Thermocontrol of Solute Permeation across Polymer Membrane Composed of Poly(N,N-dimethylaminoethyl methacrylate) and Its Copolymers

Soon Hong Yuk[1]* and Sun Hang Cho[2]

[1] Department of Polymer Science and Engineering, Hannam University, Taejeon 306-791, Korea
[2] Advanced Materials Division, Korea Research Institute of Chemical Technology, Taejeon 305-600, Korea

Abstract Polymer membranes composed of N,N-dimethylaminoethyl methacrylate (DMAEMA) and acrylamide (AAm) (or ethyl acrylamide (EAAm)) were prepared to demonstrate the thermocontrol of solute permeation. Poly DMEMA has a lower critical solution temperature (LCST) at around 50°C in water. With the copolymerization of DMAEMA with AAm (or EAAm), a shift in the LCST to a lower temperature was observed, probably due to the formation of hydrogen bonds between the amide and N,N-dimethylamino groups. However, the temperature-induced phase transition of poly (DMAEMA-co-EAAm) did not show a similar trend to that of poly (DMAEMA-co-AAm) in the gel state. The hydrogen bonds in poly (DMAEMA-co-EAAm) were significantly disrupted with the formation of a gel network, which led to a difference in the swelling behavior of polymer gels in response to temperature. To apply these polymers to temperature-sensitive solute permeation, polymer membranes were prepared. The permeation pattern of hydrocortisone, used as the model solute, was explained based on the temperature-sensitive swelling behavior of the polymer membranes.

Keywords: polymer membrane, thermocontrol of solute permeation, poly(N,N-dimethylaminoethyl methacrylate-co-acrylamide), poly (N,N-dimethylaminoethyl methacrylate-co-ethyl acrylamide), hydrocortisone

INTRODUCTION

Since Heskins and Guillet reported on the solution properties of poly N-isopropylacrylamide (NIPAAm) [1], numerous researchers have studied phase transition in response to external stimuli such as temperature [2,3], pH [4,5], ionic strength [6], and electric potential [7] due to the scientific or technological importance. Recently, polymer systems have been investigated that demonstrate a phase transition in response to more than one variable, in particular temperature and pH [8,9] Feil *et al.* reported on the mutual influence of pH and temperature on the swelling of ionizable and thermosensitive hydrogels [8]. Later, Chen and Hoffman studied graft copolymers that exhibit temperature-induced phase transitions over a wide range of pH 10 [9].

New types of materials with transitions resulting from both polymer-water and polymer-polymer interactions have also been reported. Tanaka *et al.* studied the volume phase transition in a gel driven by hydrogen bonding [10], while Okano *et al.* demonstrated temperature-responsive interpenetrating networks constructed with poly (acrylic acid) and poly (N,N-dimethylacryl-

amide) [11]. Previous studies by the current authors reported on a polymer system responding to temperature and pH using N,N-dimethylaminoethyl methacrylate (DMAEMA) and acrylamide (AAm) (or ethyl acrylamide (EAAm)) [12,13]. Thereafter, based on the pH/temperature sensitivity of these polymer systems, a glucose-controlled insulin delivery system was designed and characterized [13].

The purpose of the current study is to demonstrate the thermocontrol of solute (hydrocortisone) permeations across the polymer membrane with transitions resulting from both polymer-water and polymer-polymer interactions. Accordingly, polymer membranes composed of DMAEMA and AAm (or EAAm) were prepared and characterized as a function of the composition of the polymer membrane.

MATERIALS AND METHODS

Materials

The AAm monomer was purchased from Junsei Chemical Co. (Tokyo, Japan). The DMAEMA monomer, ammonium persulfate (APS), N,N-methylenebisacrylamide (MBAAm), and tetramethylethylene diamine (TEMED) were all purchased from Aldrich (Milwaukee,

* **Corresponding author**
Tel: +82-42-629-8279   Fax: +82-42-629-8279
e-mail: shyuk@mail.hannam.ac.kr

Table 1. Feed composition for poly(DMAEMA-co-AAm) in present study

Code	DMAEMA		AAm		$M_w/10^5$ [a]
	g	mol%	g	mol%	
Poly DMAEMA	14.2	100	–	–	2.8
Copolymer I	11.4	80	1.46	20	3.2
Copolymer II	9.58	67	2.40	33	3.8
Copolymer III	7.15	50	3.65	50	3.5
Copolymer IV	5.72	40	4.38	60	3.0

[a] Measured by laser scattering.

Table 2. Feed composition for poly(DMAEMA-co-EAAm) in present study

Code	DMAEMA		AAm		$M_w/10^4$ [a]
	g	mol%	g	mol%	
Poly DMAEMA	14.2	100	–	–	2.8
Copolymer I	13.5	95	0.5	5	1.7
Copolymer II	12.7	90	1.0	10	1.3
Copolymer III	11.4	80	1.9	20	1.3
Copolymer IV	7.1	50	4.9	50	2.9

[a] Measured by laser scattering.

WI, USA). The DMAEMA monomer was distilled before use and all other reagents were used as received.

Preparation of Polymer Membrane

Copolymers of DMAEMA and AAm were prepared by free radical polymerization in water at room temperature using APS as the initiator and TEMED as the accelerator. The feed compositions for the copolymers are shown in Table 1. The initiator and accelerator concentrations were 0.2 g/mL of APS and 240 µL/mL of TEMED, respectively. All polymers were purified by dialysis against distilled-deionized water and freeze-dried.

The EAAm monomer was synthesized in the laboratory using a procedure presented previously [13]. The poly(DMAEMA-co-EAAm)s were prepared by free radical polymerization as follows: 7.8 g of distilled monomers (mixtures of DMAEMA and EAAm) and 0.02 g of AIBN as the initiator were dissolved in 100 mL of a water/ethanol binary solvent mixture (5/5 by volume). The feed compositions for the copolymers are shown in Table 2. An ampoule containing the solution was sealed by conventional methods and immersed in a water bath maintained at 75°C for 15 h. After polymerization, all polymers were dialyzed against distilled-deionized water at 4°C and freeze-dried.

For the preparation of the polymer membrane, the polymerization was carried out between two Mylar sheets separated by a rubber gasket (1 mm thickness) and backed by glass plates. MBAAm was used as the crosslinker. After the polymerization, the polymer membrane was immersed in the distilled-deionized water to remove any unreacted compounds.

Tranmittance Measurements

The phase transition was traced by monitoring the transmittance of a 500 nm light beam on a Spectronic 20 spectrophotometer (Baush & Lomb). The concentration of the aqueous polymer solution was 5 wt%, and the temperature was raised from 2 to 70°C in 2-deg increments every 10 min.

Swelling Measurements

After immersion in water at the desired temperature,

the polymer membrane was removed from the water and tapped with a filter paper to remove any excess water on the gel surface. The polymer membrane was repeatedly weighed and reimmersed in water at a fixed temperature until the hydrated weight reached a constant value. After equilibration at one temperature, the polymer membrane was reequilibrated at the desired temperature. The swelling, defined as the weight of the water uptake per unit weight of dried polymer membrane, was calculated by measuring the weight of the swollen polymer membrane until the weight changes were within 1% of the previous measurement.

Permeation Experiments

Two-compartment glass permeation cells were used for the solute permeation study as a function of temperature. The thickness of the polymer membrane, at 20°C, was 0.1 cm and hydrocortisone was used as the model solute. The volume of each compartment was 6 cm^3 and the area for diffusion was 1.77 cm^2. Stirring was maintained at 600 rpm for all experiments via an internal bar magnet. The donor compartment was filled with a 2 wt% hydrocortisone aqueous solution (the water solubility of hydrocortisone at 25°C is 280 µg/cm^3) while the receptor compartment was filled with water. The entire receptor compartment was sampled and drug concentration assayed at 248 nm using a UV spectrophotometer (Shimadzu).

RESULTS AND DISCUSSION

Temperature-Induced Phase Transition of Poly (DMAEMA-co-AAm (or EAAm)) Aqueous Solution

As reported previously [12,13], polyDMAEMA and polyEAAm have a lower critical solution concentration (LCST)s at 50°C and 80°C, respectively. Poly(DMAEMA-co-AAm (or EAAm)) exhibits a LCST between 0 and 50°C depending on the copolymer composition.

The effect of the AAm (or EAAm) content on the LCST is shown in Fig. 1. When the temperature of the poly DMAEMA aqueous solution was raised above 50°C, the polymer precipitated from the solution. This was due to the hydrophobic interaction between the N,N-dimethylaminoethyl groups above the LCST. With the
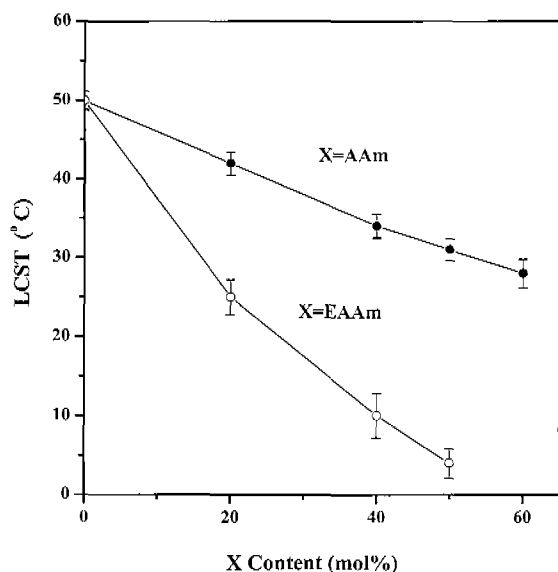
Fig. 1. LCST of poly(DMAEMA-co-AAm (or EAAm)) in water as a function of AAm (or EAAm) content (adapted from ref. 12).

Fig. 2. Temperature dependence of equilibrium swelling of poly(DMAEMA-co-AAm) membrane as a function of AAm content (adapted from ref. 13).

incorporation of AAm (or EAAm) in the copolymer, the LCST shifted to a lower temperature.[12] In general, the LCST of a copolymer increases with the incorporation of a hydrophilic comonomer.[8] However, in the case of poly(DMAEMA-co-AAm (or EAAm)), the LCST shifted to a lower temperature with the incorporation of hydrophilic AAm (or EAAm). This was due to the hydrogen bond formation between the amide (or ethylamide) in AAm (or EAAm) and the N,N-dimethylamino group in DMAEMA which protected the N,N-dimethylamino groups from exposure to water resulting in a significant hydrophobic contribution to the LCST. Because of the more hydrophobic nature of ethylamide, poly(DMAEMA-co-EAAm) exhibited a more significant temperature responsiveness than poly(DMAEMA-co-AAm).

Temperature-Sensitive Swelling Behavior of Polymer Membrane

Fig. 2 shows the temperature dependence of the equilibrium swelling of the polymer membrane composed of poly (DMAEMA-co-AAm) [14]. The transition temperature between the shrunken and swollen state shifted to the lower temperature with an increase in the AAm content in the gel network. This was in accordance with the change in the LCST of the poly (DMAEMA-co-AAm) aqueous solution as a function of the AAm content.

Fig. 3 shows the temperature dependence of the equilibrium swelling of the polymer membrane composed of poly (DMAEMA-co-EAAm) [14]. The transition temperature between the shrunken and swollen state shifted to a higher temperature with an increase in the EAAm content and a polymer membrane composed of copolymer 4 gel did not exhibit a swelling transition in
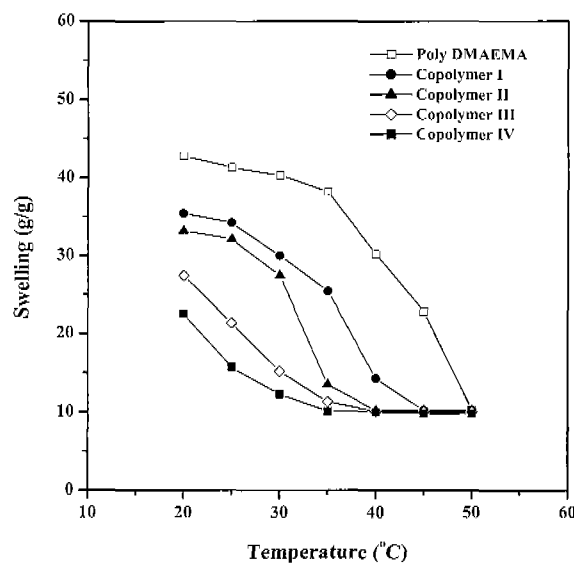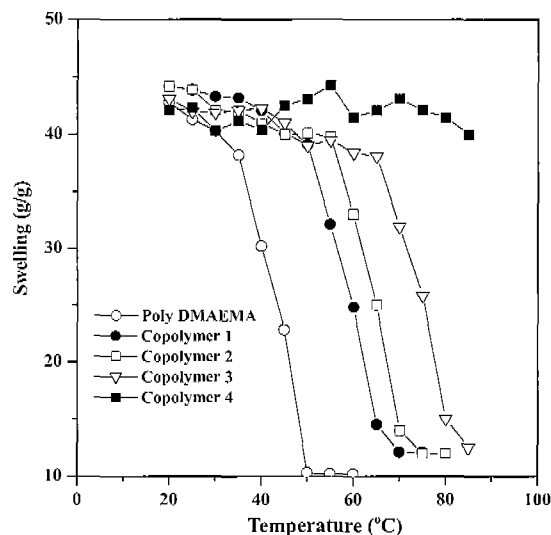

Fig. 3. Temperature dependence of equilibrium swelling of poly(DMAEMA-co-EAAm) membrane as a function of EAAm content (adapted from ref. 14).

a temperature range between 20°C and 90°C. This was contrary to the change in the transition temperature of the poly (DMAEMA-co-AAm) gel and change in the LCST of the poly (DMAEMA-co-EAAm) aqueous solution as a function of the chemical composition. This was due to the fact that the hydrogen bonds between the ethylamide and N,N-dimethylamino groups were disrupted and the hydrophobic contribution to the LCST via the hydrogen bond was restricted in the case of thepoly (DMAEMA-co-EAAm) gel. Therefore, it is reasonable to suggest that the hydrophilic contribution
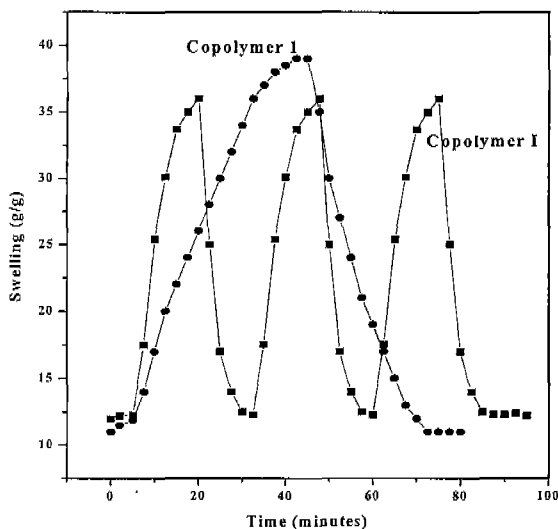
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Fig. 4. Swelling kinetics of poly(DMAEMA-co-AAm (or EAAm) membrane.

Fig. 5. Permeation of hydrocotisone above and below transition temperatures.

from the non-hydrogen-bonded EAAm to the LCST lead to the shift in the transition temperature to higher temperatures.

Based on the thermosensitivity of the poly (DMAEMA-co-AAm) and poly (DMAEMA-co-EAAm) gels as shown in Fig. 2 and 3, the swelling kinetics were observed to understand the temperature-induced swelling change of polymer gels in the molecular level. As shown in Figure 4, the swelling kinetics of the polymer membrane in response to a pulsatile temperature change was measured. Firstly, the temperature was maintained above the transition temperature for equilibrium and then decreased below the transition temperature. Rapid swelling was observed in the poly (DMAEMA-co-AAm) membrane when compared with that in the poly (DMAEMA-co-EAAm) membrane. In the case of the poly (DMAEMA-co-EAAm) membrane, the conformation change in the polymer chain in response to a pulsatile temperature change may have been restricted by steric hindrance caused by the bulky ethylamide group. In contrast, this restriction on the conformation change may have been reduced in the poly (DMAEMA-co-AAm) membrane because of reduced steric hindrance caused by the amide group.

Temperature-sensitive Permeation of Hydrocortisone

As shown in Fig. 5, the permeation of hydrocortisone across the polymer membrane was observed in response to temperature changes below and above the transition temperatures. Below the transition temperature, the polymer membrane swelled and hydrocortisone permeated through the swelled polymer membrane with a high permeation rate. With an increase in the temperature above the transition temperature, the polymer membrane deswelled and hydrocortisone permeated
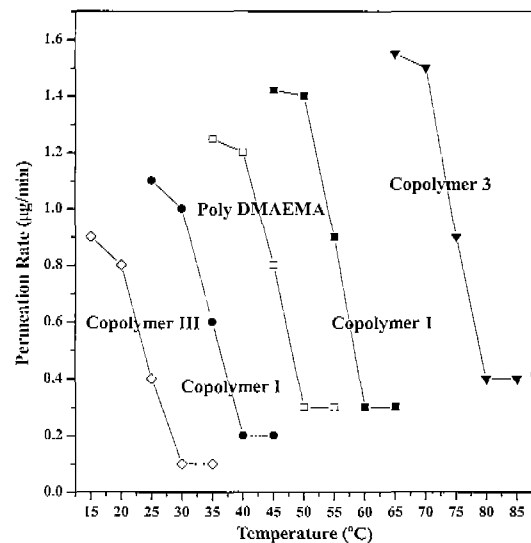
through the deswelled polymer membrane with a reduced permeation rate.

In the case of the poly(DMAEMA-co-AAm) membrane, the transition temperature shifted to a lower temperature an the increase in the AAm content in the polymer membrane. However, in the case of the poly(DMAEMA-co-EAAm) membrane, the transition temperature shifted to a higher temperature with an increase in the EAAm content in the polymer membrane.

CONCLUSION

With the formation of a crosslinked polymer network (polymer membrane), the hydrogen bonds between the AAm and N,N-dimethylamino groups were maintained in the case of poly (DMAEMA-co-AAm). However, in the case of poly (DMAEMA-co-EAAm), the hydrogen bonds between the EAAm and N,N-dimethylamino groups were disrupted. This led to the different temperature-sensitive swelling behaviors of the polymer membranes depending on the character of the comonomers, such as AAm and EAAm. The permeation of hydrocortisone in response to a temperature change was closely related to the temperature-sensitive swelling behavior of the polymer membrane.

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