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Reentrant Volume Phase Transition of Poly(2-methacryloyloxyethyl phosphorylcholine) Gel in Water/alcohol Mixture

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New crosslinked poly(2-methacryloyloxyethyl phosphorylcholine)(MPC) hydrogels which have intriguing function were prepared in aqueous medium with different crosslinkers using a redox polymerization. The poly(MPC) hydrogels showed high water content compared with that of poly(2-hydroxyethyl methacrylate) and were stable in aqueous medium with wide range of pH and ionic strength. However, the volume of the poly(MPC) gels changed dramatically with increase in ethanol composition in aqueous medium. The poly(MPC) hydrogel began to shrink at 40 vol% of ethanol composition and the volume of the poly(MPC) gel reached to about 10% of the initial volume in range between 70 vol% and 90 vol% of ethanol composition. However, the volume of poly(MPC) gel recovered in ethanol. It was confirmed that the volume change in the poly(MPC) gel was completely reversible in response to the water/ethanol mixture composition.

The hydrophobicity of alcohol influenced to the volume change of poly(MPC) gel in water/alcohol mixture. This so-called reentrant phenomenon was derived from the cononsolvency of poly(MPC) in water/ethanol mixture triggered by imbalance of force interacted among water, ethanol and poly(MPC).

Key words: 2-Methacryloyloxyethyl phosphorylcholine(MPC) polymer, hydrogel, swelling, water/alcohol mixture, volume phase transition, biomaterial

1. Introduction

Hydrogel have been already used widely in many engineering fields as high water-absorbing material, and soft material because of its intermediate property of liquid and solid. Since the volume phase transition of hydrogel induced by solvent composition in the medium was discovered by T.Tanaka in 1978[1], hydrogels had impressed so many polymer physicists as well as polymer chemists. Some have tried to make intelligent material utilizing the volume phase transition, and others have tried to elucidate the mechanism of it out of physico-chemical interest.

There are several way to bring about the volume phase transition, for example, heat[2,3], electric field[4], light[5], pH[6], and chemical substance, such as urea[7] and glucose[8]. Many compounds were targeted and many new compounds were synthesized in the light of phase transition. Especially, poly(*N*-isopropyl acrylamide) (NIPAM) hydrogels have been studied intensively by many researchers since poly(NIPAM) can change the solubility by any change of temperature[9] or solvent composition[10]. Though the volume phase transition is promising function in biomaterial to regulate the control release of drug, or cell attachment, its biocompatibility is not satisfied. Thus the poly(NIPAM) may not apply as any medical devices using *in vivo*.

Polymers having 2-methacryloyloxyethyl phosphorylcholine (MPC) moiety have phospholipid polar group and show high biocompatibility[11,12]. The structure of the MPC polymer is inspired from biomembrane surface. As the homopolymer of MPC is water-soluble polymer[13], when the poly(MPC) chains are cross-linked each other, the polymer networks can hold the solvent in its web-formed structure.

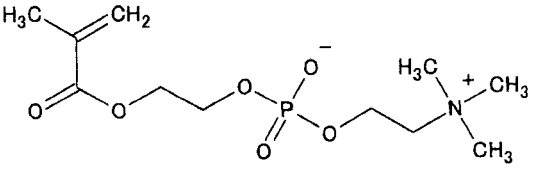

Fig. 1. Chemical structure of 2-methacryloyloxyethyl phosphorylcholine (MPC)

The water structure in the MPC polymer hydrogel is very unique, that is, free water fractions is significantly higher than compared with that in poly(2-hydroxyethyl methacrylate)(HEMA))[14]. Moreover, poly(MPC) chains do not disturb network formation of water molecules through hydrogen bonding, which is confirmed Raman spectroscopic analysis of poly(MPC) aqueous solution[15].

This property of the MPC polymer is one of the major reasons for reducing protein adsorption and cell adhesion on the surface. Thus, the biocompatibility of the MPC polymer is excellent.

Very recently, we observed that the solubility of poly(MPC) is sensitive to composition of water/ethanol mixture. Poly(MPC) can dissolve both in water and

ethanol, but precipitates in these mixtures in the range of 60-90 vol% of ethanol composition. This phenomenon, termed cononsolvency that both good solvents turn into poor solvent when mixed with each other, have to be triggered by imbalance of force interacted delicately among water, ethanol and poly(MPC).

In this study, we prepare the poly(MPC) gel with cross-linking and the swelling property of the gel in water/alcohol mixtures are investigated.

2. Material and Methods

2.1. Preparation of poly(MPC) hydrogel

MPC aqueous solution (2.5mol/L, 1.00mL), closslinke (*N,N'*-methylenebisacrylamide(Bis), ethylene glycol dimethacrylate(EGDMA), triethylene glycol dimethacrylate(TEGDMA), glycerol 1,3-diglycerolate diacrylate(GDGDA)), and ammonium peroxodisulfate (APS) aqueous solution (0.22mol/L, 0.06mL) as initiator were taken on the petri dish(3cm in diameter) all at once. The solution was stirred until fully mixed. Then, *N,N,N',N'*-tetramethylethylenediamine(0.02mL) as catalyst was added and stirring was continued for further 30sec. Transparent hydrogel was obtained after leaving it for one night.

Poly(MPC) hydrogel obtained was immersed in abundant distilled water for more than three days to remove unreacted monomer. The water was changed several times for that treatment. After fully swelled in the water, poly(MPC) hydrogel was cut into disk-shaped pieces about 14mm in diameter.

Poly(HEMA) hydrogel was also prepared by the same procedure.

2.2. Swelling Equilibrium Measurements

Samples were freeze-dried before measuring swelling ratio (q) which was calculated by the weight of hydrogel according to the equation as:

$$q = \frac{Ws - Wd}{Wd} \times 100(\%)$$

where *Wd* and *Ws* are the weight of dried and swollen hydrogels, respectively.

Before measuring weight of hydrogel, excess amount of water on the surface of hydrogel was wiped off with filter paper.

2.3. Swelling behavior in various aqueous solutions

Poly(MPC) hydrogel samples were immersed in several aqueous solutions, such as various pH buffer solutions and ionic solutions for a week. Diameters of hydrogel, *d*, were measured in five different points to get the average with digital micrometer. Relative volume, V/V_0, where V and V_0 are the volumes of the hydrogel samples after and before equilibration, respectively, were calculated by using relation as:

$$\frac{V}{V_0} \propto \left(\frac{d}{d_0}\right)^3$$

where d and d_0 were diameter of poly(MPC) gel after and before equilibration, respectively.

2.4. Swelling behavior in water/alcohol mixtures

Poly(MPC) hydrogel samples, in which concentration of crosslinker was 0.1 mol% to MPC monomer, were immersed in various composition of water/alcohol mixture for two days. Relative volume, V/V_0, was calculated by the same method mentioned above.

Poly(MPC) hydrogel swollen in water, about 14mm in diameter, collapsed completely within 24h when immersed in water/ethanol mixture(20/80, v/v), and reswelled to initial state within 48h in pure water. So the reversibility of the swelling and collapse behavior was examined by repeatedly cycling the poly(MPC) gels between water and water/ethanol mixture(20/80, v/v) for every 24h. Relative volume of poly(MPC) gel in water and water/ethanol mixture was plotted as a function of time.

3. Results and Discussion

3.1. Swelling Ratio

Table I shows the swelling ratio of each poly(MPC) hydrogels. Every hydrogel sample with different crosslinkers showed that the more crosslinkers concentration was, the smaller amount of water was absorbed. This phenomenon is corresponded to Flory's theory [16], and means indirectly that crosslinkers were introduced in hydrogel successfully.

Table I. Swelling ratio of the poly(MPC) hydrogel cross-linked with various crosslinkers

Crosslinker	Conc. (mol%)	Swelling Ratio (%)
Bis	0.1	1420
	0.5	1180
	1.0	742
EGDMA	0.1	1500
	0.5	820
	1.0	660
TEGDMA	0.1	2300
	0.5	1450
	1.0	1060
GDGDA	0.1	2930
	1.0	1190

Table II. Swelling ratio of the poly(HEMA) hydrogel cross-linked with TEGDMA.

Crosslinker	Conc. (mol%)	Swelling Ratio (%)
TEGDMA	0.1	180
	1.0	180

The poly(MPC) hydrogel cross-linked with GDGDA, that has the largest distance between two methacrylate moiety in the molecule, showed the highest swelling ratio. The swelling ratio of poly(MPC) cross-linked with 0.1% TEGDMA was 10 times higher than that of poly(HEMA) gel (Table II).

The relative volume of poly(MPC) hydrogel equilibrated in aqueous solutions with various pH and ionic strength is shown in Tables III and IV. Since most of the high water-absorbing polymer gels have ionic

group in its structure, the swelling behavior of them is depended on the ionic concentration in aqueous medium. However, poly(MPC) hydrogel was not absolutely affected by those ions.

Table III. The relative volume of poly(MPC) hydrogel, cross-linked with 0.1% TEGDMA, after equilibrated in various pH buffer solutions compared with that in pure water(pH 5.96).

pH	Relative Volume (V/V_0)
2.11	0.95
4.01	0.97
7.45	0.98
9.18	0.94
12.1	1.0

Table IV. The relative volume of poly(MPC) hydrogel, cross-linked with 0.1% TEGDMA, after equilibrated in various ionic solutions compared with that in pure water.

Ionic concentration	Relative Volume (V/V_0)	
(M)	NaCl	$CaCl_2$
2.0	1.1	1.0
1.0	1.1	1.0
0.1	0.99	1.0

3.2. Swelling behavior in water/alcohol mixture

Fig. 2 show the relative volume of poly(MPC) gel cross-linked with various crosslinkers in water/ethanol mixture. Every poly(MPC) gels gradually shrank with increase in the composition of ethanol in the medium, and collapsed in turbid at 70-90 vol% of ethanol composition. With this phenomena, the surface of gel turned into very adhesive. Around the composition of ethanol, poly(MPC) gel was slowly getting its transparency while immersed for 1 week or more. This was because that microphase transition of poly(MPC) gel was still going on. However, as the volume of poly(MPC) gel did not change any longer after two days immersion treatment, so the value at the two days was adopted as a relative volume of poly(MPC) gel. This turbid state was expressed clearly in the plot. When the ethanol composition became much higher, the swelling ratio of poly(MPC) gel increased and became transparent (Fig. 3).

The swelling behavior did not depend on the chemical structure of crosslinkers and the effect of ion groups at the end of polymer chain derived from APS could not be observed. These facts indicated that this unique swelling behavior of poly(MPC), in response to the ethanol composition, is considered to be due to the nature of the MPC moieties.

In the water/ethanol mixture in the poly(MPC) gel, there are several interactions working among water, ethanol, and poly(MPC) chains. The water molecules interacted with the poly(MPC) chain weakly. By increasing with ethanol composition in the medium, the water molecules on the poly(MPC) chain may be withdrawn by the ethanol molecules, because of much strong interactions between ethanol and water, compared with that between poly(MPC) chain and water. This phenomena induced dehydrating poly(MPC) chain and the swelling ratio was decreased. In the medium with high ethanol composition, the ethanol molecules interacted with poly(MPC) chain directly and the swelling ratio was high.

The same experiments were carried out in other water/alcohol mixtures, using methanol, 2-propanol, and *t*-butanol as an alcohol component.

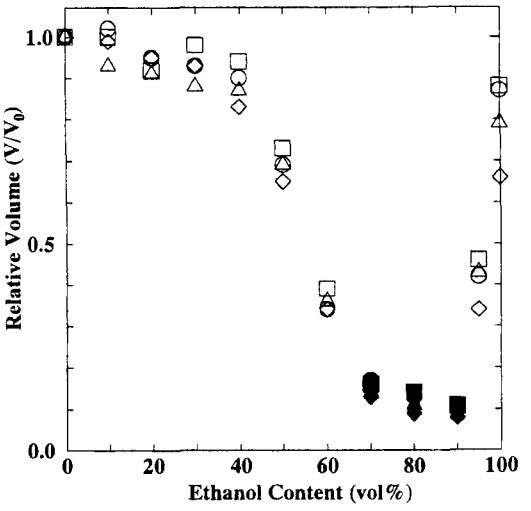

Fig. 2. Swelling behavior of poly(MPC) gel cross-linked with various crosslinkers((○,●)Bis, (□,■)EGDMA, (△,▲)TEGDMA, (◇,◆)GDGDA) in various water/ethanol mixtures. Filled marks represent turbid state.

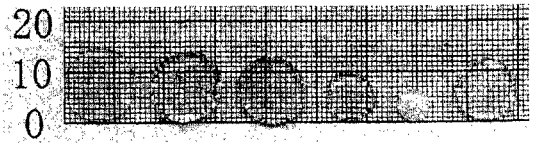

Fig. 3. The picture of poly(MPC) gel cross-linked with TEGDMA in water/ethanol mixtures. Starting from the left, poly(MPC) gel in 0%, 20%, 40%, 60%, 80% (turbid), and 100% of ethanol composition, respectively. The numeric value in the vertical axis is in mm unit.

Fig. 4 demonstrates the swelling behavior of poly(MPC) gel cross-linked with 0.1% TEGDMA in water/alcohol mixture.

The swelling ratio of poly(MPC) gel depended not only the composition of alcohol in the medium but also the hydrophobicity of alcohols. The poly(MPC) hydrogel showed no impressive shrinkage in water/methanol mixture and kept its transparency through all composition range of methanol. However, in the case of water/2-propanol mixture, poly(MPC) gel began to shrink at less alcohol composition compared with the water/ethanol mixture. The much of dramatically effects water observed in water/*t*-butanol mixture. The poly(MPC) gel collapsed most less alcohol composition among these water/alcohol mixtures, and it could not swell again in even pure *t*-butanol.

This fact means that the poly(MPC) gels have good molecular recognition property.

In methanol, ethanol, and 2-propanol, the poly(MPC) could be dissolved due to good solvation of alcohol molecules to the poly(MPC) chains.

On the contrary, in case of *t*-butanol, having the highest hydrophobicity and ability of making clathrate of water around them among those alcohols, it simply acts as a poor solvent to poly(MPC).

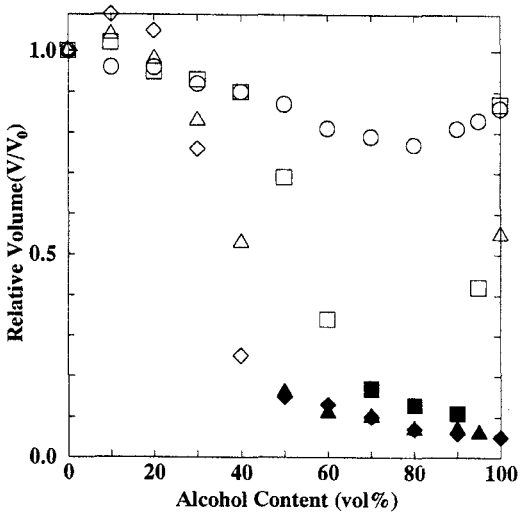

Fig. 4. Swelling behavior of poly(MPC) gel in various water/alcohol((○)methanol, (□ , ■)ethanol, (△ , ▲)2-propanol, (◇,◆)*t*-butanol) mixtures. Filled marks represent turbid state.

3.3. Repeated contraction

Fig. 5 shows the repeatability of swelling-shrinking cycles of poly(MPC) gel cross-linked with TEGDMA. The poly(MPC) hydrogel swollen in water collapsed completely within 24h when the gel was immersed in water/ethanol mixture with 80vol% ethanol, and reswelled in water to more than 90vol% of initial state within 24h.

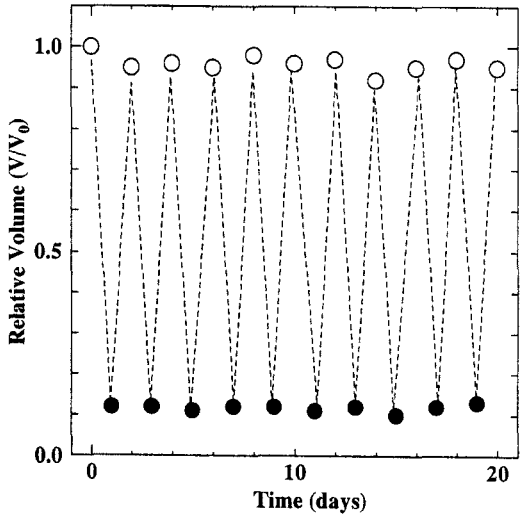

Fig. 5. Repeated contraction and relaxation of the poly(MPC) cross-linked with TEGDMA gel in pure water and water/ethanol (20/80, v/v) mixture. Open and filled marks represent swollen and collapsed, respectively.

4. Conclusion

The poly(MPC) gels could prepare by conventional radical polymerization initiated with the redox system in aqueous medium.

The swelling behavior of the poly(MPC) gel is very unique; that is, the value is very high compared with that of poly(HEMA) and is not affected by any pH and metal ions.

Most interesting phenomena observed in the poly(MPC) gel is swelling/deswelling behavior in water/alcohol mixture. The swelling ratio strongly depends on the ethanol composition in the medium. The volume of the poly(MPC) gel is about 10 % of that in water, when the gel is immersed in 40 vol% ethanol aqueous solution, but it recovered about 90 % in pure ethanol. This responsibility is reversible. The swelling/deswelling in response to the alcohol composition is also depended to the chemical structure, hydrophobicity of the alcohol. That means, the poly(MPC) gel has molecular recognition property. By using this unique character of the poly(MPC) gel, novel smart biomaterial with highly biocompatibility will be realized.

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