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Polymer 47 (2006) 1390–1396
polymer
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Water structure and improved mechanical properties of phospholipid polymer hydrogel with phosphorylcholine centered intermolecular cross-linker

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Received 12 May 2005; received in revised form 1 November 2005; accepted 11 December 2005
Available online 18 January 2006

Abstract

We investigated the water structure and the mechanical properties of 2-methacryloyloxyethyl phosphorylcholine (MPC) polymer hydrogels cross-linked with a novel hydrophilic 2-(methacryloyloxy)ethyl-[*N*-(2-methacryloyloxy)ethyl]phosphorylcholine (MMPC) for soft contact lenses (SCL) applications and commercial methacrylic cross-linkers were in addition used for comparison with MMPC. Water structure in hydrogels, which influences the protein adsorption by dehydration was determined by differential scanning calorimetry. MMPC increased the freezing water content of the MPC polymer hydrogel compared with hydrophilic *N*,*N*′-methylenebisacrylamide (BIS) at the same water content. MMPC also improved fracture strength of the MPC polymer hydrogel to 120 kPa in tensile, which was considerably higher than that hydrogel cross-linked with BIS. It is suggested that MMPC shows higher cross-linking reactivity with MPC than BIS. We concluded that the MMPC increase both the free water content and the tensile properties. The MPC polymer hydrogel cross-linked with MMPC can be a useful SCL biomaterial.

Keywords: Hydrogel; Hydrophilic cross-linker; Phospholipid polymer

1. Introduction

Chemically cross-linked polymer hydrogels that in addition have a high water percentage possess several unique characteristics such as elasticity, softness, transparency and permeability [1–4]. As a result, such hydrogels are widely used for low elastic biomedical applications and have been used in a broad range of product [5,6]. Specifically, 2-hydroxyethyl methacrylate (HEMA) is a frequently used soft contact lenses (SCL) material [5]. We have intensively studied biomaterials based on original bioinspired polymer containing 2-methacryloyloxyethyl phosphorylcholine (MPC) (Fig. 1(a)), due to their excellent biocompatibility, blood-compatibility and anti-fouling properties [7–14]. The unique characteristics of MPC originate from the zwitterionic phosphorylcholine headgroup found in the biological membrane. Recent reports have described some fundamental aspects on the synthesis and characterization on MPC based hydrogels cross-linked with commercially available methacrylic cross-linker, such as triethylene glycol dimethacrylate (TEGDMA) and ethylene glycol dimethacrylate (EGDMA) [15,16].

In this report, we have focused on the physical properties of MPC polymer hydrogels for the SCL application. In general, the high water content of hydrogels cause mechanical weaknesses and reduced biocompatibility due to dehydration of the lens [17]. To overcome this, the equilibrium water content (EWC) of the MPC polymer hydrogel need to be adjusted to around 80%, which is equal to that of cornea. A typical approach to adjust the EWC is to regulate the cross-link density in the hydrogel network. Usually, MPC polymer hydrogels cross-linked with TEGDMA and EGDMA provide an EWC that is too high (over 90%), since the hydrophobicity of their cross-linker limit their solubility in aqueous media to about 1 mol% [15,16]. To control the EWC and cross-link density of MPC polymer hydrogel, hydrophilic cross-linkers are needed. In addition, previous papers reported the water structure on the MPC polymer-coated surface on various polymers and protein adsorption onto a polymer surface is strongly related to the 'free water' contents around polymer chains [8,13]. Thus the water structure in hydrogel networks is important because anti-fouling properties are required for SCL material.

To satisfy these requirements, we used a new type of MPC based intermolecular cross-linker having

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doi:10.1016/j.polymer.2005.12.043

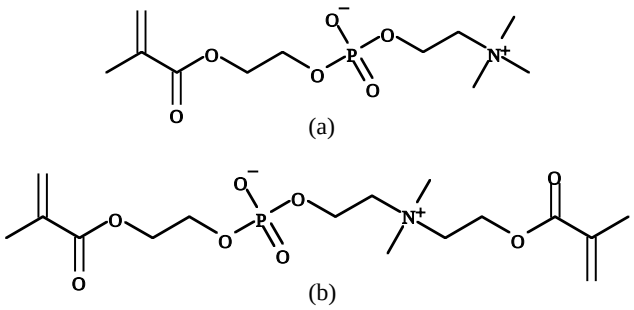

Fig. 1. Chemical structure of phospholipid monomers, (a) MPC and (b) MMPC.

a phosphorylcholine-like group in the center of the molecule previously reported by us: 2-(methacryloyloxy)ethyl-[*N*-(2-methacryloyloxy)ethyl]phosphorylcholine (MMPC) (Fig. 1(b)) [18]. This is a hydrophilic MPC analogue developed to have affinity both to water and to the methacrylic cross-linking units. MMPC was expected not only to adjust the EWC, cross-link density and to enhance the mechanical strength but also to increase the free water content of the MPC polymer hydrogel. A hydrophilic cross-linker; *N*,*N*′-methylenebisacrylamide (BIS), is commercially available and often used as a cross-linking reagent for acryl amide and *N*-isopropyl acrylamide in aqueous media [19], was used as a reference. In this paper, we discuss the differences between MMPC and BIS for adjusting the EWC, cross-link density, water structure, and the mechanical properties of MPC polymer hydrogels. In addition, the transparency of the MPC polymer hydrogel in the visible light wavelength was evaluated for SCL applications.

2. Experimental

2.1. Materials

MPC [7], MMPC [18] were prepared by previous methods. TEGDMA, EGDMA (Tokyo Kasei, Tokyo, Japan) and BIS (Kanto Chemical, Tokyo, Japan) were used without further purification. Ammonium peroxodisulfate (APS, Kanto Chemical) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA, Kanto Chemical) were extra-pure grade reagents. All other solvents were extra-pure reagent grade and used without further purification. Phosphate buffer saline (PBS) stock solution (#14200-075, Invitrogen Co., Tokyo, Japan) was diluted and used with tenth.

2.2. Preparation of MPC polymer hydrogel

The MPC aqueous solution (2.5 mol/L), a cross-linker, and 1.3 mol% of APS aqueous solution (0.22 mol/L) as an initiator were placed on a Petri dish. MMPC and BIS were used from 1.0 to 5.0 mol% for monomer concentration. The contents to reach higher concentration of TEGDMA and EGDMA were limited up to 1.0 mol% of monomer because of their hydrophobicity. The solution in the Petri dish was stirred for 30 min to be fully mixed. Then, as a catalyst, TMEDA was added and stirring was continued for another 30 s. The solution was placed in a reaction spacer containing a pair of plastic plates with 0.1–1.0 mm thickness. The obtained MPC polymer hydrogel was immersed in excess distilled water for 2 days for swelling and purification. The water was changed several times. The purified and equilibrated MPC polymer hydrogel was cut into desired shapes. We abbreviated the MPC polymer hydrogels by concentration of the initial alphabet of cross-linker and concentrations in feed (Table 1).

Table 1
Preparation condition of MPC polymer hydrogel

Code	Cross-linker	Concentration in feed (mol%)	MPC in feed (mol/L)
M1	MMPC	1.0	2.5
B1	BIS	1.0	2.5
E1	EGDMA	1.0	2.5
T1	TEGDMA	1.0	2.5
M3	MMPC	3.0	2.5
B3	BIS	3.0	2.5

2.3. Characterization of MPC polymer hydrogel

The transparency of MPC polymer hydrogel was examined by using UV/vis spectrophotometer (V-560, JASCO, Tokyo, Japan). The measurements were performed from 230 to 700 nm wavelength with 1.0 mm thickness of MPC polymer hydrogels at room temperature.

The EWC of MPC polymer hydrogel was determined by gravimetrical method. Dried hydrogels were obtained by lyophilization. The equation of the EWC is as follows;

$$\mathrm{EWC}\% = \left(1 - \frac{W_\mathrm{d}}{W_\mathrm{s}}\right) \times 100$$

Here, W_d is the weight of dried hydrogel and W_s is the weight of swollen hydrogel. The numbers of specimens were five. We also evaluated the EWC changes of MPC polymer hydrogel and commercial SCL in PBS (pH = 7.1, 0.01 mol/L). The method is the same as pure water system.

Differential scanning calorimetry (DSC) equipment (DSC 6100, Seiko Instruments, Chiba, Japan) was used to measure thermal properties of polymer hydrogel, such as the glass transition temperature (T_g). The weight of 3–5 mg of a lyophilized hydrogel was sealed in the aluminum (Al) pan and the heating measurements were performed from −100 to 250 °C at a rate of 10 °C/min. The Al pans were sonicated in acetone before use. The amount of the phase transition of water in the hydrogel was calculated by enthalpy of fusion around 0 °C on heating process. After the surplus water was removed by filter paper, a piece of about 5–10 mg weight was cut off and weighed accurately. Then, specimen was sealed in Al pan not to dehydrate. The DSC curves were monitored both cooling and heating run from −50 to 50 °C at a rate of 5 °C/min.

The fracture stress and strain (S–S) of MPC polymer hydrogels were examined using a tensile test machine (STA-1150, ORIENTEC, Tokyo, Japan). The samples were cut into a dumbbell shape (12.5 mm × 2.5 mm × 1.0 mm) and

strained with 10 mm/min cross-head speed. Each hydrogel was examined five times. Compression measurements were performed on the hydrogels using a compressive tester (TMA/SS6000, Seiko Instruments, Japan). The cylindrical hydrogel samples of 10 mm in diameter and 1.5 mm thickness were set on the lower stage and compressed by the probe (2.6 mm in diameter) using a step mode at 25 °C. Measurements were performed five times for each sample and the result was statistically calculated. All the hydrogels were sprayed with water not to dehydrate on their surfaces in the mechanical experiments.

3. Results and discussion

3.1. Transparency

Fig. 2 shows the light transmittance of M1 and E1 for the thickness of 0.1 mm calculated by the Bouguer's conversion and that of ACUVUE® (Johnson and Johnson, USA) which is a commercially available sample in the visible light wave range (230–700 nm). MPC polymer hydrogels with any cross-linker exhibited the high transparency in the wide range of the wavelength. The transmittance for ACUVUE® suddenly decreased below 350 nm because of the UV protection treatment. Usually, benzotriazole or benzophenone is incorporated for UV absorbing. Therefore, MPC polymer hydrogel may also have UV protecting ability by incorporation with them. These results indicate that MPC polymer hydrogels are useful SCL biomaterials in terms of light transmittance in the range of visible light wavelengths.

3.2. EWC in water and PBS

Fig. 3 shows the relations between the EWC of MPC polymer hydrogel and the in feed cross-linker concentration. The EWC of the MPC polymer hydrogels decreased with an increased cross-linker concentration in feed and especially

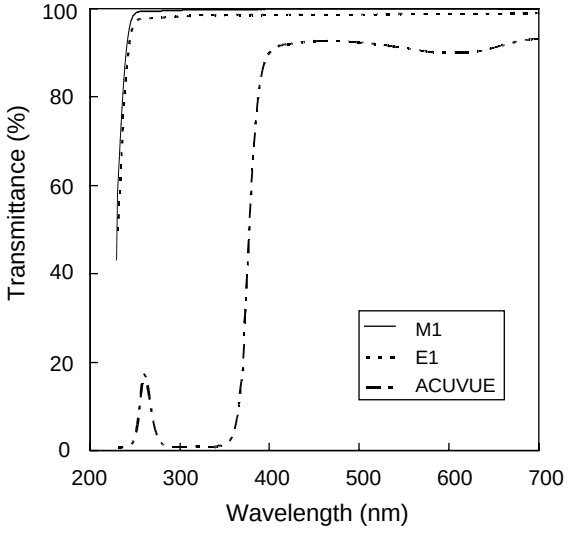

Fig. 2. Transparency of MPC polymer hydrogels and commercial SCL (ACUVUE®).

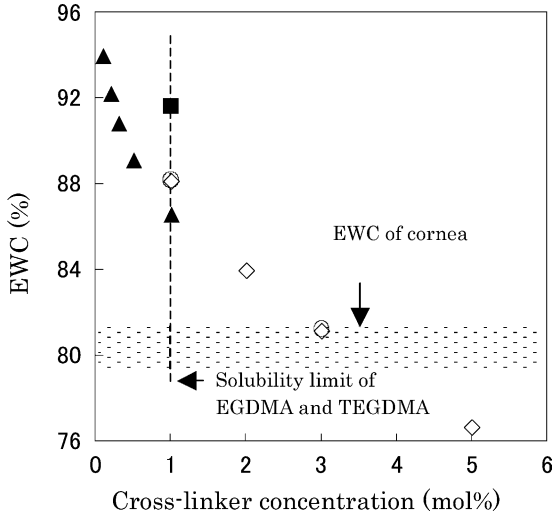

Fig. 3. EWC change of MPC polymer hydrogel by alteration of cross-linker concentration in feed, MMPC (◇), BIS (○), EGDMA (▲), TEGDMA (■).

MMPC enabled to adjust the EWC to that of cornea (82%) [20] at 3 mol% (M3). Conventional methacrylic cross-linkers, TEGDMA and EGDMA were not able to adjust the EWC to around 82% for SCL materials because their hydrophobicity prevents hydrogel preparation over 1 mol% in feed. BIS also suppressed the EWC of the MPC polymer hydrogels to around 82%. There were little differences between MMPC and BIS with regards to the EWC.

No EWC change of MPC polymer hydrogels between those in water and PBS was observed. This was because the MPC polymer chain is zwitterionic and thus electroneutral; which was based on the salt formation in the each MPC unit. This result denoted that the MPC polymer hydrogel has the volume stability for ionic strength, which is important for optical system. However, the EWC of ACUVUE® decreased from 69% to 58% by soaking in water to PBS solution. Because ACUVUE® is the copolymer of HEMA and methacrylic acid (MA), the carboxyl group of MA is affected by ions of salt solution and water molecules in the hydrogel were pulled away to counterbalance by the osmotic pressure.

3.3. Water structure in MPC polymer hydrogels

Generally, the water structure in the polymer hydrogel can be distinguished into 'free water', 'freezing bound water', and 'non-freezing bound water' [21,22]. Free water does not take part in hydrogen bonding with polymer molecules. It has a similar transition temperature, enthalpy and DSC curves as pure water. Freezing bound water interacts weakly with polymer molecules. Non-freezing bound water is complex with the polymer chain through hydrogen bonds. We categorized the water structures in the hydrogel into three types. The total content of freezing water ($W_{freezing}$) was calculated by DSC, from the area under the endothermic curve for water-swollen hydrogels to melting endothermic heat of fusion for pure water. The calibration of the instrument with pure water yielded the enthalpy of fusion of water as $\Delta H_w = 333.3$ J/g, and this value

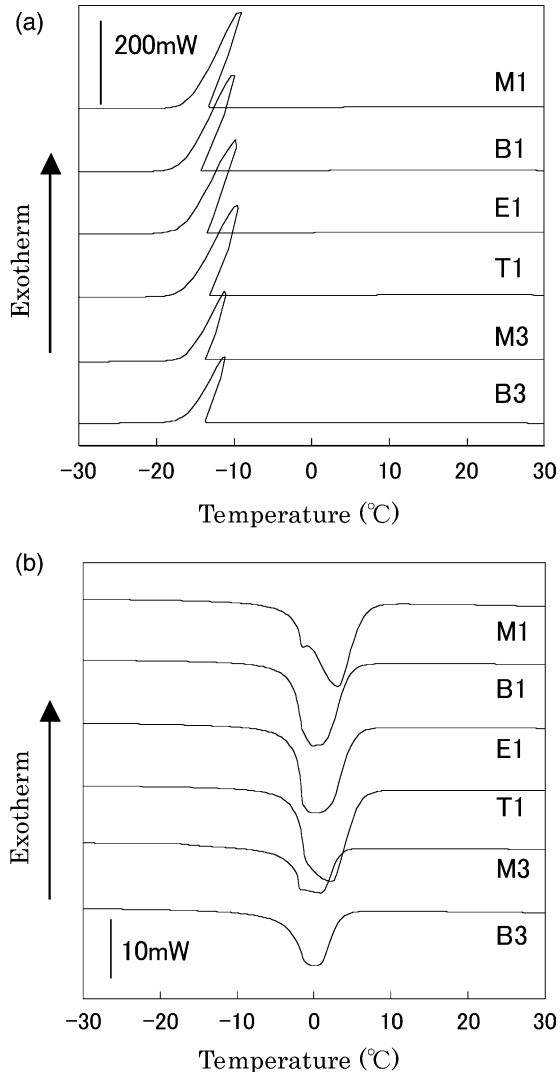

Fig. 4. DSC thermograms of MPC polymer hydrogels. Exothermic curves on cooling (a) and endothermic curves on heating (b). Free water in the hydrogel was supercooled (a). The enthalpy of fusion of freezing water was observed at 0 °C and broad shoulder peak of freezing bound water was detected.

was used to calculate the weights of water in the various states. Fig. 4 displays the thermograms obtained during the cooling run for MPC polymer hydrogel from 30 to −30 °C (a) and the heating run from −30 to 30 °C (b). The recrystallization transitions were shifted to lower temperature by about 16 degrees, and the integrated enthalpies of crystallization gave lower values than those of the melting transitions. The peak shape and the maximum peak temperature were dependent on the cooling and heating rates [23]. Normally, the sharp and clear peak originated from freezing bound water is observed around −10 °C at heating process for some HEMA based hydrogels and this freezing bound water is often referred to as 'intermediate water' [24]. In the MPC polymer hydrogels, the small sharp peaks and the broad peaks of freezing bound water were detected. The hydrogels showed the broad shoulder peaks from −30 to −5 °C originated from the freezing bound water. No further endothermic peak was observed to −100 °C in the cooling run. The shoulder peak area of freezing bound water was

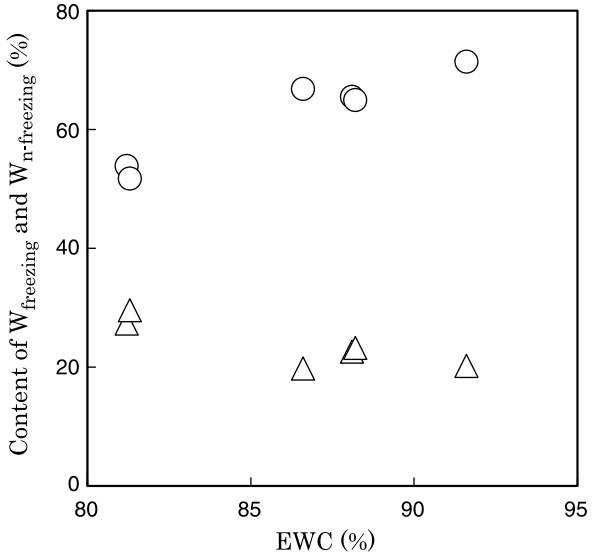

Fig. 5. Relationships between free water contents ($W_{freezing}$, ○) and bound water contents ($W_{n\text{-}freezing}$, △) for EWC on MPC polymer hydrogels.

very low and lapped over free water. The total contents of free water (W_{free}) and freezing bound water ($W_{f\text{-}bound}$) were determined by direct integration of the endothermic peaks from about −30 to 10 °C (ΔH).

$$W_{freezing} = W_{free}(\%) + W_{f\text{-}bound}(\%) = \frac{\Delta H}{\Delta H_w} \times 100$$

We also determined the content of non-freezing bound water ($W_{n\text{-}freezing}$) indirectly by subtracting $W_{freezing}$ from the EWC.

$$W_{n\text{–}freezing}(\%) = EWC - W_{freezing}$$

In this equation, the quantities of freezing water and non-freezing bound water are calculated as weights relative to the total weight of swollen hydrogel and expressed finally as percentages [21]. The $W_{freezing}$ calculated by the endothermic peak on heating run for each hydrogel is summarized in Table 2 and the calculated mean values are presented. Their statistical errors were all within 4%. Small differences of the water structure in the MPC polymer hydrogels caused by the type of cross-linker were observed. The MPC polymer hydrogels cross-linked with MMPC showed higher percentage of $W_{freezing}$ and lower percentage of $W_{n\text{-}freezing}$ than that of cross-linked with BIS unless their EWC were almost the same. This tendency became clearer at 3 mol% than 1 mol%. This result indicated that MMPC has a weak interaction to water molecules compared

Table 2
Water structure in MPC polymer hydrogels and ACUVUE®

Code	EWC (%)	$W_{freezing}$ (%)	$W_{n\text{-}freezing}$ (%)	$W_{freezing}/W_{n\text{-}freezing}$
M1	88.1	65.5	22.6	2.9
B1	88.2	65.0	23.1	2.8
E1	86.6	66.8	19.8	3.4
T1	91.6	71.4	20.2	3.5
M3	81.2	53.9	27.3	2.0
B3	81.3	51.7	29.6	1.8
ACUVUE®	69.0	45.6	23.4	2.0

with BIS. In other words, the mobility of water molecules around MMPC keeps the state of bulk water rather than that of BIS. Fig. 5 shows the relations between the EWC and the content of $W_{freezing}$ and $W_{n\text{-}freezing}$ of MPC polymer hydrogel. When decreasing the EWC from 90 to 80%, the content of $W_{n\text{-}freezing}$ increased about 10% while the content of $W_{freezing}$ decreased about 20%. These rapid changes on $W_{n\text{-}freezing}$ and $W_{freezing}$ were caused by the change in polymer density in the MPC polymer hydrogels.

3.4. Mechanical properties of MPC polymer hydrogel

Fig. 6 exhibits the tensile stress (σ) and strain (ε) relations at fracture points of MPC polymer hydrogels with various cross-linkers and in feed concentrations. All the hydrogels showed linear S–S relations, that is, elastic deformations. When increasing the MMPC or BIS content in the MPC polymer hydrogel, the fracture stress and elastic modulus (E_T) increased, while elongation at break point decreased. M3 and B3 had similar EWC and E_T, however, the fracture stress of M3 was 170% higher than that of the B3. This suggests that the tensile performances are more related to chain distribution and entanglement and less dependent on the water content. We suggest that these differences originate from the increased of cross-linker, that is, the methacrylic cross-linker MMPC has better reactivity for MPC than the acrylic cross-linker BIS. Fracture stress and strain were also dependent on the cross-linker type at a concentration of 1 mol%. The results indicate that the change of cross-linker has a pronounced effect on tensile properties and nano-structure of the hydrogels.

To examine the elasticity of the MPC polymer hydrogels, compression tests were performed. Fig. 7 shows the $S(\sigma)-S(1-\varepsilon)$ curves obtained for the MPC polymer hydrogel cross-linked with MMPC. As a reference, *S–S* relation for five-plied ACUVUE® was checked in the same way. Comparing the M3 and ACUVUE® curves, there is a difference in the compression

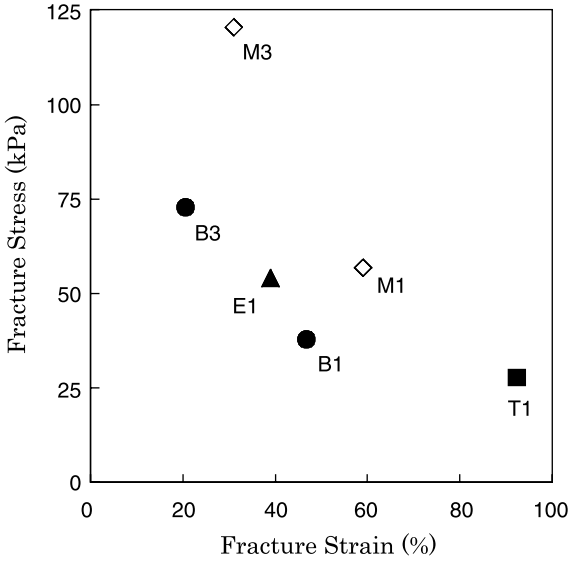

Fig. 6. Tensile tests representing the relationship between stress and strain of the MPC polymer hydrogels with various cross-linkers at fracture points.

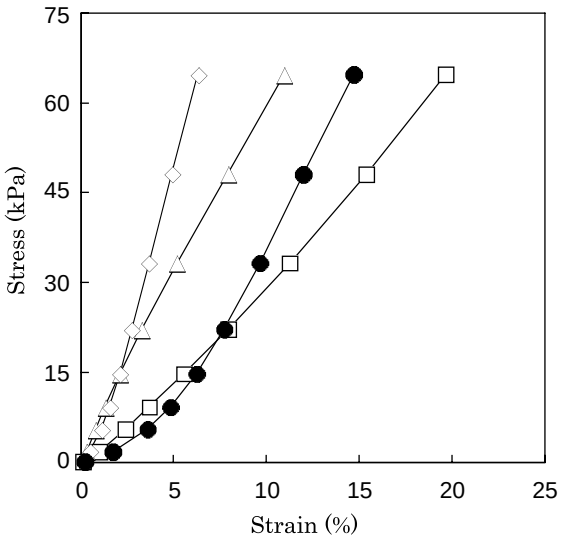

Fig. 7. Compression tests on M1 (□), M2 (△), and M3 (◇) compared with ACUVUE® (●).

strain at tensions below 15 kPa. Above 15 kPa the *S–S* curve for ACUVUE® became linear and there is no obvious difference between the modulus of the materials. M3 still keeps the same *S–S* relation as ACUVUE® in this range. When increasing the MMPC concentrations, the *S–S* curves became steep, due to the higher cross-link density in the polymer hydrogel.

3.5. Cross-link density and distance

According to the theory of rubber elasticity, the elastic modulus is related to the effective network chain concentration of the swollen hydrogel, v_e/V (cross-link density) by the following equation [25,26].

$$\frac{v_e}{V} = \frac{\sigma(\varphi_2/\varphi_0)^{2/3}}{RT|\alpha-\alpha^{-2}|}$$

where σ is in the unit of Pa, v_e/V is in mol/m^3, φ_2 is the volume fraction at swollen state, φ_0 is the swelling fraction (W_d/W_s), R is 8.314 J/mol K, T is the absolute temperature in K and α is the deformation ratio. The deformation ratio α is the ratio of elastically deformed length L to initial length L_0 of the hydrogel. Cross-link densities were calculated by the fracture point for tensile and by 5% strain point for compression [27], respectively. Further, the averaged cross-link distance (mesh size), ξ was estimated from the cross-link density using the following equation.

$$\xi = \left(\frac{N_A v_e}{V}\right)^{-1/3}$$

where N_A is the Avogadro's number. The cross-link densities, v_e/V, averaged mesh size, ξ, calculated by the tensile and compression results were listed on the Table 3. The EWC and the cross-link density of M1 was the same as B1 at tensile mode. This relation was valid between M3 and B3, too. These results prove that the same EWC represent the same cross-link

Table 3
Estimated cross-link densities and cross-link distances calculated from the Young's modulus

Code	φ_2	φ_0	Tensile		Compression	
			ν_e/V (mol/m^3)	ξ (nm)	ν_e/V (mol/m^3)	ξ (nm)
M1	0.09	0.12	16	4.7	33	3.7
B1	0.12	0.12	16	4.7	25	4.1
E1	0.12	0.13	23	4.1	49	3.2
T1	0.07	0.08	6	6.6	11	5.3
M3	0.16	0.19	60	3.0	87	2.7
B3	0.21	0.19	61	3.0	81	2.7

density. Table 3 also indicates that the EWC of MPC polymer hydrogel decrease when increasing the cross-link density. The supplemental observation from Table 3 is that the cross-link densities in compression mode were higher than those of in tensile mode for each hydrogel. However, the reason for the higher cross-link densities in compression mode is unclear.

3.6. Thermal property

The DSC thermograms from −50 to 230 °C on lyophilized MPC polymer xerogel with different cross-linker are shown in Fig. 7. As a reference, HEMA polymer hydrogel cross-linked with 1 mol% of TEGDMA was synthesized. The bulk HEMA monomer was used for this reference and the synthetic method was the same as that of MPC polymer hydrogel. As for HEMA polymer hydrogel, the T_g was observed at 110 °C. This result well matches that of the HEMA polymer [28]. In the MPC polymer xerogels, however, no glass transitions were observed in this temperature range. That is, the thermal decomposition occurred before the glass transitions did. These results conclude that the T_g of MPC polymer chain is more than 230 °C and the MPC chain is more rigid than the HEMA polymer chain. The base line shifts around −20 °C were not T_g. These shifts were generated by the rapid cooling process by liquid nitrogen and they could not be reproduced (Fig. 8).

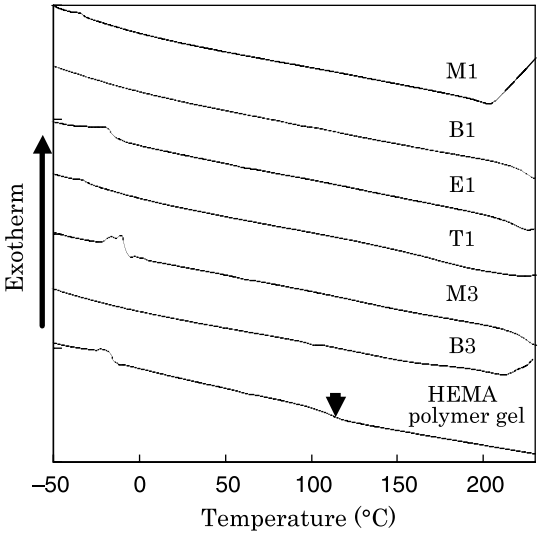

Fig. 8. DSC measurements of lyophilized MPC polymer hydrogels with various cross-linkers and concentrations in feed.

4. Conclusions

We synthesized MPC polymer hydrogels with a focus on the cross-linker to adjust the EWC and to enhance the mechanical properties for new ophthalmic materials, especially for SCL biomaterials. In addition, a novel water-soluble methacrylic cross-linker having a phosphorylcholine-like group, MMPC was applied to increase the free water content in the MPC polymer hydrogel. As a result, the free water content was slightly increased compared to a conventional hydrophilic cross-linker, BIS. We concluded that the phosphorylcholine-like group in MMPC increases the $W_{freezing}$ by loosely interacting with water molecules. The MMPC also enhanced the tensile properties with utilizing its hydrophilicity. In case of tensile tests, the fracture stress exceeded 120 kPa at M3, which had been considerably higher than for the conventional cross-linker. And, the MMPC was found to be higher reactivity in polymerization with MPC monomers than BIS. The novel cross-linker, MMPC, has a good potential for making soft biomaterials, particularly SCL.

Acknowledgements

The present research is supported in part by a Grant for the 21st Century COE Program 'Human-Friendly Materials Based on Chemistry' from the Ministry of Education, Culture, Sports, Science, and Technology of Japan.

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