMAA/PNIPAAm IPN samples (●) containing 70 mol % of PNIPAAm and pure PMAA (■) samples.

Equilibrium swelling studies indicated that these IPN samples were capable of responding to environmental pH, temperature, and ionic strength. Figure 1 showed the pH influence on the swelling ratio of the IPNs. Note that the data were in the range of pH values from 3.0 to 9.0. The swelling curve of the IPN exhibited a sharp transition at approximately pH 5.5, the pK_a of pure PMAA. Around that pH, the volume swelling ratio of IPN changed from 2 to 5 as pH increased. Beyond this pH, the equilibrium swelling value became more or less constant. This transition was due to the local ionization of the pendant carboxylic acid group. At a pH above the pK_a of the network, the pendant groups were ionized, and the gels swelled to a large degree due to the development of a large osmotic swelling force due to the presence of the ions.

The swelling ratio of the IPN was not as high as that of the pure PMAA gel even though the PMAA gel was made from the same concentration MAA solution that was used in the preparation of the IPN. This was because the incorporation of the second network increased the apparent cross-linking density of the IPN, which in turn decreased the swelling ratio of the IPN versus the pure PMAA. In addition, the existence of the second network decreased the carboxylic group density of the system compared to that of the pure PMAA hydrogel, thus resulting in a lower swelling ratio.

Figure 2 showed the temperature influence on the swelling behavior of the IPNs. Two IPN samples with the same PNIPAAm concentration were used in this study. One was swollen in buffer solution with pH 4.06 while the other was swollen in pH 6.16. The temperature of the solutions was increased from 20 to 45 °C. Deswelling transitions were detected in both IPN samples. At low temperatures the IPNs had higher swelling ratios due to the fact that the PNIPAAm component was swellable at temperatures lower than 32 °C. As temperature increased, the delicate hydrophilic/hydrophobic balance in the PNIPAAm network was broken. Dehydration took place in the PNIPAAm

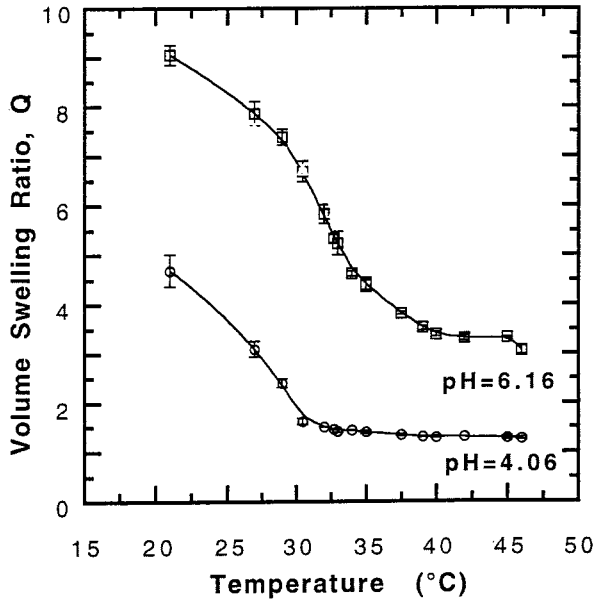

Figure 2. Equilibrium swelling behavior as a function of temperature at pH 4.06 (○) and pH 6.16 (□) for PMAA/PNIPAAm IPNs containing 70 mol % of PNIPAAm.

network, which resulted in the subsequent aggregation of the PNIPAAm chain and led to the deswelling of the IPNs. In the pH 4.06 sample, since the PMAA component of the IPN was in a collapsed state, the increase of temperature decreased the swelling ratio all the way from 4.8 to 1.0. However, for the IPN sample at pH 6.16, since the PMAA component was in the swollen state, as temperature increased, the swelling ratio dropped from 8.2 to 3.4 instead of going all the way to 1.0. The swelling/deswelling transition due to temperature changes in IPNs was a range that includes 32 °C, the LCST of PNIPAAm, but the transition was not as sharp as what it was in pure PNIPAAm gels. The existence of the PMAA network may interfere the hydrophilic/hydrophobic balance of the PNIPAAm network, so that the dehydration may not take place at the same time, resulting in a graduate deswelling transition.

Ionic strength also plays an important role in the IPN swelling behavior. We have investigated the ionic strength influence on the swelling behavior by using swelling agents such as NaCl solutions with different ionic strength. The temperature and pH were kept constant. As noted in Figure 3, the swelling ratio of PNIPAAm was almost constant as the ionic strength increases to 0.1 M (physiological state), because PNIPAAm was not ionizable. On the contrary, the swelling ratio of PMAA dropped drastically as the ionic strength increased, which was due to the shielding effect caused by the counterions at high ionic strength. The IPN sample deswelled at the beginning, and it flattened out when the ionic strength approached 0.1 M. The behavior of the IPN sample was a combination of the behavior of PMAA and PNIPAAm hydrogels.

The oscillatory swelling experiments were also conducted to investigate whether the responses to the environmental pH and temperature were reversible and to examine how fast the IPNs could respond to the stimuli. In Figure 4, the two samples were stored in constant pH solutions, pH 4.0 and pH 7.4; the temperature of the solution was varied between 22 and 37 °C from time to time. In Figure 5, temperature was kept constant while pH was varied from 4.0 to 7.4. As shown

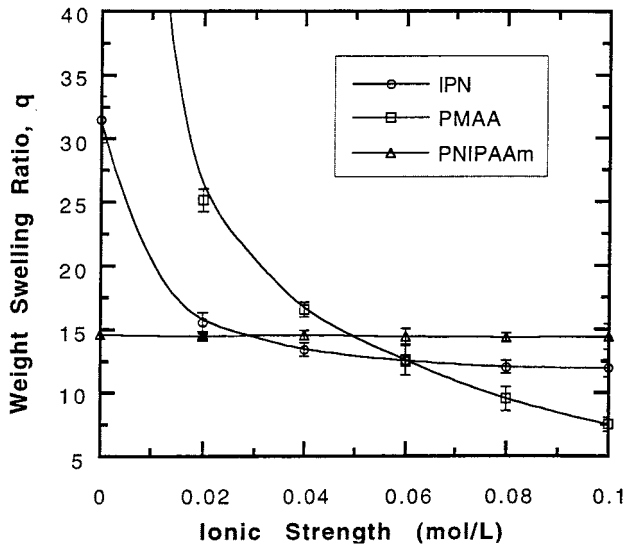

Figure 3. Equilibrium swelling behavior as a function of ionic strength at pH 7.0 and 22 °C for PMAA/PNIPAAm IPN containing 70 mol % of PNIPAAm (○), PMAA (□), and PNIPAAm (△).

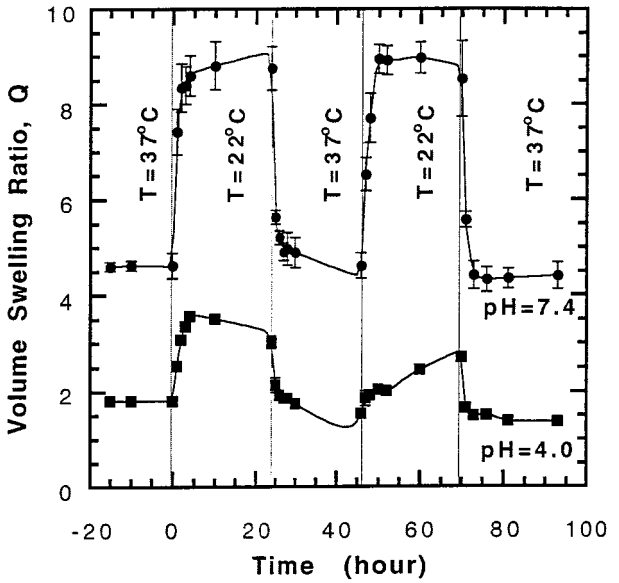

Figure 4. Oscillatory swelling behavior as a function of time and temperature at pH 7.4 (●) and 4.0 (■) for PMAA/PNIPAAm IPN samples containing 70 mol % of PNIPAAm.

in Figure 4, the IPN were able to respond to pH and temperature pulses. The responses were reversible.

Thermal Analysis. The DSC for pure PNIPAAm showed a secondary transition at 32 °C, which was the indication of the LCST, as shown in Figure 6. At the temperature of LCST, water in the hydrogel separated from the system and led to a smaller heat capacity. DSC experiments were conducted on PMAA/PNIPAAm IPN hydrogels swollen at different pH values. The results showed that the difference in pH had great influence on the LCST transitions of the IPN hydrogels (Figure 7). At pH 4.3, there was no significant transition detected around 32 °C. Transition temperatures were detected and increased as pH increased. This was because at low pH the aggregation of PMAA decreased the mobility of the PNIPAAm network as well as the water uptake of the IPN, resulting in drastically lowering the temperature sensitivity of the IPN hydrogel. However, at higher pH value, the swollen PMAA al-

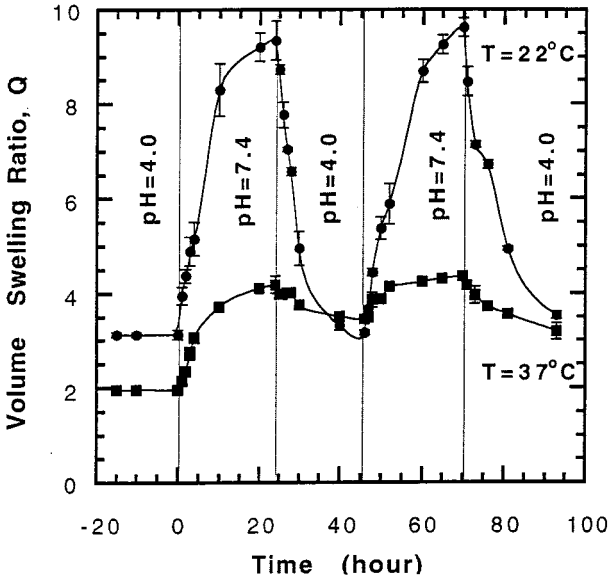

Figure 5. Oscillatory swelling behavior as a function of time and pH at temperature 22 (●) and 37 °C (■) for PMAA/PNIPAAm IPN samples containing 70 mol % of PNIPAAm.

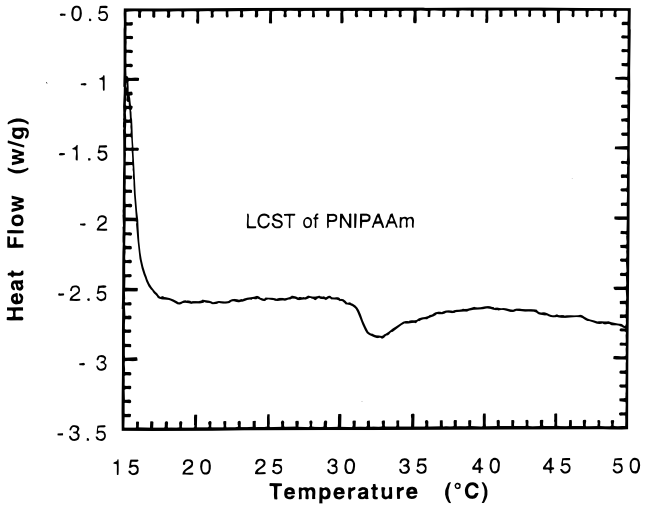

Figure 6. Differential scanning calorimetry thermogram of pure PNIPAAm swollen in deionized water, at a temperature ramp rate of 2 °C/min.

lowed the PNIPAAm to have a higher mobility, which made the IPN more temperature-sensitive.

The LCST transitions detected in the IPNs samples were in the range 31−32 °C. There was no significant deviation from the LCST of the pure PNIPAAm. This is a major difference between a PNIPAAm-based IPN and a PNIPAAm copolymer in which the LCST will be greatly influenced by the copolymer concentration. Thus, the formation of IPN gives us a relatively independent polymer system in which each network may retain its own property.

Permeation Studies. Model drugs with different sizes were used as solutes, and permeation experiments were carried out as described. Permeability coefficients were determined from the concentration data obtained from the permeation studies, using the following equation:[31]

$$\ln\left(1 - \frac{2C_t}{C_0}\right) = -\frac{2A}{V}Pt \qquad (1)$$

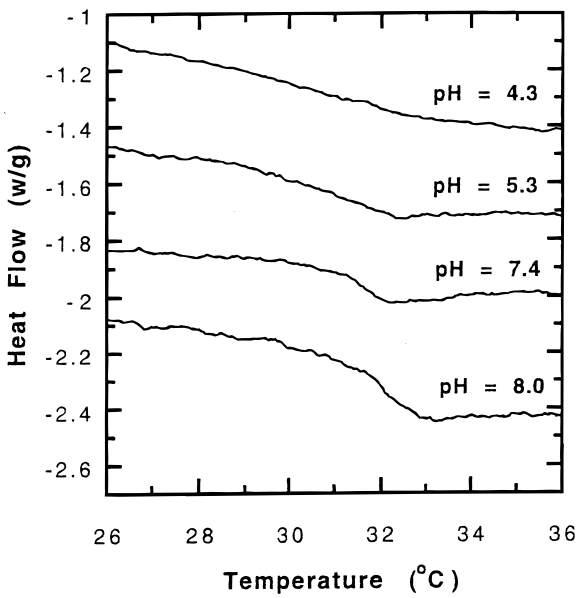

Figure 7. Differential scanning calorimetry thermograms of PMAA/PNIPAAm IPNs at pH 4.4, 5.3,7.4, and 8.0.

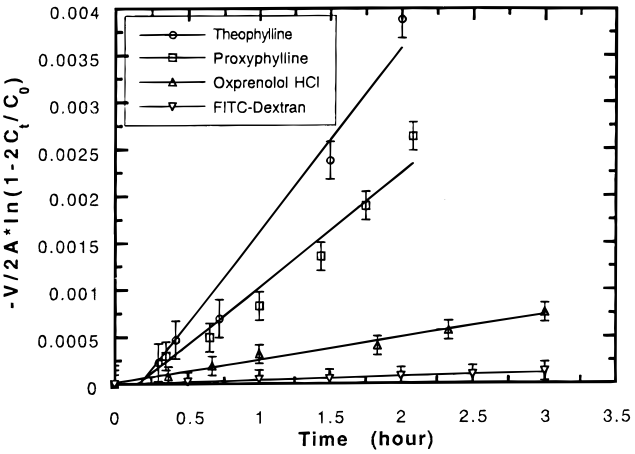

Figure 8. Solute permeation of theophylline (○), proxyphylline (□), oxprenolol HCl (△), and FITC-dextran (▽) through PMAA/PNIPAAm IPN. The slope represents the permeability of each solute.

Here, C_t is the solute concentration in the receptor cell at time t, C_0 is the initial solute concentration of the donor cell, V is volume of each half-cell (the volume in each half cell is 2.7 mL), A is the effective area of permeation (A = 0.636 cm^2), and P is the membrane permeability coefficient. To determine the permeability coefficient, P, a plot of $-(V/2A)\ln[1 - 2(C_t/C_0)]$ versus time, t, was constructed. The linear portion yields a slope of the permeability coefficient, P.

A significant size exclusion phenomenon was observed for the IPN membranes. Theophylline (r_h = 1.3 Å), proxyphilline (r_h = 2.3 Å), oxprenolol HCl (r_h = 2.6 Å), and FITC-dextran (r_h = 49 Å) were used as model drugs in the diffusion study where r_h denotes the hydrodynamic radius of the solute. The solute size, membrane mesh size, pH, temperature, and the affinity of the solute with the membrane may affect the permeation of the solute. Figure 8 shows a plot for the permeation of the four different model drugs through a PMAA/PNIPAAm IPN membrane containing 70 mol % of PNIPAAm in pH 7.4 buffer solution. As mentioned, the slope of each linear curve represents the permeability

Table 1. Permeability and Diffusion Coefficient of Oxprenolol HCl at Four Different pH and Temperature States

sample	weight swelling ratio, Q	thickness, l (mm)	permeability $\times 10^5$ (cm/s)	partition coeff, K_d	diffusion coeff $\times 10^6$ (cm^2/s)
oxprenolol (25 °C, pH = 7.4)	18.21	2.51	1.83	0.98	4.68
oxprenolol (25 °C, pH = 4.0)	3.19	1.23	1.38	0.93	1.82
oxprenolol (37 °C, pH = 7.4)	11.99	2.35	2.67	0.96	6.54
oxprenolol (37 °C, pH = 4.0)	2.49	1.10	0.99	0.92	1.18

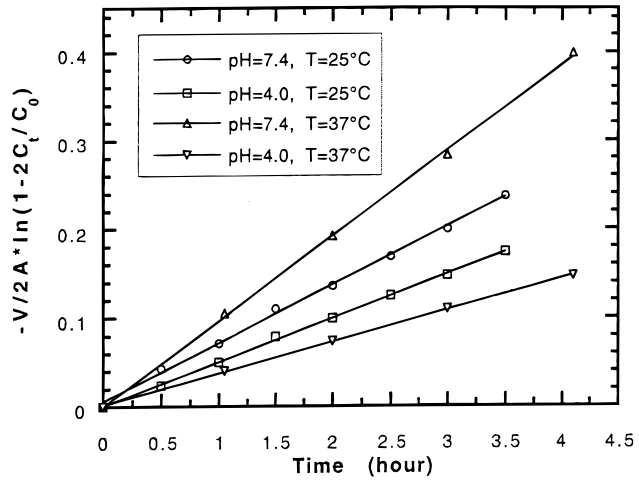

Figure 9. Permeation behavior of oxprenolol HCl for four different pH and temperature conditions.

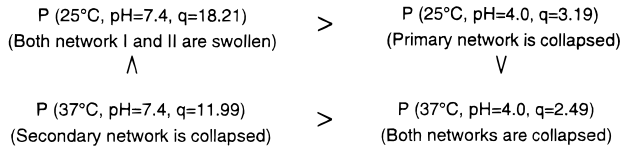

Figure 10. Relationship of the permeabilities for oxprenolol HCl permeation.

of each solute. As expected, higher permeability was observed for smaller model drug. From theophylline to FITC-dextran, the permeability decreased, which was an indication of the size exclusion behavior in the IPN membrane: at the same gel swollen state, the IPNs show higher permeability for the smaller solutes.

Temperature and pH influences on permeation have been investigated. Oxprenolol HCl (r_h = 2.6 Å) and vitamin B_{12} (r_h = 8.5 Å) were used as model drugs. In the pH influence study, the IPN membrane was kept at a temperature of 25 °C, and the experiment was conducted at pH 7.4 and 4.0. In addition to the size exclusion phenomenon, the results showed that the IPNs had higher permeability at pH 7.4 when the PMAA network was at swollen state, which is what we expected. However, in the temperature influence study, the results showed that for each model drug the IPNs permeability was higher at 37 °C than that at 27 °C, even though as we know that the PNIPAAm component is collapsed and the IPN has a lower swelling ratio at 37 °C. In that, a mechanism is needed to explain the permeation behavior instead of the explanation only from swelling ratio of the IPN system.

To further investigate the pH and temperature effects on permeability, we analyzed the permeation of oxprenolol HCl under the four possible pH and temperature conditions as shown in Figure 9. As indicated before, the four slopes of the linear curves represent four different permeabilities of the same IPN sample. The relationships between these permeabilities are indicated in Figure 10.

Here, P is permeability and q is weight swelling ratio. PMAA is the pH-sensitive network I, also called the primary network, and PNIPAAm is the temperature-sensitive network II, also called the secondary network. From Figure 10, we noted that at low temperature and high pH both networks were swollen, and the IPN had the highest swelling ratio. When pH decreases, the primary network collapsed, and the swelling ratio dropped drastically. The permeability decreased with the swelling ratio. The same observation was noted at high temperature when we reduced the pH from 7.4 to 4.0. We could see that the permeability decreased with the collapse of the primary network.

The behavior was different when we changed the temperature. At pH = 7.4 and T = 37 °C, the secondary network was collapsed. The swelling ratio also decreased but not as much as the previous case. The permeability at this state was higher than the state when both networks were swollen, even though it had a lower swelling ratio. This was probably because the primary network was still swollen, and the aggregation of the secondary network at higher temperature did not decrease the swelling ratio too much. Instead, it left space and opens gates for the drug to permeate through.

$$D_m = \frac{Pl}{K_d} \tag{2}$$

The diffusion coefficient can be calculated from the permeability using eq 2. Here, l is the membrane thickness in the swollen state at constant pH and temperature, and K_d is the solute partition coefficient calculated from experimental data using the following equation:

$$K_d = \frac{C_m}{C_s} \tag{3}$$

where C_m and C_s are the concentrations of the solute in the membrane and in the surrounding solution at equilibrium. They can be calculated using solute mass balance. The partition coefficients determined for oxprenolol under different pH and temperature conditions were close to one, indicating that there were not significant bindings between the solute and the polymer (Table 1).

By varying the pH and temperature conditions, the thicknesses of the membranes varied due to the swelling ratio change, the solute partition coefficients did not change much, but the diffusion coefficients of oxprenolol were changed by six times (Table 1).

Conclusions

Temperature- and pH-sensitive IPN hydrogels of PMAA and PNIPAAm were prepared by a sequential UV polymerization. These hydrogels were shown to exhibit swelling transition at a temperature range of 31−32 °C, the LCST of the PNIPAAm network, and a pH value of approximately 5.5, the pK_a of PMAA. This result indicates that the responses of each network in

these IPNs are relatively independent from each other, which is also verified by the results from DSC. Permeation study results indicate a significant size exclusion behavior while model drugs with different sizes permeate through the IPN membranes. Both pH and temperature have great influence on the permeability. A hypothesis mechanism has been proposed to explain the phenomena that the model drug has the highest permeability at the physiological state of 37 °C and pH 7.4, which is desirable in membrane and drug delivery applications.

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