Fabrication of Cationic Poly(vinyl alcohol) Films Cross-Linked Using Copolymers Containing Quaternary Ammonium Cations, Benzoxaborole, and Carboxy Groups

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ABSTRACT: Water-insoluble cationic poly(vinyl alcohol) (PVA) films were fabricated using a mixed aqueous solution of PVA and poly[(2-(methacryloyloxy)ethyl]trimethylammonium chloride (METAC)-co-methacrylic acid (MAAc)-co-5-methacrylamido-1,2-benzoxaborole (MAAmBO)] copolymer (3D). The surface of the PVA film is typically negatively charged, and simple fabrication methods for water-insoluble PVA films with cationic surface charges are required to expand their application fields. METAC, which has a permanent positive charge owing to the presence of a quaternary ammonium cation, was selected as the cationic unit. The MAAc and MAAmBO units were used as two types of cross-linking structures for the thermal cross-linking of the hydroxy and carboxy groups of the MAAc unit (covalent bonding) as well as the diol and benzoxaborole groups of the MAAmBO unit (dynamic covalent bonding). The films were thermally cross-linked at 135 °C for 4 h without the addition of materials. After immersion in surplus water at 80 °C for 3 h, the cross-linked PVA/3D films retained almost 100% of their weights. The ω-potential of the water-insoluble PVA/3D film was 9.4 ± 0.8 mV. The PVA/3D film was strongly dyed using anionic acid red 1 (AR1) because of its positively charged surface. Interestingly, it could also be slightly dyed using cationic methylene blue (MB) and became transparent (original state) after immersion in water for 2 days. These results suggested that positive and negative charges coexisted in the PVA/3D film, and the surface properties were positively inclined. Moreover, the degree of hemolysis of the PVA/3D films was similar to that of the negative control, which showed high blood compatibility. To our knowledge, this is the first report on the fabrication of water-insoluble cationic PVA films using two types of cross-linking structures containing carboxy and benzoxaborole groups. The cross-linked PVA films were analyzed using Fourier transform infrared (FT-IR) spectroscopy, differential scanning calorimetry (DSC), and contact angle (CA) and ω-potential measurement, as well as by determining the mechanical properties, adsorption of charged molecules, and biocompatibility. These readily fabricated water-insoluble PVA films with positive charges can show potential applications in sensors, adsorption systems, and antimicrobial materials.

1. INTRODUCTION

Poly(vinyl alcohol) (PVA), a water-soluble polymer, has been applied in glues, displays, and food packaging materials.1–3 PVA materials also have been used in biomedical applications because of their excellent biocompatibilities, low protein adsorption, and high chemical stability.4,5 For example, PVA can amplify hematopoietic stem cells by replacing serum albumin in a normal cell culture system.6 Boron neutron capture therapy (BNCT), which employs a complex of PVA and p-boronophenylalanine (BPA), has also been used.7 BPA is a powerful BNCT drug that can accumulate in tumors via cancer-related amino acid transporters. The diol groups of PVA can interact with BPA through dynamic covalent bonding, which improves the tumor accumulation of the conjugated materials. Furthermore, PVA with ultralow molecular weight distribution (<1.01) can inhibit ice recrystallization, and this phenomenon can be applied to develop better cryopreservative systems.8 To expand the applications of PVA materials, physical and chemical cross-linking processes are used as the preparation methods for water-insoluble PVA.1 For physical cross-linking, hydrogen bonding, crystallization, and coordinate bonding are used.9–11 These interactions are weak, and their stability in aqueous solutions has scope for improvement. Physically cross-linked PVA materials are typically dissolved by immersion in hot water for several hours. On the other hand, chemical cross-linking can obtain the water-insoluble PVA, which usually
requires toxic compounds or specialized equipment such as γ-ray irradiation. Glutaraldehyde is one of the most commonly used cross-linking agents for PVA materials; however, it is toxic, expensive, difficult to synthesize, and not environmentally friendly.

Recently, thermal cross-linking between the hydroxy groups of PVA and carboxy group has been reported as a simple fabrication method for obtaining chemically cross-linked water-insoluble PVA materials. Cross-linking agents with carboxy groups such as citric acid, maleic acid, poly(acrylic acid) (poly(AAc)) have low toxicities and are inexpensive. The copolymers consisting of (meth)acrylic acid monomers can tolerate both thermal cross-linking and addition of other functionalities to the PVA materials. Therefore, the thermal cross-linking method was selected for obtaining one of the cross-linked PVA structures in this study.

Combinations of more than two types of cross-linking structures have attracted considerable attention in recent years for improvement of their mechanical properties. Li et al. prepared covalently cross-linked poly(acrylamide) (poly(AAm)) in the PVA solution. After polymerization, PVA in the poly(AAm) matrix was physically cross-linked via annealing. The PVA-poly(AAm) hydrogel with both chemical and physical cross-linked structures showed superior mechanical properties, including an elastic modulus of 5 MPa, a strength of 2.5 MPa, and a fracture energy of 14 000 J/m². Importantly, the hydrogels contained 60−80% water, and these mechanical properties were comparable to those of the cartilage.

In a previous study reported by our research group, functionalized PVA films were prepared using a copolymer containing benzoxaborole and carboxy groups. The films were cross-linked via two types of covalent bonding, dynamic covalent bonding between the added borax and hydroxy groups and thermal cross-linking between the hydroxy and carboxy groups. With appropriate thermal cross-linking and copolymer compositions, the functionalized PVA films remained intact (almost 100%) after immersion in water at 80 °C for 3 h. All films without any thermal cross-linking were dissolved in water under identical conditions. The cross-linked PVA films were degraded owing to the oxidizing characteristics of the NaClO·5H₂O aqueous solution and completely dissolved in water within 25 h at 25 °C. However, the surfaces of all the cross-linked PVA films were negatively charged because of the anionic properties of the PVA, carboxy, and benzoxaborole...
groups. If water-insoluble PVA materials with cationic surface charges can be realized, their applications can be expanded to sensors, adsorption, and antimicrobial materials. Only a few reports on water-insoluble cationic PVA materials have been published in the literature. For example, a cationic PVA film was prepared using a blend of PVA and cationic tannin polymers.29 The PVA network was cross-linked using the toxic glutaraldehyde. Xiao et al. prepared physically cross-linked cationic PVA nanofibers for the adsorption of an anionic dye using a mixture of PVA, poly(hexadimethrine bromide), and chitosan.30 However, cationic poly(hexadimethrine bromide) was not covalently bonded to the PVA network. Moreover, chitosan, which could form hydrogen bonds with the hydroxy groups of PVA, showed pH-responsivity to the surface charges. Jin et al. reported that the surface of the PVA/chitosan hydrogel beads showed a positive ζ-potential under acidic conditions and negative ζ-potential under basic conditions.31 The zero point of the ζ-potential was observed at a pH of ~6.6, which was close to the pKₐ values of 6.3–6.6 for the amino group in chitosan.

In this study, water-insoluble cationic PVA films were easily fabricated using a mixed aqueous solution of PVA and poly[[2-(methacryloyloxy)ethyl]trimethylammonium chloride (METAC)-co-methacrylic acid (MAAc)-co-S-methacrylamido-1,2-benzoxaborole (MAAmBO)] copolymer (3D, D means dimension) (Figure 1). METAC, which has a permanent positive charge owing to the presence of a quaternary ammonium cation, was selected as the cationic unit.32 The hydroxy groups of PVA were cross-linked via two types of interactions, i.e., thermal cross-linking of the hydroxy and carboxy groups of the MAAc unit (covalent bonding) as well as the diol and benzoxaborole groups of the MAAmBO unit (dynamic covalent bonding). As a control, poly(MAAc) (1D), poly(METAC-co-MAAc) (2D), and poly(METAC-co-MAAc-co-MAAmBO) (3D) were polymerized via free radical polymerization (Figure S1). The MAAc (carboxy group) and MAAmBO (benzoxaborole group) units were combined with the hydroxy groups of PVA via covalent bonding and dynamic covalent bonding, respectively. The carboxy groups could form covalent bonds (ester bonds) with the hydroxy groups of PVA via thermal cross-linking. The benzoxaborole unit was selected for dynamic covalent bonding with the diol group, which exhibited stronger interaction in comparison to the typical phenyl boronic acid.33 Combinations of more than two types of physical and/or chemical cross-linked structures can enhance the mechanical properties of the cross-linked PVA materials.17 In our previous reports, water-insoluble PVA films were prepared using two types of chemically cross-linked structures by mixing copolymers with carboxy and benzoxaborole groups.28,33 The mechanical properties of all of the mixed PVA films enhanced after thermal cross-linking via additional covalent bonding between the carboxy and hydroxy groups. However, as these were mixed copolymers with PVA, cationic groups in the copolymers were not used because of the electrostatic interaction with anionic carboxy and benzoxaborole groups, resulting in intra- and intermolecular aggregation. Scerist et al. prepared a multilayer comprising layer-by-layer films consisting of poly(allylamine hydrochloride) and poly(AAc) formed through electrostatic interactions.34 Electrostatic interactions have also been employed for the fabrication of graphene films using anionic and cationic functionalized graphene nanosheets.35 Therefore, to use both anionic and cationic units in a copolymer, optimized compositions are required to prevent electrostatic aggregation and precipitation in aqueous solutions. In this study, copolymers with coexisting anionic (carboxy and benzoxaborole units) and cationic (quaternary ammonium cation unit) units were successfully polymerized, and no precipitation was observed in water. These water-soluble copolymers led to the fabrication of mixed films with PVA.

Table 1 lists the properties of the polymerized copolymers. The molecular weight (Mₙ) and molecular weight distribution (Mₙ/Mₘ) were 72 800 g/mol and 1.52 for 1D, 58 900 g/mol and 1.60 for 2D, and 16 200 g/mol and 1.14 for 3D copolymers (Figure S2). The MAAmBO units in 3D copolymer were covered with 1,4-butanediol to prevent the adsorption to the GPC columns. The relatively small Mₙ and narrow Mₙ/Mₘ might come from the adsorption by the unmodified MAAmBO units. The compositions of the copolymers were calculated using the molar ratios of MAAc, METAC, and MAAmBO units, determined by ¹H NMR spectroscopy. Table 1. Characterization of 1D, 2D, and 3D Copolymers

| copolymer | METAC contenta | MAAc contenta | MAAmBO contenta | Mₙ (g/mol) | Mₙ/Mₘb |
|-----------|----------------|---------------|-----------------|------------|--------|
| Poly(MAAc) (1D) | 100 | 72 800 | 1.52 |
| Poly(METAC-co-MAAc) (2D) | 49.5 | 50.5 | 58 900 | 1.60 |
| Poly(METAC-co-MAAc-co-MAAmBO) (3D) | 46.3 | 39.7 | 14.3 | 16 200 | 1.14 |

“aThe monomer contents were calculated by ¹H NMR. bDetermined by GPC using phosphate buffer at 40 °C. The MAAmBO groups of 3D copolymer were covered with 1,4-butanediol. D of 1D, 2D, and 3D means dimension.

2. RESULTS AND DISCUSSION

2.1. Characterization of Poly(MAAc) (1D), Poly(METAC-co-MAAc) (2D), and Poly(METAC-co-MAAc-co-MAAmBO) (3D) Copolymers. Copolymers of poly(MAAc) (1D), poly(METAC-co-MAAc) (2D), and poly(METAC-co-MAAc-co-MAAmBO) (3D) were polymerized via free radical polymerization (Figure S1). The MAAc (carboxy group) and MAAmBO (benzoxaborole group) units were combined with the hydroxy groups of PVA via covalent bonding and dynamic covalent bonding, respectively. The carboxy groups could form covalent bonds (ester bonds) with the hydroxy groups of PVA via thermal cross-linking. The benzoxaborole unit was selected for dynamic covalent bonding with the diol group, which exhibited stronger interaction in comparison to the typical phenyl boronic acid. Combinations of more than two types of physical and/or chemical cross-linked structures can enhance the mechanical properties of the cross-linked PVA materials. In our previous reports, water-insoluble PVA films were prepared using two types of chemically cross-linked structures by mixing copolymers with carboxy and benzoxaborole groups. The mechanical properties of all of the mixed PVA films enhanced after thermal cross-linking via additional covalent bonding between the carboxy and hydroxy groups. However, as these were mixed copolymers with PVA, cationic groups in the copolymers were not used because of the electrostatic interaction with anionic carboxy and benzoxaborole groups, resulting in intra- and intermolecular aggregation. Scerist et al. prepared a multilayer comprising layer-by-layer films consisting of poly(allylamine hydrochloride) and poly(AAc) formed through electrostatic interactions. Electrostatic interactions have also been employed for the fabrication of graphene films using anionic and cationic functionalized graphene nanosheets. Therefore, to use both anionic and cationic units in a copolymer, optimized compositions are required to prevent electrostatic aggregation and precipitation in aqueous solutions. In this study, copolymers with coexisting anionic (carboxy and benzoxaborole units) and cationic (quaternary ammonium cation unit) units were successfully polymerized, and no precipitation was observed in water. These water-soluble copolymers led to the fabrication of mixed films with PVA.

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spectroscopy (Figure S3). The calculated molar percentages of the copolymers were 49.5 mol % METAC and 50.5 mol % MAAc for 2D copolymers and 46.3 mol % METAC, 39.7 mol % MAAc, and 14.3 mol % MAAmBO for 3D copolymers. The 2D and 3D copolymers might have a polyampholyte (or zwitterionic)-like structure. These 1D, 2D, and 3D copolymers were mixed with PVA in different weight ratios in an aqueous solution to prepare the conjugated films.

2.2. Characterization of Thermally Cross-Linked PVA/1D, PVA/2D, and PVA/3D Films. 2.2.1. Stability Tests of Films in Water at 80 °C. The 1D, 2D, and 3D copolymers were dissolved in water and mixed with PVA aqueous solution in different weight ratios (copololymer contents: 10, 25, 50, and 75 wt %) to fabricate the films using a simple cast method. The mixed PVA/copolymer aqueous solutions were dried overnight under reduced pressure and thermally cross-linked at 135 °C for 4 h. Thermal cross-linking was used to combine polymeric materials with hydroxy and carboxy groups. This chemical thermal cross-linking can afford a new field of applications for the PVA materials because of their high stabilities in hot water. Physically cross-linked PVA materials are typically dissolved by immersion in hot water for several hours because of the relatively weak interactions. In our previous work, water-insoluble PVA films were prepared using poly(MAAc-co-MAAmBO) copolymers. Thermal cross-linking for more than 4 h was required at 135 °C to achieve almost 100% of the residual weights of the films after immersion in water at 80 °C for 3 h.28

Figure 2 shows the data for the stability tests of the thermally cross-linked PVA/1D, PVA/2D, and PVA/3D films. The films were immersed in a large amount of water at 80 °C for 3 h. The PVA/1D, PVA/2D, and PVA/3D films without thermal cross-linking completely dissolved in water at 80 °C after immersion for 3 h. Pure PVA films subjected to thermal treatment also dissolved in water under identical conditions. As shown in Figure 2A, the residual weights of the PVA/1D films are ~100% for 10 wt % (104.6 ± 1.0%), 25 wt % (107.4 ± 2.0%), and 50 wt % (104.9 ± 1.3%) 1D copolymers in the mixture. For PVA/1D_75 wt %, 60.7 ± 7.6% of the residual weight was retained. The calculated OH/MAAc molar ratio in the PVA/1D films decreased with an increase in the 1D copolymer content in the mixture (10 wt %, 17.6; 25 wt %, 5.87; 50 wt %, 1.96; and 75 wt %, 0.65). The uncross-linked parts of the film could be increased by increasing the short polymeric chains of the 1D copolymer in comparison to those of PVA. Electrostatic repulsion could also occur among the carboxy groups. At 10, 25, and 50 wt % 1D copolymer, the swelling ratios of the PVA/1D films were 2.09 ± 0.08, 1.78 ± 0.15, and 1.46 ± 0.18, respectively, and the water contents that could be incorporated into 1 g of dry films were 1.82 ± 0.18, 1.09 ± 0.03, and 1.17 ± 0.03 g, respectively (Figure 2B). These results suggested that the number of cross-linking sites increased with an increase in the 1D copolymer content in the films, allowing control over the hydrogel properties. For PVA/1D_75 wt %, the swelling ratio and water content were 1.54 ± 0.15 and 2.68 ± 0.88 g, respectively. As shown in Figure 2C, the residual weights of the PVA/2D films were 20.9 ± 2.9% (10 wt %), 33.7 ± 2.1% (25 wt %), 80.2 ± 3.6% (50 wt %), and 51.7 ± 7.5% (75 wt %). The lower residual weights compared to those of the PVA/1D films may be due to the
solubility of the 2D copolymers in water. 2D copolymers contain both anionic (MAAc) and cationic (METAC) units, which lead to intra- and intermolecular electrostatic interactions. When the 2D copolymers were added to water, aggregation and precipitation were observed at 50 and 75 wt % 2D copolymers; the amounts of water-insoluble precipitation of 50 and 75 wt % were 1.2 mg (0.8 wt % against the complete 2D copolymer) and 19.5 mg (8.7 wt %), respectively. The aggregation of 2D copolymers hinders cross-linking with PVA, resulting in the release of uncross-linked PVA and 2D copolymers from the films. The solubility in water is affected by the polymer concentration, composition, and molecular weight, and the structural design of the copolymers is important for the fabrication of functionalized films. Electrostatic repulsion between the METAC units of the cross-linked PVA/2D films is another reason for the unstable structures of the films. The cross-linked PVA/2D films exhibited relatively high swelling ratios and water contents (Figure 2D). In particular, PVA/2D_10 wt % film absorbed a large amount of water and the swollen hydrogel was unable to maintain its shape. Dou et al. prepared a composite film of keratin/PVA cross-linked via dialdehyde starches. Around 65–72% of cross-linked composite films were retained after immersion in water at 37 °C for 24 h. Cai et al. reported that the residual weights of the poly(electrolyte-coated) sericin/PVA films depended on the solution pH values. In our previous study, the mixed films of PVA and ethylene glycol-based temperature-responsive copolymer with benzoxaborole groups showed different residual weights at different solution pH values (24 h immersion at 37 °C). The films showed cross-linking between the diols of PVA and benzoxaborole groups via dynamic covalent bonding. At pH values of 2 and 12, the residual weights of the films with different compositions were less than 82%. One of the reasons for the relatively low residual weights could be the low molar ratios (2.3–4.9 mol %) of the benzoxaborole groups as the cross-linking sites in the copolymers. However, poly(MAAmBO) (with benzoxaborole groups) homopolymers cannot dissolve in water because of their hydrophobicity. In contrast, poly(MAAC-co-MAAmBO) copolymers afforded 100 mol % cross-linking sites with PVA via covalent (thermal cross-linking of hydroxy and carboxy groups) and dynamic covalent (diol and benzoxaborole groups) bonding. The PVA/poly(MAAC-co-MAAmBO) films that were thermally cross-linked at 135 °C for 4 h showed almost 100% of residual weights after immersion in water at 80 °C for 3 h. The water-insoluble films were degraded by the oxidizing environment of the aqueous NaClO−5H2O solution within 25 h at 25 °C. Moreover, these multiple types of cross-linking parts were expected to improve the mechanical properties of the PVA films. Therefore, a 3D copolymer of poly(METAC-co-MAAC-co-MAAmBO) was designed for the fabrication of cationic PVA films. The content of the METAC units in the 3D copolymer (METAC, 46.3 mol %; MAAC, 39.7 mol %; and MAAMBO, 14.3 mol %) was similar to that of the 2D copolymer (METAC, 49.5 mol %; MAAC, 50.5 mol %). As shown in Figure 2E, the residual weights of the PVA/3D films were 62.5 ± 3.6% (10 wt %), 98.1 ± 1.9% (25 wt %), 99.6 ± 5.1% (50 wt %), and 90.9 ± 1.5% (75 wt %). Almost 100% of the films were containing 25 and 50 wt % 3D copolymers were retained. Coexisting interactions such as hydrogen bonding, covalent bonding (thermal cross-linking between hydroxy and carboxy groups), dynamic covalent bonding (between diol and benzoxaborole groups), electrostatic interactions (between ammonium cation and carboxy groups), and repulsions (i.e., electrostatic repulsion of the similarly charged ammonium cations and carboxy groups) and the balance between these are the key factors affecting the physicochemical properties of the prepared films. The 3D copolymers were dissolved in water at the concentrations used for film fabrication. Low residual weights of 10 and 75 wt % could be correlated to the small number of cross-linking sites in the polymeric chains as well as the electrostatic repulsion between the charged units. Based on these results, the optimal ratios for fabricating water-insoluble 3D/PVA films were 25 and 50 wt % 3D copolymers in the mixtures. The swelling ratio and water content at 25 wt % were 1.9 ± 0.2 and 1.24 ± 0.04 g, respectively, and those at 50 wt % were 1.7 ± 0.2 and 0.89 ± 0.24 g, respectively (Figure 2F). The swelling ratios and water contents of the PVA/3D films were similar (p > 0.05) to those of the PVA/1D films with the same mixing ratios (25 and 50 wt %), even though hydrophilic ammonium cation groups were present. These results suggested that complex gel networks were formed by the above coexisting interactions. When the fabrication of water-insoluble PVA/3D films is expanded to other polymeric materials such as nanofibers, a longer thermal cross-linking time and a higher molecular weight of PVA or 3D copolymer might be necessary because of their large surface areas. Next, the thermodynamic properties of the films were analyzed.

2.2. Thermodynamic Properties of Films. Physicochemical properties of the PVA films before and after thermal cross-linking were compared. The FT-IR spectra of PVA, PVA/1D, PVA/2D, and PVA/3D films before and after thermal cross-linking are shown in Figures S4 and S5. The pure PVA film was also treated with the same thermal cross-linking process as the control. For the PVA films, the FT-IR peaks of PVA were observed at ~1418 cm−1 (CHOH), 1328 cm−1 (CO), 1087 cm−1 (CO), 2940 cm−1 (CH), and 3272 cm−1 (OH), and no change was observed after thermal treatment. All PVA/1D, PVA/2D, and PVA/3D films showed a peak at ~1694 cm−1, which corresponded to the C==O group of the mixed 1D, 2D, and 3D copolymers. In the PVA/3D films, the peak at ~1145 cm−1 was ascribed to the boron moiety of the benzoxaborole units in the 3D copolymers. For PVA, the wide absorption band at ~3272 cm−1 was ascribed to the O−H stretching vibration of the hydroxy group, which was sensitive to the formation of hydrogen bonds. Dai et al. prepared a conjugated film of PVA and copper-based metal–organic frameworks (MOFs). The hydroxy FT-IR peak of the conjugated PVA film (2.0 wt % of MOF) showed a blue shift of ~14 cm−1, suggesting the strong hydrogen-bonding interaction between PVA and MOF. In the PVA/1D films, the blue shifts of 19 cm−1 (10 wt %), 21 cm−1 (25 wt %), 83 cm−1 (50 wt %), and 108 cm−1 (75 wt %) were observed for the hydroxy FT-IR peaks of PVA in comparison to those of pure PVA. The blue shifts were attributed to the hydrogen-bonding interactions between PVA and the carboxy groups of the 1D copolymer, and the value of the blue shift increased with an increase in the content of 1D copolymer in the films. The blue shifts before thermal cross-linking were 5 cm−1 (10 wt %), 2 cm−1 (25 wt %), 24 cm−1 (50 wt %), and 37 cm−1 (75 wt %) for the PVA/2D films and 6 cm−1 (10 wt %), 22 cm−1 (25 wt %), 39 cm−1 (50 wt %), and 33 cm−1 (75 wt %) for the PVA/3D films. The values of the blue shifts were lower than those of the 1D copolymer because of the low content of the MAAc units in the 2D and 3D copolymers. The blue shifts were also observed for all PVA/1D, PVA/2D, and PVA/3D films (PVA/1D, 26
the slight shifts of the C\(^1\D\) peaks were observed for the PVA/3D copolymer. The decreased crystallization of PVA upon mixing with other materials have been reported by several research groups. Li et al. prepared a dual physically cross-linked hydrogel consisting of PVA crystallites and hyaluronic acid-Fe\(^3+\) networks.\(^{41}\) The use of the 1D copolymer decreased the crystallization of PVA compared to the use of 2D copolymers. The decreased crystallization of PVA/1D was consistent with the FT-IR data showing large blue shifts in the hydroxy peak due to the hydrogen-bonding interactions between PVA and 1D polymers (Figures S4 and S5). Similar phenomena are reported previously.\(^{15}\) PVA and poly(AAc) membranes (20 wt % of poly(AAc)) were prepared, and a shift of 2 cm\(^{-1}\) for the C=O peak was observed after thermal cross-linking (absolute values of the peak shift were within 8 cm\(^{-1}\)). Similar results describing the slight shifts of the C=O peak have been reported previously.\(^{15}\) PVA and poly(AAc) membranes (20 wt % of poly(AAc)) were prepared, and a shift of 2 cm\(^{-1}\) for the C=O peak was observed after thermal cross-linking (absolute values of the peak shift were within 8 cm\(^{-1}\)). Similar results describing the slight shifts of the C=O peak have been reported previously.\(^{15}\) PVA and poly(AAc) membranes (20 wt % of poly(AAc)) were prepared, and a shift of 2 cm\(^{-1}\) for the C=O peak was observed after thermal cross-linking (absolute values of the peak shift were within 8 cm\(^{-1}\)). Similar results describing the slight shifts of the C=O peak have been reported previously.\(^{15}\) PVA and poly(AAc) membranes (20 wt % of poly(AAc)) were prepared, and a shift of 2 cm\(^{-1}\) for the C=O peak was observed after thermal cross-linking (absolute values of the peak shift were within 8 cm\(^{-1}\)). Similar results describing the slight shifts of the C=O peak have been reported previously.\(^{15}\) PVA and poly(AAc) membranes (20 wt % of poly(AAc)) were prepared, and a shift of 2 cm\(^{-1}\) for the C=O peak was observed after thermal cross-linking (absolute values of the peak shift were within 8 cm\(^{-1}\)). Similar results describing the slight shifts of the C=O peak have been reported previously.\(^{15}\) PVA and poly(AAc) membranes (20 wt % of poly(AAc)) were prepared, and a shift of 2 cm\(^{-1}\) for the C=O peak was observed after thermal cross-linking (absolute values of the peak shift were within 8 cm\(^{-1}\)). Similar results describing the slight shifts of the C=O peak have been reported previously.\(^{15}\) PVA and poly(AAc) membranes (20 wt % of poly(AAc)) were prepared, and a shift of 2 cm\(^{-1}\) for the C=O peak was observed after thermal cross-linking (absolute values of the peak shift were within 8 cm\(^{-1}\)).

Table 2 shows the thermodynamic properties, including the glass transition temperature (\(T_g\)), melting point (\(T_m\)), enthalpy change (\(\Delta H_m\)), degree of crystallization (\(\chi_c\)), and temperature of 10\% weight loss (\(T_{d,10\%}\)) before and after thermal cross-linking. The corresponding values of pure PVA were similar after thermal treatment. For the PVA/1D_10 wt % film, the corresponding values were 73.9 ± 3.0 °C (\(T_g\)), 193.8 ± 1.1 °C (\(T_m\)), −16.7 ± 0.5 J/g (\(\Delta H_m\)), and 318 °C (\(T_{d,10\%}\)). No signals were observed for \(T_g\), \(T_m\), and \(\Delta H_m\) of PVA/1D with 25, 50, and 75 wt % 1D copolymer. For the PVA/2D films, the values of \(T_g\), \(T_m\), and \(\Delta H_m\) were decreased with an increase in the 2D copolymer in the mixture. The \(T_g\), \(T_m\), and \(\Delta H_m\) values of the PVA/1D and PVA/2D films were similar after thermal cross-linking. The decreases in the \(T_g\), \(T_m\), \(\Delta H_m\), and \(T_{d,10\%}\) values were attributed to an increase in the 1D or 2D copolymer content in the films, resulting in decreases in the crystallization and hydrogen bonding of PVA.\(^{33}\) The use of the 1D copolymer decreased the crystallization of PVA films compared to the use of 2D copolymers. The decreased crystallization of PVA/1D was consistent with the FT-IR data showing large blue shifts in the hydroxy peak due to the hydrogen-bonding interactions between PVA and 1D polymers (Figures S4 and S5). Similar phenomena affording a decrease in the crystallization of PVA upon mixing with other materials have been reported by several research groups. Li et al. prepared a dual physically cross-linked hydrogel consisting of PVA crystallites and hyaluronic acid-Fe\(^3+\) networks.\(^{33}\) The \(T_m\), \(\Delta H_m\), and \(\chi_c\) values decreased with an increase in the hyaluronic acid content. The \(\chi_c\) of pure PVA was 51.8 ± 7.8%, which decreased to 34.6 ± 1.5% upon adding 1.5 wt % hyaluronic acid. Uslu et al. reported the disappearance of the \(T_m\) of PVA (i.e., amorphous) upon adding boron compounds as cross-linking agents (PVA/boron = 1/0.8).\(^{42}\) He et al. prepared a conjugated material comprising PVA and keratin by employing hydrogen-bonding interactions, affording a decrease in the enthalpy values of PVA.\(^{43}\) For the PVA/3D films, the values of \(T_m\), \(\Delta H_m\), and \(\chi_c\) decreased with an increase in content of the 3D copolymer in the mixture. Similar values of these parameters were observed for the PVA/3D films after thermal cross-linking. The large difference in \(T_m\) (PVA/3D_50

| Table 2. Thermodynamic Properties of Films before and after Thermal Cross-Linking |  |
|---|---|---|---|---|---|
| code | \(T_g\) (°C) | \(T_m\) (°C) | \(\Delta H_m\) (J/g) | \(\chi_c\) (%) | \(T_{d,10\%}\) (°C) |
| PVA | 67.3 ± 0.5 | 225.4 ± 1.0 | −61.8 ± 5.5 | 44.6 ± 4.0 | 274 |
| 1D | 84.1 ± 3.1 | 174.0 ± 1.1 | −0.9 ± 0.1 | N.D. | 245 |
| 2D | N.D. | N.D. | N.D. | N.D. | 225 |
| 3D | N.D. | N.D. | N.D. | N.D. | 225 |
| PVAA/1D_10 wt % | 73.9 ± 3.0 | 193.8 ± 1.4 | −16.7 ± 0.5 | 13.4 ± 0.4 | 318 |
| PVAA/1D_25 wt % | N.D. | N.D. | N.D. | N.D. | 301 |
| PVAA/1D_50 wt % | N.D. | N.D. | N.D. | N.D. | 274 |
| PVAA/1D_75 wt % | N.D. | N.D. | N.D. | N.D. | 249 |
| PVAA/2D_10 wt % | 72.5 ± 0.6 | 224.6 ± 0.4 | −57.0 ± 1.1 | 45.7 ± 0.9 | 318 |
| PVAA/2D_25 wt % | 67.4 ± 1.2 | 217.2 ± 0.5 | −37.3 ± 1.9 | 35.8 ± 1.9 | 308 |
| PVAA/2D_50 wt % | 59.5 ± 0.3 | 186.0 ± 2.7 | −7.1 ± 0.9 | 10.2 ± 1.3 | 264 |
| PVAA/2D_75 wt % | 51.0 ± 0.4 | 184.4 ± 2.3 | −1.5 ± 0.3 | 4.3 ± 0.8 | 255 |
| PVAA/3D_10 wt % | 70.8 ± 0.9 | 217.3 ± 0.4 | −46.0 ± 1.8 | 36.9 ± 1.4 | 320 |
| PVAA/3D_25 wt % | 75.2 ± 0.4 | 188.7 ± 0.3 | −12.5 ± 1.0 | 12.0 ± 0.9 | 294 |
| PVAA/3D_50 wt % | 79.8 ± 1.5 | 122.0 ± 0.7 | −0.2 ± 0.1 | 0.3 ± 0.2 | 275 |
| PVAA/3D_75 wt % | N.D. | N.D. | N.D. | N.D. | 266 |

"N.D. = not determined. \(^{b}\)The \(\chi_c\) values of films were calculated using the following formula: \(\chi_c = (\Delta H_m / \Delta H_m^{\infty}) \times (\text{film weight} / \text{PVA weight})\)."
Increases in the signals for addition of glycerol (10 wt %, 75 °C) accompanied by a slight decrease in the crystallinity degree.44 wt %, 87.8 °C increased with an increasing amount of Ag nanoparticles (0.19 wt %, 44 °C) was observed in comparison to that of the original PVA (63 °C).45 Cheng et al. reported an increase in the ζ value of the conjugated PVA and PVA-grafted graphene oxide (PVA-g-GO) by employing the reduced mobility of the polymer chains and hydrogen bonding between the oxygen-containing groups on the GO sheets and hydroxy groups of PVA.46 The Tg value of PVA-g-GO (1.5 wt %)/PVA was 80.3 °C (PVA, 72.2 °C). Mbhele et al. investigated the physicochemical properties, including Tg of the conjugated materials consisting of silver nanoparticles and PVA.37 The Tg value of PVA (76.1 °C) increased with an increasing amount of Ag nanoparticles (0.19 wt %, 87.8 °C; 0.33 wt %, 94.9 °C; and 0.73 wt %, 97.0 °C). Increases in the Tg values of the composites were explained by the reduced mobility of the polymeric chains. In this study, the 3D copolymers contain benzoxaborole groups and one benzoxaborole group can interact with two hydroxy groups of PVA via dynamic covalent bonding. The multiple and flexible dynamic covalent bonding might lead to the reduced mobility of the polymer chains, resulting in an increase in the Tg value of the PVA/3D films. The flexible dynamic covalent bonding of the benzoxaborole groups in copolymers afforded strong (cis-diol) or weak (4,6-diol) interactions with the glycol polymers containing mannose and galactose groups.50

2.3. Surface Properties of Thermally Cross-Linked Films. 2.3.1. ζ-Potentials of PVA/1D and PVA/3D Films. The surface properties of thermally cross-linked films were analyzed. The PVA/1D and PVA/2D films with 25 or 50 wt % copolymers were selected as the cross-linked films because of their high stability in water. These films showed almost 100% residual weights (Figure 2) after immersion in water at 80 °C for 3 h. Figure 3 shows the ζ-potentials of the PVA/1D and PVA/2D films. For PVA/1D_25 wt %, the ζ-potential was −7.7 ± 1.9 mV. The original PVA films have a negative surface charge. Raskova et al. reported the ζ-potential of chemically cross-linked PVA films prepared using glutaric acid at different concentrations.49 At pH 7, the ζ-potentials of the cross-linked PVA films with 10, 20, and 40% glutaric acid were between −17.5 and −22.5 mV. More negative surface charges were recorded for all cross-linked PVA films with a decrease in the pH values. Poly(MAAC) also showed negative surface charge owing to the presence of carboxy groups. Li et al. reported the surface charges of poly(MAAC) nanogels cross-linked with divinylbenzene.51 The ζ-potential of the poly(MAAC) nanogel decreased from −10 to −50 mV as the pH of the solution was increased from 3 to 8. Interestingly, the ζ-potential of the PVA/1D_50 wt % film was 1.3 ± 1.2 mV despite the higher content of negatively charged poly(MAAC) in comparison to that of PVA/1D_25 wt %. During the preparation of the PVA/1D_50 wt % film, the mixed solution of PVA and 1D copolymer showed a cloud point around room temperature (25 °C) (Figure S6). No cloud point was observed in other aqueous solutions (PVA/1D_25 wt %, PVA/3D_25 wt %, and PVA/3D_50 wt %). Interestingly, the ζ-potential increased from 3 to 8. Interestingly, the ζ-potential of PVA/1D_25 wt %, the ζ-potential of PVA/1D_25 wt %, and PVA/3D_50 wt % films. The films were immersed in water overnight before the ζ-potential measurement.

PVA/3D_50 wt %) at 4–70 °C. Ye et al. reported the formation of cloud points (upper critical solution temperature (UCST) and lower critical solution temperature (LCST)) through the cation–anion interactions of mixed poly(styrenesulfonate) and poly(diallyldimethylammonium) in an aqueous solution depending on the polymer concentrations.51 In the literature reports on the cloud points triggered by various interactions, naphthalene diimide containing hydrazide and hydroxy groups showed an LCST (43 °C) and UCST (70 °C) through orthogonal hydrogen bonding and π–π stacking.52 The cloud points of PVA and 1D copolymer (50 wt %) could be due to their hydrogen-bonding interactions, and the changes in the surface properties due to the cloud point could affect the ζ-potential. Psarra et al. reported that the ζ-potentials of the substrates modified by LCST-type temperature-responsive poly(N-isopropyl acrylamide) (poly(NIPAAm)) changed by varying the solution temperature.53 For example, at pH 7, the ζ-potentials of the 105 kDa poly(NIPAAm)-modified surfaces were ~8–18 mV at 25 and 40 °C, respectively. Cationic poly(METAC) can add positive charges to the surfaces of the materials. Klimkevicius et al. reported that the ζ-potential of titania nanoparticles changed from −60 to 60 mV after poly(METAC) coating.54 Poly(METAC) was modified to lentil extracts as plant-based conjugated materials.55 The original negative charges of the lentil extracts (−5.91 mV) changed to 15.08 mV after modification with cationic poly(METAC). The ζ-potentials of the PVA/3D_25 wt % and PVA/3D_50 wt % films were 1.4 ± 1.5 and 9.4 ± 0.8 mV, respectively. The positive charge increased with increasing content of cationic 3D copolymers. Notably, PVA/3D films also possessed negative charges owing to the presence of vinyl alcohol, carboxy, and benzoxaborole units. These results suggested that the simple fabrication of cationic, water-insoluble PVA films was successfully achieved by mixing the copolymers in water, followed by their thermal cross-linking at 135 °C for 4 h.

2.3.2. Contact Angles of PVA/1D and PVA/3D Films. The contact angles of the PVA/1D and PVA/3D films were measured. Pure PVA films were hydrophilic, and their surface properties were determined by measuring the water contact angles (WCAs). The WCAs of the cross-linked PVA films

![Figure 3. ζ-Potentials of PVA/1D_25 wt %, PVA/1D_50 wt %, PVA/3D_25 wt %, and PVA/3D_50 wt % films. The films were immersed in water overnight before the ζ-potential measurement.](https://doi.org/10.1021/acsomega.1c02013)
Each film and PVA/3D_50 wt % was hard and brittle and could not be processed into a sample of dumbbell shape before thermal cross-linking. (D) Adsorption tests of PVA/1D_25 wt % and PVA/3D_50 wt % films against charged molecules aqueous solution (0.1 wt %) of anionic acid red 1 (AR1) or cationic methylene blue (MB). Each film was immersed into MB and AR1 aqueous solutions for 3 h at 20 °C. After immersion, all of the films were washed with surplus water.

Figure 4. Contact angles of PVA/1D and PVA/3D of (A) dry films and (B) swelling films after immersion in water for 20 h. The angles of 2 μL water drops on the films were measured after 5 s. (C) Maximum stresses of the PVA/1D and PVA/3D films before and after cross-linking. PVA films were treated by the same protocol as the thermal cross-linking (135 °C, 4 h). N.D. = not determined. The PVA/3D_50 wt % film was hard and brittle and could not be processed into a sample of dumbbell shape before thermal cross-linking. (D) Adsorption tests of PVA/1D_25 wt % and PVA/3D_50 wt % films against charged molecules aqueous solution (0.1 wt %) of anionic acid red 1 (AR1) or cationic methylene blue (MB).

The WCAs of the original PVA films were hydrophilic because of the water-soluble PVA and copolymers. The WCAs of the PVA films were also analyzed (Figures 4C and S7). The maximum stress values for all films increased after thermal cross-linking, the maximum stress and strain values were 98.5 ± 3.3 MPa and 28.7 ± 10.5% for PVA/1D_25 wt %, 85.2 ± 6.9 MPa and 19.1 ± 10.1% for PVA/1D_50 wt %, and 71.8 ± 4.0 MPa and 27.0 ± 9.4% for PVA/3D_25 wt %. The PVA/3D_50 wt % film was hard and brittle and could not be processed into a sample of dumbbell shape before thermal cross-linking. The maximum stress values for all films increased after thermal cross-linking (PVA/1D_25 wt %, 131.1 ± 5.1 MPa, 28.7 ± 7.0%; PVA/1D_50 wt %, 99.9 ± 13.7 MPa, 10.5 ± 3.1%; PVA/3D_25 wt %, 80.5 ± 6.0 MPa, 19.6 ± 12.2%; PVA/3D_50 wt %, 30.1 ± 3.7 MPa, 15.0 ± 2.0%). Interestingly, the cross-linked PVA/3D films showed lower maximum stress values than the PVA/1D films, even though there were two types of cross-linking structures. The mechanical properties of the hydrogels typically vary in dry and swollen states. For example, the elastic moduli of a physically cross-linked PVA nanofiber membrane decreased from 1331 ± 162 MPa in the dry state to 6.7 ± 0.7 MPa in the swollen state. In contrast, PVA materials with multiple cross-linking structures retained their strong mechanical properties in the swollen state. The PVA/3D films showed superior mechanical properties after chemical cross-linking (PVA/1D_25 wt %, 131.1 ± 5.1 MPa, 28.7 ± 7.0%; PVA/1D_50 wt %, 99.9 ± 13.7 MPa, 10.5 ± 3.1%; PVA/3D_25 wt %, 80.5 ± 6.0 MPa, 19.6 ± 12.2%; PVA/3D_50 wt %, 30.1 ± 3.7 MPa, 15.0 ± 2.0%).
immersion in an aqueous solution through two types of covalent bonding. A comparison of the mechanical properties of the functionalized PVA films in dry and swollen states will be reported in the future.

Next, the adsorption properties of the PVA/1D and PVA/3D films were analyzed against charged molecules. Based on the ζ-potential results (Figure 3), the surfaces of the PVA/1D_25 wt % and PVA/3D_50 wt % films were negatively and positively charged, respectively. Methylene blue (MB, cationic molecule) and acid red 1 (AR1, anionic molecule) were selected as the charged molecules. PVA/1D_25 wt % and PVA/3D_50 wt % films were immersed into MB and AR1 aqueous solutions (0.1 wt %) for 3 h at 20 °C. After immersion, all of the films were washed with surplus water. Figure 4D shows the dyed films for each charged molecule. Owing to the negative surface charge, the PVA/1D_25 wt % film was strongly dyed by the cationic MB, and the film remained transparent after immersion in the anionic AR1 aqueous solution. In contrast, PVA/3D_50 wt % film was dyed by the cationic MB, and the film became transparent (original state) after immersion in water for 2 days. These results suggested that positive and negative charges coexisted in the PVA/3D_50 wt % film, and the total ζ-potential was positively inclined.

2.3.3. Biocompatibilities of PVA/1D and PVA/3D Films.

Biocompatible cross-linked PVA films can be used as wound dressing materials that come into contact with blood. Therefore, the biocompatibilities of PVA/1D and PVA/3D films were determined using hemolysis tests. First, the hemolysis of 1D, 2D, and 3D copolymers, which were the components of cross-linked PVA films, was analyzed at different polymeric concentrations. PVA is known to exhibit high blood compatibility. Figure 5A−C shows the data for the hemolysis of 1D, 2D, and 3D copolymers at concentrations of 0.625−5 mg/mL. Triton-X aqueous solution was used as the positive control (100% hemolysis). For the 1D copolymer, the degrees of hemolysis increased with an increase in the polymeric concentration (0.625 mg/mL, 5.3 ± 0.4%; 1.25 mg/mL, 8.5 ± 0.4%; 2.5 mg/mL, 16.9 ± 0.6%; 5.0 mg/mL, 58.5 ± 1.6%). Poly(methacrylic acid) (1D copolymer in this study) is a polymer with low cell toxicity. At high concentrations, the 1D copolymer could show blood toxicity by interacting with the red blood cells. In contrast, 2D and 3D copolymers showed relatively low hemolysis at concentrations of 0.625−5 mg/mL. Triton-X aqueous solution was used as the positive control (100% hemolysis). For the 1D copolymer, the degrees of hemolysis increased with an increase in the polymeric concentration (0.625 mg/mL, 5.3 ± 0.4%; 1.25 mg/mL, 8.5 ± 0.4%; 2.5 mg/mL, 16.9 ± 0.6%; 5.0 mg/mL, 58.5 ± 1.6%). Poly(methacrylic acid) (1D copolymer in this study) is a polymer with low cell toxicity. At high concentrations, the 1D copolymer could show blood toxicity by interacting with the red blood cells. In contrast, 2D and 3D copolymers showed relatively low hemolysis at concentrations of 0.625−5 mg/mL (2D copolymer: 0.625 mg/mL, 3.2 ± 0.4%; 1.25 mg/mL, 5.9 ± 0.3%; 2.5 mg/mL, 7.3 ± 0.2%; and 5.0 mg/mL, 11.6 ± 0.4%; 3D copolymer: 0.625 mg/mL, 4.5 ± 0.2%; 1.25 mg/mL, 5.4 ± 0.5%; 2.5 mg/mL, 4.5 ± 0.5%; and 5.0 mg/mL, 6.7 ± 0.4%). In particular, the hemolysis of the 3D copolymer was <10% even at a high concentration of S
mg/mL. These high blood compatibilities could be attributed to the balance of biocompatible units of MAAc, METAC, and MAAmBO. Next, the hemolysis of the cross-linked PVA films was investigated. Figure 5D,E shows the hemolysis data for the PVA/1D and PVA/3D films. The degree of hemolysis of the PVA/1D film increased slightly with an increase in the 1D copolymer content (PVA/1D_25 wt %, 3.9 ± 1.1%; PVA/1D_50 wt %, 6.1 ± 2.9% (p < 0.05)). The increase in hemolysis was in agreement with the corresponding results for the 1D copolymer. For PVA/3D films, the degree of hemolysis was similar to that of the negative control (PVA/3D_25 wt %, −1.0 ± 1.7%; PVA/3D_50 wt %, −0.1 ± 1.5%). These results showed that the cross-linked PVA/1D and PVA/3D films had high blood compatibility.

3. CONCLUSIONS

Simple fabrication of water-insoluble cationic PVA films was accomplished using a mixed aqueous solution of PVA and poly(METAC-co-MAAc-co-MAAmBO) copolymers (3D). The poly(MAAc) (1D), poly(METAC-co-MAAc) (2D), and 3D copolymers were polymerized via free radical polymerization. METAC with a quaternary ammonium cation was selected to add a positive charge to the PVA film. The MAAc and MAAmBO units were used as the two types of cross-linking structures with covalent bonding (hydroxy and carboxy groups via thermal cross-linking) and dynamic covalent bonding (dial and benzoazaborole groups), respectively. FT-IR measurements showed that all films exhibited blue shifts due to the hydrogen-bonding interactions between PVA and the carboxy groups of the copolymers, and the value of the shift increased with increasing copolymer contents. All films were thermally cross-linked at 135 °C for 4 h, and the PVA/3D films retained almost 100% of their weights after immersion in surplus water at 80 °C for 3 h. The ζ-potential of the water-insoluble PVA/3D film was 9.4 ± 0.8 mV, which was strongly dyed by an anionic ARI molecule because of the positively charged surface. Interestingly, the PVA/3D film was also slightly dyed by cationic MB. These results suggested that positive and negative charges coexisted on the PVA/3D film. The negative charges were attributed to the presence of the PVA, MAAc, and MAAmBO units. Moreover, the PVA/3D films showed high blood compatibilities. These water-insoluble PVA films with a positively charged surface could be applied to sensors, adsorption systems, and antimicrobial dressing materials.

4. EXPERIMENTAL PROCEDURES

4.1. Materials. 5-Methacrylamido-1,2-benzoxaborole (MAAmBO) was synthesized and purified according to the previous protocol.53,64 Metacrylic acid (MAAc) was purchased from Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan) and purified by passing through a basic alumina column. Poly(vinyl alcohol) (PVA, M_w 89,000–98,000 g/mol, >99% hydrolyzed) and [2-(methacryloxy)ethyl]trimethylammonium chloride (METAC) solution (75 wt % in H2O) were purchased from Sigma–Aldrich (MO) and were used as received. All other chemicals and solvents were used as received.

4.2. Preparation of Poly(MAAc) (1D), Poly(METAC-co-MAAc) (2D), and Poly(METAC-co-MAAc-co-MAAmBO) (3D). Free radical polymerization was employed to synthesize poly(MAAc) (1D), poly(METAC-co-MAAc) (2D), and poly(METAC-co-MAAc-co-MAAmBO) (3D). The synthesis method of poly(MAAc) is shown below. Briefly, MAAc (3.44 g, 40.0 mmol) and 2,2′-azobis(isobutyronitrile) (AIBN) (32.8 mg, 0.00 × 10⁻² mmol) ([MAAc]_0/[AIBN]_0 = 200/1) were dissolved in 15 mL of N,N-dimethylformamide (DMF). After degassing with nitrogen gas for 30 min, the solution was polymerized for 20 h at 70 °C. The resulting 1D copolymer was purified by dialysis, first against ethanol/water (1/1 v/v) and then water, and was dried by lyophilization. The 1D copolymer was obtained as a white powder with 81% yield. Copolymers of 2D and 3D were synthesized by a similar protocol to the 1D copolymer. As the synthesis method of 2D, METAC (4.15 g, 15.0 mmol), MAAc (1.29 g, 15.0 mmol), and AIBN (24.6 mg, 1.50 × 10⁻² mmol) ([METAC]_0/[MAAc]_0/[MAAmBO]_0/[AIBN]_0 = 100/100/100/1) were dissolved in 15 mL of DMF. After degassing with nitrogen gas for 30 min, the solution was polymerized for 20 h at 70 °C. The resulting 2D polymer was purified by dialysis, first against ethanol/water (1/1 v/v) and then water, and was dried by lyophilization. The 2D polymer was obtained as a light brown powder in 67% yield.

4.3. Preparation of Thermally Cross-Linked PVA/1D, PVA/2D, and PVA/3D Films. The total weight of PVA and 1D (or 2D, 3D) copolymer was 300 mg. In the PVA/1D films, each polymer was separately dissolved in water. For example, 270 mg of PVA and 30 mg of 1D copolymer (10 wt %) were dissolved in 4 and 1 mL of water, respectively. Then, the two polymeric solutions were mixed. Mixture solutions of PVA and 1D copolymer at different compositions with 25, 50, and 75 wt % 1D copolymer were prepared using the same protocol. Mixture solutions of PVA and 2D (or 3D) copolymer were also prepared at different compositions. Because of the different solubility of 2D and 3D copolymers to water, the total amounts of water were changed (2D copolymer: 10 wt % (5 mL), 25 wt % (5 mL), 50 wt % (10 mL), and 75 wt % (10 mL); 3D copolymer: 10 wt % (5 mL), 25 wt % (5 mL), 50 wt % (8 mL), and 75 wt % (8 mL)). The ζ-potential of the water-insoluble solution of the 3D copolymer shifted to acidic conditions. For example, the ζ-potential of the 10 wt % 3D aqueous solution was 3.9. Each mixed solution was placed to a plastic dish and was dried in a 40 °C oven (1 day) and under reduced pressure (1 day). All films were thermally cross-linked in a 135 °C oven for 4 h. Films consisting of only PVA were also prepared as the control films using the same thermal cross-linking method.

4.4. Stability Tests in Water at 80 °C of PVA/1D, PVA/2D, and PVA/3D Films before/after Thermal Cross-Linking. PVA/1D, PVA/2D, and PVA/3D films having different compositions before/after thermal cross-linking were immersed for stability tests in water at 80 °C. Films were cut (around 5 mm²) as a square sample and were added to a large amount of water (1.5 mL). After immersion in water at 80 °C for 3 h, all films were washed with water and dried under reduced pressure. Polymeric films were measured using three different samples. The residual weights were calculated using the following numerical expression: (dry weight after...
immersion/dry weight before immersion) × 100. The swelling ratios were calculated using the following numerical expression: (area of the swollen film after immersion (mm²)/area of the dry film before immersion (mm²)) × 100. The water contents were calculated using the following numerical expression: (water weight of the film after immersion/dry weight of the film before immersion) × 100.

4.5. Hemolysis Tests. Hemolysis tests of the 1D, 2D, and 3D copolymers were performed by monitoring hemoglobin leakage from rabbit red blood cells (RBCs) using an Infinite M1000-SSY microplate reader (Tecan Japan Co., Kanagawa, Japan).65,66 First, 1.5 mL of rabbit RBCs were washed with 10 mL of phosphate-buffered saline (PBS) and concentrated by centrifugation at 1000 rpm for 5 min. The concentrated RBCs were redispersed in 30 mL of PBS to a final concentration of 5%. Each 1D, 2D, and 3D copolymer was dissolved in PBS at different concentrations (10, 5, 2.5, and 1.25 mg/mL). The solutions of the polymer (2 mL) and RBCs (2 mL) were mixed, and the suspension was incubated at 37 °C for 1 h. After incubation, the suspension was centrifuged at 3000 rpm for 5 min, and 200 μL of supernatant fluid was transferred to a 96-well microplate. Hemoglobin release was measured at 540 nm using a microplate reader. All samples were analyzed thrice in the hemolysis test. The RBCs in PBS were used as a negative control. As a positive control (100% hemolysis), RBCs were treated with 0.2 wt % (final concentration) Triton-X. The percentage of hemolysis was calculated using the following formula:

\[
\text{hemolysis (percent)} = \left( \frac{\text{OD of sample} - \text{OD of negative control}}{\text{OD of positive control} - \text{OD of negative control}} \right) \times 100
\]

Hemolysis tests of the PVA/1D_25 wt %, PVA/1D_50 wt %, PVA/3D_25 wt %, and PVA/3D_50 wt % films were also performed by monitoring the leakage of hemoglobin from rabbit RBCs. First, all films were immersed overnight in PBS and cut to obtain three circles (~14 mm) each sample. The circular samples of the films were placed in a 24-well microplate. Then, 200 μL of washed RBCs (in 5% PBS) and 200 μL of PBS were added to each sample. As a negative control, 200 μL of RBCs in PBS and 200 μL of PBS were added to a 24-well microplate. As a positive control (100% hemolysis), 200 μL of RBCs in PBS and 200 μL of Triton-X (0.4 wt % in PBS) were used. The RBCs on the film samples were incubated at 25 °C for 1 h. After incubation, 1600 μL of PBS was added to wash the surfaces. The suspension was centrifuged at 3000 rpm for 5 min, and 150 μL of supernatant fluid was transferred to a 96-well microplate. Hemoglobin release was measured at 540 nm using a microplate reader. The percentage of hemolysis was calculated using the same formula as that used for the aqueous copolymer solutions.

4.6. Characterizations. 1H NMR spectra of copolymers were recorded with a JNM-GSX300 spectrometer operating at 300 MHz (JEOL, Tokyo, Japan) to confirm successful synthesis and determine the chemical composition of the synthesized copolymers. The 1H NMR spectra of the 3D copolymer were measured using D_{2}O with 0.01 N NaOD to increase the solubility of MAAmBO units.

Molecular weights and polydispersities of the synthesized copolymers were determined by gel permeation chromatography (GPC) at 40 °C (0.2M phosphate buffer at pH 8, 0.7 mL/min) with Shodex SB-802.5 HQ and Shodex SB-804 HQ columns (Showa Denko K. K., Tokyo, Japan) and connected to a RID-20A refractive index detector (Shimadzu Co., Kyoto, Japan). Poly(ethylene oxide)/poly(ethylene glycol) was used as the standard sample to make the calibration curve. The MAAmBO groups of the 3D copolymer were covered with 1,4-butanediol.23

Infrared spectra were recorded using Fourier transform infrared (FT-IR) spectroscopy (FT-IR-6100, JASCO Co., Tokyo, Japan) with attenuated total reflectance mode (ATR). A range of wavenumber from 4000 to 650 cm⁻¹ and accumulation of 128 scans were used for each sample. The thermal properties of the polymeric films were measured using differential scanning calorimetry (DSC; DSC-60Plus, Shimadzu Co., Kyoto, Japan). Each sample was analyzed at a heating rate of 10 °C/min. The second scan results were used as the thermal properties. The degree of crystallization (\(\chi_c\)) of PVA and PVA/copolymers films was calculated using the following formula:

\[
\chi_c(\%) = \left( \frac{\Delta H_m}{\Delta H_m^0} \right) \times (\text{film weight} / \text{PVA weight in the film}) \times 100
\]

where \(\Delta H_m^0 = 138.6 \text{ J/g}\) is the melting enthalpy in the case of 100% of PVA crystal.44,45

Thermogravimetric analysis (TGA) was carried out using a TG-DTA2020S/MS (Bruker, MA) analyzer between 25 and 350 °C in N_{2} at a heating rate of 10 °C/min. The temperature of 10% weight loss (\(T_{d10\%}\)) was calculated from the TGA result.

The \(\zeta\)-potential was measured using an Electro Phonetic Light Scattering ELS-6000 (Otsuka Electronics Co., Ltd., Osaka, Japan). All films were kept at the given temperatures to reach the equilibrium prior to measurements.

Contact angles (CAs) were measured by a CA measuring instrument (Shimadzu Co., Kyoto, Japan) at room temperature using a 2 μL water drop. Dry films and their swollen films were measured. The swollen films were prepared via water immersion of dry films for 20 h. The CAs were measured after 5 s of contacting the films at three different places.

The mechanical properties of the polymeric films were measured using a tensile testing machine AG-X plus 50 kN (Shimadzu Co., Kyoto, Japan). All films were prepared as the sample of a 0.5 cm × 5 cm film. The tensile speed was 10 mm/min. Films were measured using three different samples.

4.7. Statistical Analysis. All data were presented as mean ± standard deviation (SD).

ASSOCIATED CONTENT

+ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c02013.

Synthesis of 1D, 2D, and 3D copolymers; GPC curves of copolymers; 1H NMR of copolymers; FT-IR spectra of films before and after thermal cross-linking; cloud point of the mixed aqueous solution of PVA and 1D copolymer; and strains of films before and after thermal cross-linking (Figures S1–S7) (PDF)
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Notes
The authors declare no competing financial interest.

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