Molecular recognition of alcohol by volume phase transition of cross-linked poly(2-methacryloyloxyethyl phosphorylcholine) gel

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Abstract
The swelling behavior of a cross-linked poly(2-methacryloyloxyethyl phosphorylcholine (MPC)) gel in various water/alcohol mixtures was investigated. When the poly(MPC) gel was immersed in various water/alcohol mixtures, a change in the gel volume was observed depending not only on the composition of the alcohol in the mixture but also on the chemical structure of the alcohol. In water/monohydric alcohol mixtures, the poly(MPC) gel had an irregular swelling behavior with a change in the composition of the alcohol, showing the so-called reentrant volume phase transition. These volume phase transition strongly depended on a hydrophobic group, i.e. the polarity of the alcohol. On the other hand, polyhydric alcohol (diol or triol) did not affect the swelling of the poly(MPC) gel even when the composition of the alcohol was changed.

These results suggest that water molecules hydrated on the poly(MPC) chains were withdrawn by hydration of the alcohol molecules and the volume of the poly(MPC) gel decreased. That is in good agreement with the hydration ability of the alcohol and its polarity. Thus, the poly(MPC) gel could recognize a difference in the polarity among the alcohol molecules.

1. Introduction

Hydrogel is very interesting material having a great ability to absorb a significant amount of water that could be used in many fields [1–3]. The change in the volume of the hydrogel has been intensively studied by many researchers with the view of an advanced materials system as a drug delivery system, sensor, actuator, etc. In such fields, the gel would swell or shrink according to the stimulation of the circumference, such as pH, ionic strength, heat, electric field, solvent, etc. [4,5].

We have currently been studying the preparation of polymeric biomaterials with excellent biocompatibility using a bioinspired concept [6]. The polymers bearing a phospholipid polar group, the 2-methacryloyloxyethyl phosphorylcholine (MPC) polymer, showed non-biofouling properties and antithrombogenicity [7–10]. These properties of the MPC polymer are due to the fact that the hydrated MPC polymer could have more free-water compared with other hydrated amphiphilic polymers including poly(2-hydroxyethyl methacrylate) [11]. The poly(MPC) is a water-soluble polymer but the interactions between the water molecules and poly(MPC) chain are very weak [12]. We considered that if some additive, which can bind water molecules on it by hydration, will dramatically change the conformation of the poly(MPC) chain. In our previous report, the reentrant volume phase transition of the poly(MPC) gel in a water/ethanol (EtOH) mixture is described [13]. The volume of the poly(MPC) gel changed with the composition of EtOH in the mixtures due to the inconsonlevency of the poly(MPC) in a water/EtOH mixture. The state of water around the poly(MPC) chain is altered by the addition of EtOH, which induces an imbalance in the molecular forces among water, EtOH and the poly(MPC) chain.

In this study, we investigated the swelling behavior of poly(MPC) gel in various alcohol aqueous solutions with attention to the polarity of the alcohol and tried to provide a recognition of the alcohol species by the volume transition of the poly(MPC) gel.
2. Materials and method

2.1. Materials

MPC is prepared by a previously reported method [14]. As a cross-linker, triethylene glycol dimethacrylate (TEGDMA, Kanto Chemical, Tokyo, Japan) was used without further purification. Ammonium peroxodisulfate (APS, Kanto Chemical) and \(N,N,N',N'-\text{tetramethylethylene}-\text{nediamine} \text{ (TMEDA, Kanto Chemical)} \) are extra-pure grade reagents. All other solvents were extra-pure reagent grade and used without further purification.

2.2. Preparation of cross-linked poly(MPC) gel

The poly(MPC) gel was prepared as previously reported [13]. The procedure is briefly described. The desired amounts of the MPC aqueous solution (2.5 mol/l), TEGDMA, and APS aqueous solution (0.22 mol/l) as the initiator were placed on a petri dish. The solution was stirred until fully mixed. TMEDA was then added and stirring was continued for another 30 s. A transparent poly(MPC) gel was obtained. The poly(MPC) gel was immersed in excess distilled water for more than 3 days for purification. The water was changed several times. After the poly(MPC) gel was fully swollen in the water, the poly(MPC) gel was cut into disk-shaped pieces with a 14 mm diameter.

2.3. Measurement of swelling volume of the poly(MPC) gel

The swollen poly(MPC) gel in water was immersed in various water/alcohol mixtures for 2 days. The diameters of the gel were measured at five different points with a digital micrometer. The relative volumes, \(V/V_0\), where \(V_0\) and \(V\) are the volumes of the gel in the water before and after equilibrium in the medium, respectively, were calculated using the following relation

\[
(d/d_0)^3 = V/V_0
\]

where \(d_0\) and \(d\) are the diameters of the gel equilibrated in the water before and after equilibrium in the medium, respectively. While measuring the volume of the poly(MPC) gel, the same sample was used and the composition of the alcohol gradually increased in increments of 10% every 2 days. All measurement was performed in triplicate. As an alcohol component, methanol (MeOH), EtOH, 1-propanol (1-PrOH), 2-propanol (2-PrOH), tert-butanol (t-BuOH), ethylene glycol (EG), and glycerin (GC) were used.

The temperature dependence of the volume of the poly(MPC) gel was measured. The poly(MPC) gel was immersed in a large quantity of water placed in a three-necked flask equipped with a mechanical stirrer. While measuring the volume of the poly(MPC) gel, the same sample was used. The water temperature was stepwise increased at 10 °C and maintained for 2 days from 40 to 100 °C. The measurement were performed in triplicate.

3. Results

MPC could polymerize with TEGDMA using a redox polymerization initiator in aqueous medium. The structure of the poly(MPC) gel is shown in Fig. 1. A transparent gel...
was obtained and the swelling degree of the poly(MPC) gel cross-linked with 0.1 mol% TEGDMA was 2300% compared to its dry state.

In Fig. 2, we summarized the characteristics of the alcohol used in this study for addition to the swelling medium of the poly(MPC) gel. We used not only monohydric alcohol with various hydrophobic alkyl groups but also polyhydric alcohols (diol and triol) to evaluate the effect of the chemical structure and polarity of the alcohol on the swelling behavior of the poly(MPC) gel.

Fig. 3 shows the alcohol composition dependence of the poly(MPC) gel at room temperature (ca. 23 °C). The addition of MeOH slightly influenced the swelling of the poly(MPC) gel with every composition. On the other hand, other alcohols induced a very unique poly(MPC) swelling behavior with an increase in the composition. For the water/EtOH mixture, when the composition of EtOH was below 40 vol%, the volume of the poly(MPC) gel slightly decreased, but above 40 vol%, the gel began to shrink with an increase in the EtOH composition. In the range between 70 and 90 vol% EtOH in the medium, the volume of the gel was about 10% of that in water. The gel reswelled in the medium with a much higher EtOH composition, and in pure EtOH, the volume was about 90% of its equilibrated state in water. In a water/1-PrOH mixture, the same composition dependence on the swelling poly(MPC) gel was observed. The composition of 1-PrOH (20 vol%), which dramatically induced a swelling change in the gel was lower than that of EtOH (40 vol%).

Fig. 4 shows the swelling behavior of the poly(MPC) gel in water/2-PrOH and water/t-BuOH mixtures. Both alcohols could significantly reduce the volume of the poly(MPC) gel when these compositions were 20 vol%. However, t-BuOH did not swell poly(MPC).

Fig. 5 shows the swelling behavior of the poly(MPC) gel in the water/EG and water/GC mixtures. In these mixtures, the volume of the poly(MPC) gel was almost constant for every alcohol composition.

Fig. 6 indicated the temperature dependence of the swelling of the poly(MPC) gel in water. The volume of the gel was almost constant in the temperature range between 20 and 60 °C, but slightly increased above 60 °C.

Fig. 7 demonstrates recognition of alcohol by volume of poly(MPC) gel. The volume of the poly(MPC) gel was different in the variety of alcohols. When the composition of the alcohol was 40 vol%, the volume of the poly(MPC) gel was almost the same for aequous mixtures containing MeOH, EtOH, EG or GC. However, it was changed in that containing 1-PrOH, 2-PrOH or t-BuOH. In an 80 vol% alcohol solution, a dramatic reduction in the volume of

| Abb. | Structure      | Mw  | Boiling point (°C) | Solubility parameter ε (10^-3 J^1/2 m^-3/2) |
|------|----------------|-----|-------------------|------------------------------------------|
| MeOH | CH3OH          | 32.04 | 64.65            | 29.7                                     |
| EtOH | CH3CH2OH       | 46.07 | 78.30            | 26.0                                     |
| 1-PrOH | CH3CH2CH2OH  | 60.10 | 97.15            | 24.3                                     |
| 2-PrOH | CH3  |
|       | CH3CHOH       | 60.10 | 82.40            | 23.5                                     |
| t-BuOH | CH3COH       |
|        | CH3           | 74.12 | 82.45            | 21.7                                     |
| EG   | HOCH2CH2OH    | 62.07 | 197.6            | 29.9                                     |
| GC   | HOCH2CH2OHOH  | 92.09 | 290.5            | 33.8                                     |

Fig. 2. Chemical structure and properties of alcohol molecules used in this study.

Fig. 3. Swelling behavior of poly(MPC) gel in various water/alcohol mixtures (⊙ MeOH, ▲ EtOH, □ 1-PrOH).
the poly(MPC) gel was observed for the aqueous mixtures containing EtOH, 1-PrOH, 2-PrOH or t-BuOH. For this combination of swelling behavior at these alcohol compositions, the alcohol species was distinguished by the swelling behavior of the poly(MPC) gel.

4. Discussion

In our previous article, we observed a reversible change in the volume of the cross-linked poly(MPC) gel in response to the concentration change of EtOH in an aqueous medium [13]. Here, we also discussed the swelling behavior of the poly(MPC) gel in various water/alcohol mixtures. The poly(MPC) is a water-soluble polymer and also dissolved in alcohols with a short alkyl chain. However, it precipitates in the water/alcohol mixture, particularly, the water/EtOH mixture. This phenomenon suggested to us that when a cross-linked poly(MPC) gel is immersed in the water/alcohol mixture, we can distinguish the alcohol species in the mixture. Therefore, we used several alcohols (Fig. 2) for addition to the medium that swells the poly(MPC) gel.

As shown in Figs. 3–5, the swelling behavior of the poly(MPC) gel strongly depended on the alcohol species.

![Fig. 4. Swelling behavior of poly(MPC) gel in water/2-PrOH mixture (○) and water/t-BuOH mixture (△).](image)

![Fig. 5. Swelling behavior of poly(MPC) gel in water/EG mixture (○) and water/GC mixture (△).](image)

![Fig. 6. Temperature dependence of the swelling behavior of poly(MPC) gel in water.](image)

![Fig. 7. Comparison of volume of poly(MPC) gel in water/alcohol mixture at 40 (open column) and 80 (closed column) vol% alcohol compositions.](image)
From the viewpoint of polarity of the alcohol, these swelling behaviors were well correlated.

Generally, the interactions between polymer chain and a solvent play an important role for dominating the solubility of polymer in the solvent. That is, higher affinity of a solvent for a polymer makes it easier to dissolve a polymer into a solvent. However, it is difficult to precisely predict the solubility behavior of a polymer–solvent system without any index for the interaction between a polymer and a solvent. The solubility parameter, \( \delta \), the good indicators for consideration of the polarity in the chemical compounds [15], is related to cohesive energy density, may be obtained experimentally, and is a numerical value that indicates the relative solvency behavior of a specific solvent. In practice, the \( \delta \) is obtained from the square root of the cohesive energy density. Comparison of solubility parameters can be used as an approximate miscibility predictor, that is, the molecules containing the similar value of \( \delta \) are to be miscible with each other with ease. However, this does not take into account specific interactions, i.e., hydrogen bonding between molecules.

The poly(MPC) gel did not show a dramatic volume change in the MeOH, EG and GC systems. These solubility parameters are above \( 29.7 \times 10^{-3} J^{1/2} m^{-3/2} \). On the other hand, in the EtOH, 1-PrOH and 2-PrOH systems, the poly(MPC) gel shrank in a specific composition of the alcohols but reswelled in the pure alcohol. These alcohols are in the range between \( 23.5 \times 10^{-3} \) and \( 26.0 \times 10^{-3} J^{1/2} m^{-3/2} \). A much low polarity alcohol, such as \( t \)-BuOH also induces volume change in the poly(MPC) but did not induce reswelling even in pure \( t \)-BuOH. Thus, the volume change in the poly(MPC) gel is related to the polarity of the aqueous alcoholic solution and it is possible to recognize the alcohol species in the mixture by observation of the swelling behavior of the poly(MPC) gel.

The hydroxyl group of an alcohol interacts with water and produces hydrogen bonding between these molecules [16]. That is, the hydration state of the poly(MPC) may be broken by the formation of hydrogen bonding between the water and alcohol and the poly(MPC) gel may collapse. However, the total polarity of the water/alcohol mixture is another key factor to solvate the poly(MPC) chain. In the alcohol rich region, the alcohol can solvate on the poly(MPC) chain and the gel reswells.

There are many research studies about the properties of water/alcohol mixtures with attention to the hydrophobic alkyl group in the alcohol molecules from MeOH to \( t \)-BuOH, fully miscible alcohols with water at room temperature [17–19]. An alkyl group in alcohol molecules organizes the water molecules around itself by so-called hydrophobic hydration. The alcohol molecules with a more hydrophobic group can possibly undergo dehydration from the solute in the solution. Thus, the poly(MPC) gel began to shrink at a lower alcohol composition in the water/alcohol mixture when a much more hydrophobic alcohol was added to the solution.

A similar cononsolvency and reentrant volume phase transition in water/alcohol mixtures have been observed in the poly(N-isopropylacrylamide(NIPAAm)) gel [20–23]. However, the volume change in the poly(NIPAAm) gel did not have a good correlation to the polarity of the alcohol. That is, every alcohol could induce a collapse in the poly(NIPAAm) gel at almost the same composition of alcohols. The poly(MPC) gel began to shrink by a change in the state of the water hydrated around the poly(MPC) chain. If the water is attached on the polymer chains by the so-called hydrophobic hydration, a change in temperature strongly affects the swelling behavior of the gel, just like as in the poly(NIPAAm) case. That is, the poly(MPC) gel might show the LCST in water. As shown in Fig. 6, however, the poly(MPC) gel did not significantly shrink but rather slightly shrunk above 60°C, and it did not have the LCST. Moreover, no volume change in the poly(MPC) gel was observed even in the saturated sodium chloride aqueous solution. From these observations, it could be concluded that the mechanism of the volume change in the poly(MPC) gel is different from that of poly(NIPAAm) gel.

The reentrant volume phase transition of the poly(MPC) gel in a water/alcohol mixture is summarized as follows. The poly(MPC) chains can hold many water molecules around them but interaction between them is very weak. This is understandable from the results that the poly(MPC) gel did not shrink even when the surrounding temperature was increased or sodium chloride was added to the medium. Moreover, Kitano et al. [12] reported that the poly(MPC) chains did not disturb the hydrogen bonding between water molecules, that is, they had a small effect on the water structure, which was revealed by Raman spectroscopy of the poly(MPC) aqueous solution. The volume change in the poly(MPC) gel depended on the dehydration ability of the alcohol. The poly(MPC) gel would hardly shrink in the water/MeOH mixture because the MeOH has a lower ability to dehydrate. However, when a nonpolar alcohol was added to the medium, the poly(MPC) gel easily dehydrated due to the alcohol and collapsed. If the alcohol was a good solvent for the poly(MPC), the poly(MPC) gel reswelled in the alcohol-rich region. For a polyhydric alcohol such as EG and GC, the poly(MPC) gel was stabilized without any perturbation occurrence. These alcohols did not strongly hydrate with water molecules and withdrawal of the water molecules around the poly(MPC) chain hardly occurred. From these results, we concluded that the poly(MPC) gel shows a very unique swelling behavior in the water/alcohol mixture and the alcohol species could be recognized by the volume phase transition of the poly(MPC) gel.

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