ELSEVIER

S0032-3861(96)00548-4

Polymer Vol. 38 No. 5, pp. 1227–1232, 1997

0032-3861/97/$17.00 + 0.00

Preparation of pH/temperature responsive polymer membrane by plasma polymerization and its riboflavin permeation

Young Moo Lee* and Jin Kie Shim
Department of Industrial Chemistry, Hanyang University, Seoul 133-791, Korea
(Received 21 July 1995; revised 26 March 1996)

pH and temperature sensitive polymer membrane was prepared by grafting acrylic acid and *N*-isopropylacrylamide on the surface of porous polyamide membrane by plasma polymerization technique. Simultaneous plasma polymerization of two monomers yielded the membrane sensitive both to pH and temperature. Graft yield was lowered when acrylic acid content was over 10 wt% in monomer mixture. X-ray photoelectron spectra and Fourier transform infra-red attenuated total reflection spectra of graft membrane confirmed the incorporation of functional monomers. Through surface graft membranes, the permeation of riboflavin as a model drug was conducted and the permeation behaviour was discussed.

(Keywords: polymer membrane; plasma polymerization; pH/temperature sensitive)

INTRODUCTION

Stimuli-sensitive polymer drug delivery, especially using temperature and pH-sensitive hydrogels and polymeric membranes, may be applied to enhance environment-sensitive properties. Temperature-sensitive polymers demonstrate lower critical solution temperatures (LCSTs) which provide reversible high swelling at low temperatures and low swelling at high temperatures[1–4]. Similarly, pH-sensitive polymers synthesized with either acidic or basic components demonstrate reversible swelling/deswelling in acidic or basic medium[5–14].

Hoffman and Dong[7] combined these two properties by synthesizing crosslinked pH/temperature-sensitive hydrogels. Positively charged hydrogels were prepared by copolymerizing in varying ratios of *N*-isopropylacrylamide and *N,N'*-dimethylaminopropylmethacrylamide. Kim *et al.*[15] made beads formed from linear pH/temperature polymers, poly(*N*-isopropylacrylamide-*co*-butylmethacrylate-*co*-acrylic acid) and reported on the release of insulin through the polymeric system. In this study we intend to prepare pH/temperature sensitive graft membrane.

There have been several studies reported on the surface modification of porous membranes by grafting acrylic monomers utilizing corona discharge, glow discharge and ultraviolet (u.v.) techniques[16–20]. Iwata and coworkers reported on the graft polymerization of acrylamide onto a polyethylene[16,17] using corona discharge and of *N*-isopropylacrylamide onto a poly(vinylidene fluoride)[18] using glow discharge technique. Osada *et al.*[19] grafted poly(methacrylic acid) onto a porous poly(vinyl alcohol) membrane using plasma treatment and their ion transport, albumin and poly(ethylene glycol) permeation behaviours were studied. X-ray photoelectron spectroscopy (X.p.s.) was utilized to confirm the graft reaction[16–18]. Recently Ito *et al.*[20] reported on the water permeation through porous polycarbonate membrane having poly(carboxylic acid) on the membrane surface by pH and ionic strength. Masuoka *et al.*[21] grafted *N,N*-dimethylacrylamide onto porous polypropylene membrane using plasma techniques.

In our previous studies[22–24], we have reported on the grafting of acrylic monomers onto porous polyurethane and polyamide membranes for pH and temperature-sensitive membranes prepared by chemical[22], ultraviolet and plasma[23] initiation methods. In a recent report[24], we have determined the size of the graft chain that affects the permeability of the solute upon changing pH or ionic strength of the solution.

The aim of this study is to synthesize the intelligent stimuli-responsive material device by grafting acrylic acid (AAc) and *N*-isopropylacrylamide (NIPAAm) onto the porous polyamide membrane by plasma polymerization technique. The effects of graft density on the pH/temperature-dependent permeability of riboflavin as a model drug through poly(amide-*g*-NIPAAm) and poly(amide-*g*-(AAc-NIPAAm)) membranes (PNA) were examined.

EXPERIMENTAL

Materials

AAc was from Junsei Chemical Co. and was used after vacuum distillation. NIPAAm (Tokyo kasei Chemical Co.) was used after recrystallization in hexane and toluene (40/60 vol%). Riboflavin was purchased from Junsei Chemical Co. and was used without any further treatment. Porous polyamide membrane from Gelman Science Co. was 127 μm thick with 0.45 μm pores. They were used after cleaning in methanol.

* To whom correspondence should be addressed

Preparation of poly(amide-g-NIPAAm) and poly(amide-g-(AAc-NIPAAm))

For the plasma polymerization, a bell jar type plasma reaction apparatus was used to accommodate AAc and NIPAAm monomers. This low pressure glow discharge apparatus has a radio-frequency generator (13.56 MHz, 0–300 W Power) and an impedence matching circuit.The power for the glow discharge was supplied on the upper electrode (diameter 15 cm) made of stainless steel and lower electrode was connected to the temperature controller and the heat source (291–473 K). After washing and drying, the porous polyamide membrane was applied to 50 mTorr and 30 W argon plasma for 30 s. The sample was exposed immediately in the air and immersed in the monomer solution. The AAc and NIPAAm monomer solutions were prepared by dissolving each monomers in deionized water (see *Table 1* for sample designation). To remove the oxygen remaining in the solution, nitrogen gas was bubbled into the solution at room temperature for 30 min. The graft polymerizion of AAc and NIPAAm onto the plasma-treated polyamide was performed for 2 h at 60°C. During the polymerization, dry nitrogen gas was continuously bubbled into the solution. The graft membrane was agitated in deionized water at 60°C for 24 h to eliminate the homopolymer probably formed on the surface, and then dried at −50°C for 24 h using a freeze-dryer.

The grafting amount of treated polyamide membranes was calculated as follows:

$$\text{Graft yield}\ (\mu g\,cm^{-2}) = \frac{W_t - W_0}{A} \times 100$$

where W_0, W_t and A represent the weight of the membrane before and after the graft reaction and membrane area, respectively.

Permeability

For the measurement of the permeability of riboflavin, a two-chamber diffusion cell (each chamber 25 ml) was stirred with a magnetic stirrer to eliminate the boundary layer resistance. Measurements were made at 37°C or at pH 7.4 at different temperatures. One compartment of the cell was filled with phosphate buffer, and the other with a solution of riboflavin. The pulsatile release of riboflavin was conducted when the pH of one compartment of the cell was changed repeatedly between 7 and 4, or when the inner temperature of the two-chamber diffusion cell was changed repeatedly between 30 and 50°C. Aliquots of the buffer solution were taken out after a given period of time. The u.v. absorbance of the solution was measured with u.v.–vis spectrophotometer

Table 1 Effect of feed composition on the graft yield of surface modified polyamide membranes using plasma polymerization method at 60°C for 2 h

Sample	Feed composition (NIPPAm/AAc(w/w))	Concentration (wt%)	Graft yield ($\mu g\ cm^{-2}$)
PA	–	20	–
PNA1	100/0	20	202
PNA2	95/5	20	222
PNA3	90/10	20	297
PNA4	85/15	20	197

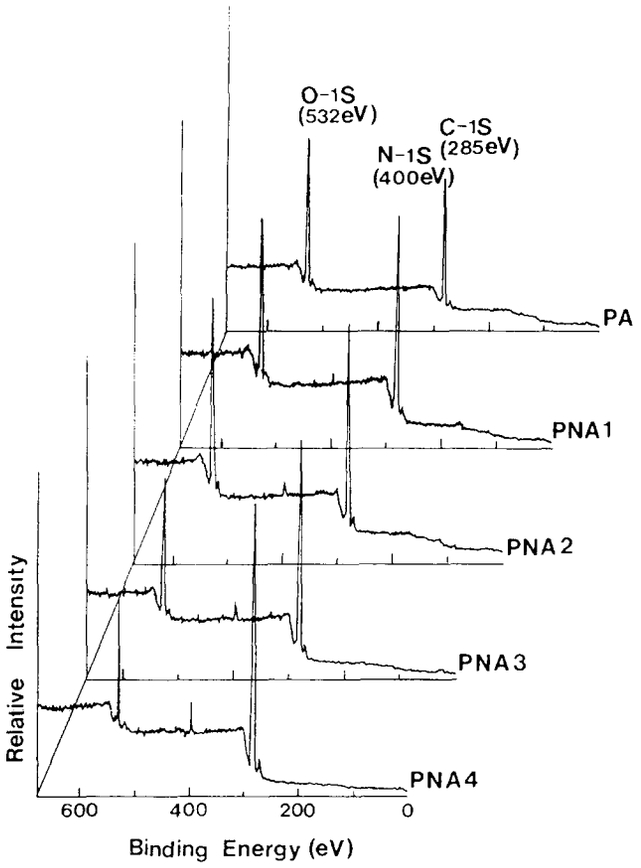

Figure 1 X.p.s. survey scan spectra of polyamide and grafted polyamide surfaces

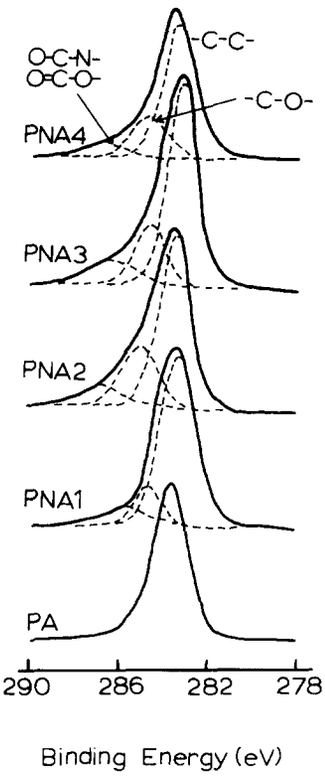

Figure 2 X.p.s. carbon 1S core level spectra of polyamide and grafted polyamide surfaces

(UV-2101pc, Shimadzu Co.) at 444 nm in wavelength to determine the concentration of riboflavin in the feed and in the permeate. The solute permeability coefficient P was calculated from the equation which was obtained from mass balance equation[12], i.e.

$$P = \frac{-d}{A(1/V_1 + 1/V_2)t} \ln\left(\left(1 + \frac{V_1}{V_2}\right)\frac{C_t}{C_0} - \frac{V_1}{V_2}\right) \quad (1)$$

where V_1, V_2, A, d, C_0 and C_t were volumes of the concentrated and the dilute compartment, membrane area (2.54 cm^2), thickness and the concentration of the concentrated compartment at times 0 and t, respectively.

RESULTS AND DISCUSSION

Characterization

One of the advantages of plasma polymerization technique was that the polymerization reaction was only limited to the surface of the membrane. After the plasma exposure, the membrane was taken out of the plasma reactor and was exposed in the air. Upon dipping into the 20 wt% monomer solutions, the graft reaction initiated very rapidly. Peroxides seem to be the most plausible species for initiating the graft copolymerization onto the plasma-treated surface. One of the reasons is that the plasma-treated membranes were always stored not in a vacuum, but in air prior to the graft copolymerization. During this storage period in air, most of the free radicals eventually remaining on the surface region of the film must be converted to peroxides. The mechanism of this kind of reaction involves the generation of the free radicals from the main chain of the polymer and the formation of peroxide upon air exposure followed by the initiation and propagation of the monomers[17,21].

The surfaces of AAc- and NIPAAm-grafted polyamide membranes were analysed by X.p.s.[25–28] as shown in *Figures 1–3*. *Figure 1* demonstrates the survey scan spectra of the AAc- and NIPAAm-grafted polyamide surfaces. *Figures 2* and *3* show carbon 1S and oxygen 1S core level scan spectra of the ungrafted and the grafted polyamide membranes. The PNA membrane surface showed new peaks resulting from the incorporation of –C–O– at ~ 286.6 eV and ester carbon atoms at ~ 289.1 eV (O=C–O–). The poly(amide-*g*-NIPAAm) (PNA1) surface showed a new peak ~ 288.0 eV as O=C–N, indicating the presence of *N*-isopropyl groups on the polyamide surface. The oxygen peak in C=O groups appeared at 529 eV for membranes. The peak at high binding energy region (533.5 eV) is a peak for the oxygen in –OH groups, indicating the presence of –COOH groups on the PNA membrane surface. As the AAc content increases, the –OH peak becomes larger relative to the peak of the C=O bond.

Figure 4 shows the Fourier transform infra-red attenuated total reflection (*FT*i.r. ATR) spectra of grafted polyamide membrane surfaces, indicating that the peaks of the carbonyl bond (~ 1730 cm^{-1}) in poly(amide-*g*-(AAc-NIPAAm)) (PNA3) and two methyl groups in isopropyl bond (~ 1370 cm^{-1}) in NIPAAm. This proves the presence of carboxylic acid and NIPAAm groups on the grafted polyamide surface.

In the present study, the graft yields of polymer range between 197–297 $\mu g\,cm^{-2}$ (see *Table 1*) and increase with increasing the AAc content except for PNA4 sample. When the AAc content was more than 10 wt% of the feed composition, the graft yield of membrane decreased. Cabaness *et al.*[29] reported that the content of acrylic acid and acrylamide in their copolymers could be controlled by changing pH of the reaction medium. Their result also showed that upon increasing pH, the reactivity ratio decreased and increased, for acrylic acid and acrylamide respectively. The pH of the feed solution in *Table 1* decreased from 4.7 to 2.7 as the acrylic acid increased. Therefore, the lower graft yield in PNA4 is probably due to the low reactivity of NIPAAm at above 10 wt% of acrylic acid in the feed composition, because of the low pH.

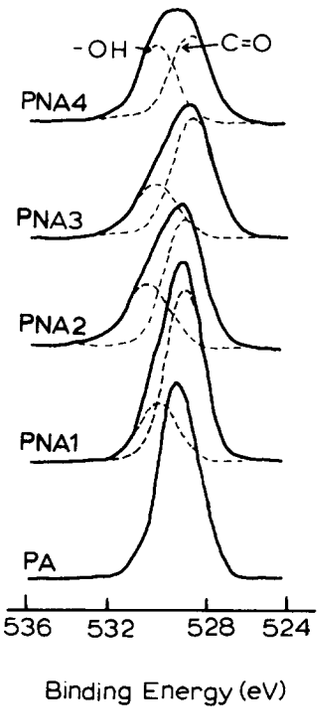

Figure 3 X.p.s. oxygen 1S core level spectra of polyamide and grafted polyamide surfaces

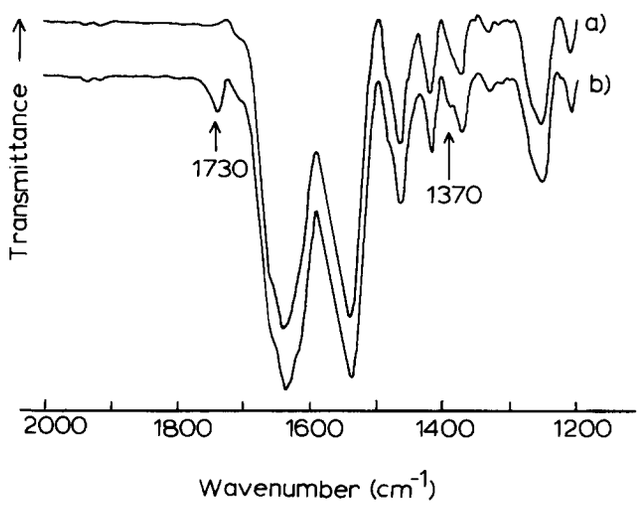

Figure 4 *FT* i.r. ATR spectra of (a) PA and (b) PNA3 membrane

Riboflavin permeation

Riboflavin release patterns of PA and PNA membranes at different pH regions and at 37°C were demonstrated in *Figure 5*. Permeation of riboflavin was also measured at various temperatures and at neutral pH, as shown in *Figure 6*. In PA and PNA1 membranes that did not have acrylic acid on the polyamide surface, the release profile of riboflavin was constant as pH varied. However, PNA2, PNA3 and PNA4 membranes showed the pH-dependent release of riboflavin. The permeability of riboflavin decreased from 6.3×10^{-6} cm^3 $cm\,cm^{-2}\,s^{-1}$ at pH 4 to around 5.7×10^{-6} cm^3 $cm\,cm^{-2}\,s$ at pH 7. The absolute permeability value was one order of magnitude higher than that of PVDF membrane[24] in our previous study due to larger pore radius of PA membrane. However, the magnitude of the decrease of permeability at pH 4–7 was somewhat lower than that of the PVDF membrane. This may be caused by one or two possible causes, large pore size of the PA membrane and lower acrylic acid content in the feed solution.

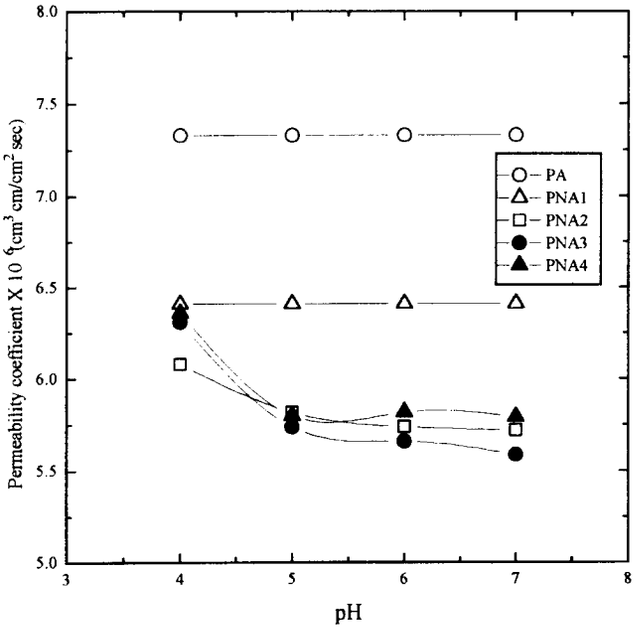

Figure 5 Effect of pH on the permeation of riboflavin through PA and PNA membranes measured at 37°C

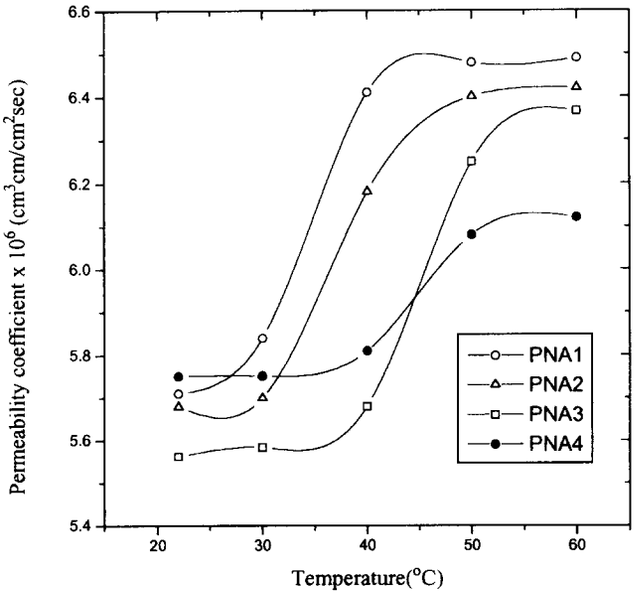

Figure 6 Effect of temperature on the permeation of riboflavin through PA and PNA membranes measured at pH 7

An effective graft chain for permeation is present on the inner pore or on the edge of the pore and may shrink or enlarge upon change of pH. Large pore size may reduce the effectiveness of the pH-dependent permeation of small solutes unless the graft chain is long enough to cover the pores. Competitive AAc and NIPAAm reaction reduced the number of the AAc content in the chain and lowered the pH sensitivity which is defined as the ratio of permeability at pH 4 and pH 7.

The effective pore size of the PNA membranes at any pH can be calculated using a simple Hagen–Poiseuille's law[16,18], that is

$$J = \frac{n\pi r^4 AP}{8\eta d} \tag{2}$$

where j = filtration rate, n = number of pores per cm^2, A = surface area of the membrane (cm^2), r = pore radius, P = applied pressure, η = viscosity of flowing liquid, and d = thickness of membrane.

The permeability coefficient in grafted membrane depends mainly on the smallest path in the skin layer. Therefore, the permeation through graft membrane becomes

$$J = \frac{n\pi r_1^4 AP}{8\eta d_g} \tag{3}$$

where r_1 = effective pore radius of the grafted layer at arbitrary pH and d_g = thickness of the grafted layer of the membrane.

From equation (3) the effective pore radius of graft membrane at any pH can be obtained by the ratio of flux or permeability coefficient of virgin and graft membrane

$$\frac{r_0}{r_1} = \left[\frac{J_0}{J_i}\right]^{1/4} \tag{4}$$

Here, J_0 and J_i are the fluxes of solute through the PA and PNA membranes respectively, at 37°C in varying pH ranges.

The effective pore radius was reduced from 2250 Å to 2103 Å upon grafting and expansion of the graft chain at pH 7 (*Table 2*). The above results show the possibility of controlling the pH region, in which the riboflavin permeability changes most sensitively with pH, by choosing the nature of the polymers to be grafted. This information is important in the design of a polyelectrolyte-grafted porous membranes for a drug delivery system under physiological conditions.

As NIPAAm is grafted on the porous polyamide membrane using the plasma grafting technique, the permeability changes with temperature. Poly(NIPAAm)[1,2] is known to have a lower critical solution temperature (LCST), at around 31–33°C. Below LCST, poly(NIPAAm) forms hydrogen bonds with water and exists in solution form. However, above LCST, inter- and intramolecular interaction in poly(NIPAAm) is much stronger, resulting in an undissolved state. In this state, the hydrogen bonding between grafted poly(NIPAAm) (PNA1) and water breaks down and the mobility of the polymer chain, inter- and intramolecular interactions as

Table 2 Determination of effective pore radii and effective areas for permeation at pH 4 and 7 through pH-sensitive polyamide membranes estimated by equation (4)

Sample	pH 4		pH 7		
	r (Å)	A^a ($\times 10^6$ Å^2)	r (Å)	A ($\times 10^6$ Å^2)	$\frac{A_{pH4}}{A_{pH7}}$ (%)
PA	2250	15.90	2250	15.90	100.0
PNA1	2176	14.88	2176	14.88	100.0
PNA2	2147	14.48	2115	14.05	103.1
PNA3	2167	14.75	2103	13.89	106.2
PNA4	2172	14.82	2121	14.13	104.9

[a] A = Effective membrane area for permeation of solute

Table 3 Determination of effective pore radii and effective areas for permeation at 30 and 50°C through temperature-sensitive polyamide membranes estimated by equation (4)

Sample	Temp 30°C		Temp 50°C		
	r (Å)	A^a ($\times 10^6$ Å^2)	r (Å)	A ($\times 10^6$ Å^2)	$\frac{A_{50°C}}{A_{30°C}}$ (%)
PA	2250	15.90	2250	15.90	100.0
PNA1	2126	14.20	2182	14.96	100.3
PNA2	2113	14.03	2175	14.86	105.9
PNA3	2102	13.88	2162	14.69	105.9
PNA4	2118	14.09	2147	14.48	102.8

[a] A = Effective membrane area for permeation of solute

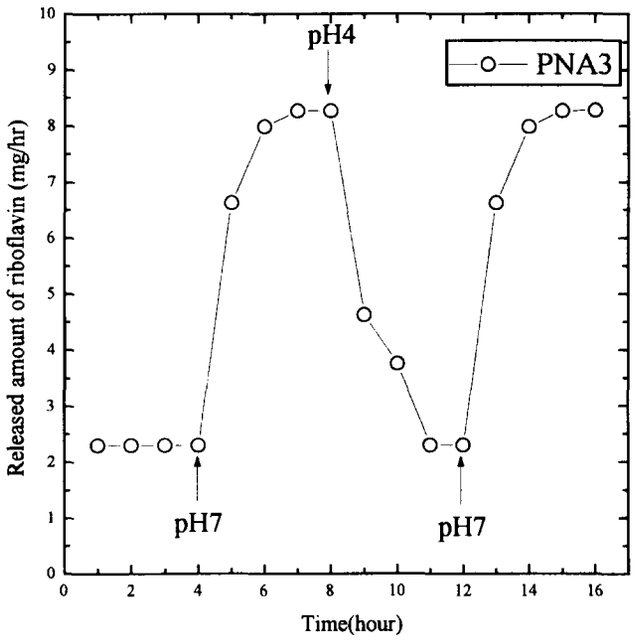

Figure 7 Reversible release pattern of riboflavin from PNA3 membrane with stepwise changing of the pH between 7 and 4 measured at 37°C

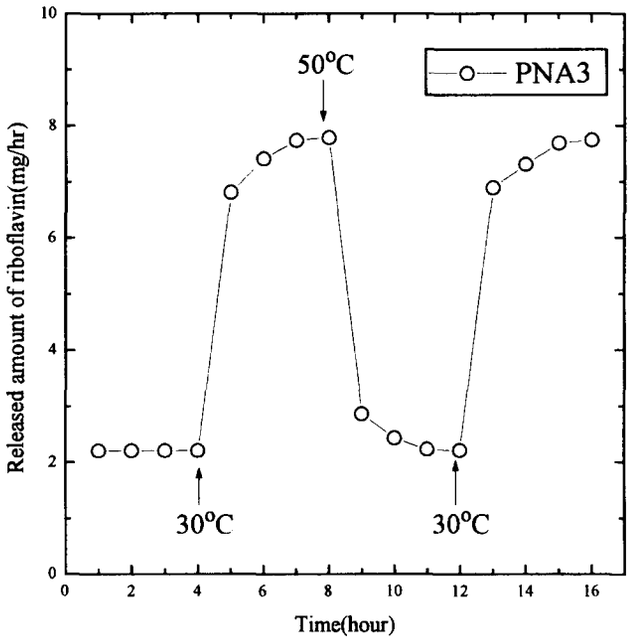

Figure 8 Reversible concentration control of riboflavin from PNA3 membrane with stepwise changing of the temperature between 30 and 50°C measured at pH 7

well as the hydrophobic interaction due to the presence of the alkyl groups in the polymer chain increase[30]. The grafted poly(NIPAAm) chain shrinks, leading to an enlargement of the effective pore size in porous polyamide membrane. Using the same Hagen–Poiseuille's equation, and equation (4), the effective pore radius was calculated to be 2113 Å at 30°C and the graft chains shrink to 2175 Å at 50°C for PNA2 membrane, resulting in an expansion of the effective area for permeation, as indicated in increase in $A_{50°C}/A_{30°C}$ in *Table 3*.

PNA2, PNA3 and PNA4 used the acrylic acid as a comonomer with NIPAAm. In this case, the transition temperatures of riboflavin permeation change from 35 to 50°C, as illustrated in *Figure 6*. According to Mueller[31], as the carbon in the alkyl chain in alkylamide increased, the LCST decreased from 50°C. This result is explained by the fact that, as the length of the alkyl chain increases, the solubility of the polymer in water is lowered, leading to a drop in the LCST. Acrylamide homopolymer, which does not possess any alkyl chains, does not show the

LCST at below 95°C. In the present study, the hydrophilic acrylic acid was copolymerized with NIPAAm on the surface of the polyamide membrane and imparted the hydrophilic interaction to the copolymer, contributing to the increase in LCST of graft copolymer on polyamide membrane surface.

pH/temperature-responsive change of riboflavin release

In order to study the pH/temperature-dependent change of the permeability of riboflavin, the permeation of riboflavin through the PNA3 membrane was investigated by alternating the pH from 7 to 4 (*Figure 7*), and the temperature from 30 to 50°C (*Figure 8*). It is seen that a discontinuous change in concentration of riboflavin was brought about by stepwise change of the temperature of pH. When the permeation experiment of riboflavin through the PNA3 membrane was conducted by changing pH or temperature, the riboflavin release increased rapidly but reverted to the same permeability within an hour. These results demonstrate the possibility of controlled release of solutes such as a drug, riboflavin, through the poly(amide-*g*-(AAc-NIPAAm)) membrane by changing both pH or temperature.

CONCLUSIONS

We have prepared the pH/temperature-sensitive polymer membranes by grafting AAc and NIPAAm on the surface of polyamide membrane utilizing plasma polymerization technique. The structure of the graft chain was confirmed by X.p.s. spectra and *FT* i.r. ATR spectra. AAc and NIPAAm-grafted polymer membranes showed the temperature and pH-dependent permeation behaviours of riboflavin. Effective pore radii and effective areas for riboflavin permeation generally increased as the concentration of acrylic acid increased in the feed AAc/NIPAAm monomer mixture. The phase transition temperature increased from 31°C to about 50°C depending on the amount of AAc added to the NIPAAm reaction medium as a comonomer. The permeability regulation through PNA3 membrane in response to pH/temperature changes could be reproduced repeatedly.

ACKNOWLEDGEMENTS

The authors greatly acknowledge the financial support of the present study by the Korea Science and Engineering Foundation under the grant 92-32-00-02.

REFERENCES

1 Okano, T., Bae, Y.H., Jacobs, H. and Kim, S. W. *J. Controlled Release* 1990, **11**, 255
2 Okano, T., Bae, Y. H. and Kim, S. W. *Pharmaceut. Res.* 1991, **8**, 624
3 Nozawa, I., Suzuki, Y., Sato, S., Sugibayashi, K. and Morimoto, Y. *J. Biomed. Mater. Res.* 1991, **25**, 243
4 Okahata, Y., Lim, H. J., Nakamura, G. and Hachiya, S. *J. Am. Chem. Soc.* 1983, **105**, 4855
5 Kitano, H., Akatsuka, Y. and Ise, N. *Macromolecules* 1991, **24**, 42
6 Siegel, R. A., Falamarzian, M., Firestone, B. A. and Moxley, B. C. *J. Controlled Release* 1988, **8**, 179
7 Hoffman, S. and Dong, L. *J. Controlled Release* 1991, **15**, 141
8 Park, T. G. and Hoffman, A. S. *J. Appl. Polym. Sci.* 1992, **46**, 659
9 Iwata, H. and Matsuda, T. *J. Membrane Sci.* 1988, **38**, 185
10 Klumb, L. A. and Horbett, T. A. *J. Controlled Release* 1992, **18**, 59
11 Sung, Y., Jun, M. S. *J. Appl. Polym. Sci.* 1982, **27**, 133
12 Kim, J. H., Kim, J. Y., Lee, Y. M. and Kim, K. Y. *J. Appl. Polym. Sci.* 1992, **44**, 1823
13 Chung, J., Ito, Y. and Imanishi, Y. *J. Controlled Release* 1992, **18**, 45
14 Ito, Y., Kotera, S., Ibana, M., Kono, K. and Imanishi, Y. *Polymer* 1990, **31**, 2157
15 Kim, Y. H., Bae, Y. H. and Kim, S. W. *J. Controlled Release* 1994, **28**, 143
16 Iwata, H., Kishida, A., Suzuki, M., Hata, Y. and Ikada, Y. *J. Polym. Sci., Polym. Chem. Edn* 1988, **26**, 3309
17 Suzuki, M., Kishida, A., Iwata, H. and Ikada, Y. *Macromolecules* 1986, **19**, 1804
18 Iwata, H., Oodate, M., Uyama, Y., Amemiya, H. and Ikada, Y. *J. Membrane Sci.* 1991, **55**, 119
19 Osada, Y., Honda, K. and Ohta, M. *J. Membrane Sci.* 1986, **27**, 327
20 Ito, Y., Inaba, M., Chung, D. J. and Imanishi, I. *Macromolecules* 1992, **25**, 7313
21 Masuoka, T., Hirasa, O., Suda, Y. and Ohnishi, M. *J. Radiat. Phys. Chem.* 1989, **33**, 421
22 Kim, J. H., Lee, Y. M. and Chung, C. N. *J. Korean Ind. Eng. Chem.* 1992, **3**, 296
23 Lee, Y. M., Ihm, S. Y., Shim, J. K., Kim, J. H., Cho, C. S. and Sung, Y. K. *Polymer* 1994, **36**, 81
24 Lee, Y. M. and Shim, J. K. *J. Appl. Polym. Sci.* 1996, **61**, 1245
25 Palit S. R. and Ghosh, P. *J. Polym. Sci.* 1962, **58**, 1225
26 Dilks, A. and VanLaeken, A. 'Physiocochemical Aspects of Polymer Surfaces' (Ed. K. L. Mittal), Plenum Press, New York, 1982, p. 749
27 Beamson, G. and Briggs, D. 'High Resolution XPS of Organic Polymers' Wiley, Chichester, England, 1992, pp. 110, 188
28 Clark, D. T., Cromarty, B. J. and Dilks, A. H. R. *J. Polym. Sci., Polym. Chem. Edn* 1978, **16**, 3173
29 Cabaness, W. R., Yen-Chin Lin, T. and Parkanyi, C. *J. Polym. Sci., Part A-1* 1971, **9**, 2155
30 Mandel, M. *Eur. Polym. J.* 1970, **6**, 807
31 Mueller, K. F. *Polymer* 1992, **33**, 3470