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Development of photocrosslinked polyacrylic acid hydrogel as an adhesive for dermatological patches: Involvement of formulation factors in physical properties and pharmacological effects

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Abstract

Photocrosslinked polyacrylic acid hydrogel is a promising candidate adhesive for dermatological patches. In this study, we investigated the effects of the composition and molecular weight of the polymer on the characteristics of the hydrogel. Several photocrosslinkable polymers with different photocrosslinkable moieties or molecular weights were prepared, and various physical properties were measured. Differences in photocrosslinkable modifications markedly affected the swelling behavior of the hydrogel. The molecular weight of the polymer had a significant effect on various physical properties, such as the viscosity of the polymer solution, gel formation, and the swelling behavior of the prepared hydrogels. The pharmacological effects of the hydrogel were also evaluated using carrageenan-induced edema in rats. Application of the hydrogels maintained the skin surface at a reduced temperature throughout the experimental period, and the cooling effect was accompanied by an anti-inflammatory response. Because we can freely control the physical properties of the hydrogel and anticipate the significant pharmacological effects, photocrosslinked polyacrylic acid hydrogel is an attractive candidate adhesive for dermatological patches.
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Keywords: Photopolymerization; Polyacrylic acid; Hydrogel; Dermatological patch adhesive

1. Introduction

Hydrogels are formed by three-dimensional polymer networks in the aqueous phase. They can retain a large amount of water while maintaining their mechanical strength. Today, numerous hydrogels are used in pharmaceuticals, especially as adhesives for dermatological patches, such as cataplasm, which is used for local inflammation and wound dressing. Most of the hydrogels used as adhesives for dermatological patches are composed of polyacrylic acid (PAA) and its salts, and chemical crosslinking is used to increase their mechanical strengths. This chemical crosslinking is achieved by the formation of ionic interactions between the carboxyl groups of the polymer and polyvalent cations such as calcium, copper, and aluminum. Although chemical crosslinking methods are very popular for this purpose, plenty of room for improvement still exists. For instance, this crosslinking is affected by changes in the surrounding aqueous phase, such as changes in pH, temperature, or polymer concentration, because the ionic bond is weak and unstable by nature. Appropriate characteristics, such as rigid gel strength, high water capacity, and sufficient adhesiveness, are required for the hydrogel to act as an adhesive for dermatological patches. However, adjusting all of the characteristics to the appropriate levels with the conventional method is difficult.

To overcome the shortcomings of the conventional method, we investigated the application of photopolymerization to the preparation of hydrogels. Photopolymerization, which is triggered by light irradiation, has recently been gaining great attention in medical fields, because it allows the rapid conversion of a monomer or macromer solution to a gel or solid under physiological conditions. Various hydrogels for use in drug delivery systems have been prepared with this technique using mono-, di-, or multifunctional vinylated monomers or macromers, such as 2-hydroxyethyl methacrylate (HEMA) (Atkins et al., 1995; Lyman et al., 1996; Lu and Anseth, 1999), poly(ethylene glycol) dimethacrylate (Hill-West et al., 1994; Cruise et al., 1999; Elisseeff et al., 2000; Bryant and Anseth, 2001), poly(ethylene

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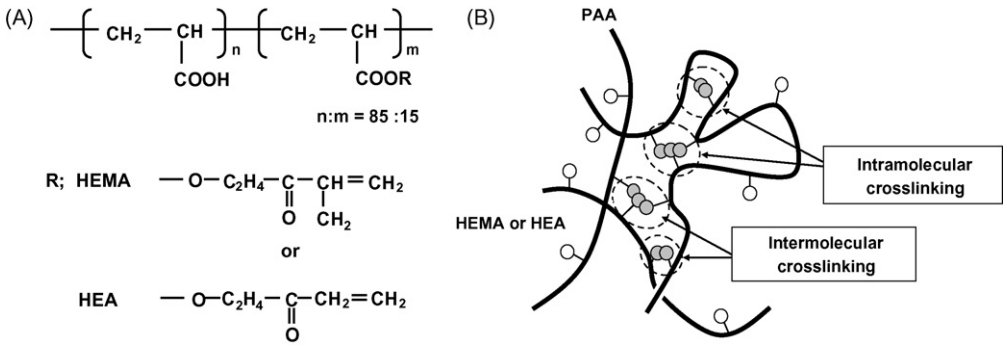

Fig. 1. Photocrosslinkable PAA and photocrosslinked PAA hydrogel. (A) Chemical structure of photocrosslinkable PAA. The HEMA or HEA photoreactive moiety was introduced into PAA of different molecular weights (5000, 250,000, or 1,000,000) at 15 mol% of the total carboxyl groups of the polymer. (B) The photopolymerization mechanism caused the formation of crosslinked PAA networks via the intermolecular and intramolecular crosslinking of HEMA or HEA in the PAA molecules.

glycol) diacrylate (Burdick and Anseth, 2002), methacrylated sebacic acid (Burdick et al., 2001), chitosan-introduced azide and lactose moieties (Ono et al., 2000; Obara et al., 2003), and styrenated gelatin (Matsuda, 2002; Nakayama et al., 2001; Okino et al., 2002). In a previous study, we synthesized a new photocrosslinkable polymer, PAA modified with HEMA (PAA–HEMA), and succeeded in making a photocrosslinked PAA–HEMA hydrogel (Onuki et al., 2005). Because the gel is formed by covalently crosslinking the HEMA in the polymer (Fig. 1), it is expected that this hydrogel is much more stable to the changes in the surrounding aqueous phase compared to the conventional hydrogel. In addition, the hydrogel can retain larger amounts of water when its crosslink density is reduced. According to preliminary experiments, the water concentrations of typical commercial products were approximately 75% (data not shown). By contrast, this hydrogel is capable of retaining over 85% water (Onuki et al., 2005). This is a great advantage for its use in dermatological patches, because the water contained in the hydrogel is intimately related to its cooling effect. Furthermore, the characteristics of the prepared hydrogel can be controlled by manipulating the preparation conditions. We have already clarified the effects of several formulation factors on the characteristics of the hydrogel (Onuki et al., 2005). These include the polymer concentration in the aqueous phase, the degree of modification with HEMA, and the initiator concentration. We assume that other factors also exert significant influence on the characteristics of the hydrogel. Clarifying the relationships between these factors and the hydrogel characteristics will provide us with profound insights and facilitate the design of specific formulations.

In this study, we focused on the effects of the composition and molecular weight of the polymer on the characteristics of the hydrogel. Several photocrosslinkable polymers with different photocrosslinkable moieties or molecular weights were prepared (Fig. 1), and various characteristics of the reaction solutions and prepared hydrogels were measured. We also evaluated the cooling effects and anti-inflammatory effects of the hydrogels using a carrageenan-induced rat paw edema model.

2. Materials and methods

2.1. Materials

PAA (molecular weights 5000, 250,000, and 1,000,000), 2-hydroxyethyl acrylate (HEA), and 2,2-dimethoxy-2-phenylacetophenone (DMPA) were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). HEMA, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDAC), and lambda-carrageenan were purchased from Sigma–Aldrich Co., Ltd. (St. Louis, MO, USA). All other reagents were of chemical grade.

2.2. Synthesis of photocrosslinkable polymers

PAA–HEMA and PAA–HEA were synthesized according to the method described previously (Onuki et al., 2005). In brief, after the elimination of the inhibitor by filtration, 7.22 g of HEMA or 6.45 g of HEA was added to 2.00 g of PAA dissolved in purified water, and the mixture was stirred. EDAC (0.80 g) dissolved in purified water was added to the mixture, which was then stirred for 4 h at room temperature to complete the reaction. The reaction mixture was dialyzed five times in the dark against purified water using a seamless cellulose tube (size 36; Union Carbide Co., Ltd., Houston, TX, USA). The pH of the solutions was adjusted to pH 4.5 by the addition of 5 M NaOH solution as required. The solution was lyophilized using a freeze-dryer (FD-1; Tokyo Rikakikai Co., Ltd., Tokyo, Japan) under reduced pressure. A white cotton-like substance was obtained. The degree of modification with HEMA or HEA was fixed at 15 mol%. Neutralization titration was performed to confirm the modifications with HEMA and HEA. In brief, after the dialysis of the reaction mixture of PAA and HEMA or HEA, the solution was lyophilized without adjustment of the pH. After the obtained polymer was dissolved in purified water (the concentration of polymer was fixed at 0.4%), phenolphthalein was added to the polymer solution as an indicator; this solution was neutralized using an aqueous solution of 0.1 M NaOH. The result confirmed that equimolar amounts of HEMA and HEA were introduced into the PAA (data not shown).

2.3. Preparation of photocrosslinked hydrogels

The designated amounts of photocrosslinkable PAA were dissolved in phosphate-buffered saline (pH 7.4). DMPA dissolved in ethanol was then added to the aqueous solution as the initiator. The amount of DMPA was fixed at 1.0% relative to the polymer weight, except in specified instances. UV irradiation was then applied using a UV curing system (Aicure ANUP5204; Matsushita Electric Works, Ltd., Tokyo, Japan). The wavelength of the illumination ranged from 200 to 400 nm, and the irradiation time was 5 min. The light intensity at 365 nm was 28 mW cm^{-2}, as measured with a photometer (UIT-150; Ushio Inc., Tokyo, Japan).

2.4. Gel fraction and degree of swelling

The gel fraction and degree of swelling were measured according to a previous report (Onuki et al., 2005). Photocrosslinked PAA hydrogels of 0.5 g (weight of the solid content, W_{solid}) on a polystyrene disk were equilibrated in 60 mL of purified water for 24 h at room temperature and then weighed after the excess water was carefully removed (W_{water}). After the elimination of water by freeze-drying, the remaining solid was weighed (W_{gel}).

The gel fraction (%) was calculated as:

$$\text{Gel fraction}\,(\%) = \frac{W_{gel}}{W_{solid}} \times 100.$$

The degree of swelling was calculated as:

$$\text{Degree of swelling} = \frac{W_{water}}{W_{gel}}.$$

2.5. Rheological characteristics of the reaction solution

The rheological behavior of the reaction solution was measured with a viscometer (TV-30; Toki Sangyo Co. Ltd., Tokyo, Japan). Measurements were made at 25 ± 0.1 °C. Aqueous solutions (10%) of each polymer were used as the samples. The samples were carefully applied to the lower plate, and equilibrated in the viscometer for 3 min. Continuous shear analysis was then performed. The shear rate increased continuously from 0.38 to 114.9 s^{-1}. The duration at each measurement point was set at 1 min. The viscosity values were calculated from the slope of the shear stress/shear rate data for each sample.

2.6. Probe tack

Photocrosslinked hydrogel seats were prepared using the same method, with backing layers of a nonwoven fabric. The thickness of the hydrogel was 1 mm. The probe tack was then measured with a Probe Tack tester (5 mm diameter orifice, 1 cm s^{-1}; Rigaku Kogyo Co., Ltd., Tokyo, Japan) at 25 °C.

2.7. Pharmacological effects of hydrogels

The animal experiments in this study complied with the regulations of the Committee on Ethics in the Care and Use of Laboratory Animals at Hoshi University. Male Wistar rats weighing 180–200 g were purchased from Sankyo Labo Service Co., Inc. (Tokyo, Japan). The animals were housed under conditions of controlled temperature (23 ± 1 °C) and relative humidity (55 ± 5%), and were allowed free access to water and food during acclimatization. Carrageenan-induced rat paw edema was established according to previous reports (Shin et al., 2000; Arora and Mukherjee, 2002; Hendradi et al., 2003). In brief, after anesthetization with an intraperitoneal injection of sodium pentobarbital (50 mg kg^{-1}; Dainippon Pharmaceutical Co., Ltd., Osaka, Japan), the rats were restrained in a supine position on a thermostatically controlled board at 37 °C. Hind-paw edema was induced by injecting 0.1 mL of a homogeneous suspension of 1% (w/v) carrageenan in saline. After the injection of carrageenan, hydrogel patches were immediately applied to the hind paws. These hydrogel patches were backed with nonwoven fabric, and the concentration of the polymer contained in each sample of hydrogel was fixed at 0.05 g cm^{-2}. In the control group, the region of hind-paw edema was covered with nonwoven fabric without hydrogel. The thickness and skin surface temperatures of the hind paws were measured at designated intervals using a micrometer caliper and a noncontact thermometer (Thermofocus; Tecnimed Srl., Varese, Italy), respectively. The degree of edema was expressed as a percentage relative to the hind-paw thickness before the injection of carrageenan.

3. Results and discussion

3.1. Effects of the composition and molecular weight of the polymer on gel characteristics

The properties of PAA are markedly affected by changes in its composition. In this study, we prepared PAA–HEMA and PAA–HEA (Fig. 1), and then investigated the effects of the polymer composition. Unlike the HEMA moiety, the HEA moiety does not have a methyl group at the end of the double bond. Because the methyl group is regarded as an obstacle to photopolymerization, a more efficient reaction should occur when PAA–HEA is used as the base polymer. The characteristics of the hydrogel that we initially measured were the gel fraction and degree of swelling. These are usually used in evaluating the functions of hydrogels (Okino et al., 2002; Coughlan and Corrigan, 2006; Zhang and Zhuo, 1999; Okano et al., 1990; Onuki et al., 2005). The gel fraction represents the degree of conversion to hydrogel. As described in Section 2, after the hydrogel was swollen, excess amounts of water were eliminated. At the same time, polymers that were not involved in gel formation were removed with the water. Therefore, the value of the gel fraction decreases with a decrease in gel formation. The degree of swelling is affected by numerous factors, such as crosslink density, entanglement of the polymer chains, and the hydrophilicity of the polymer. In general, because a solid hydrogel is less swellable in water, we can estimate the mechanical strength of the hydrogel from the degree of swelling. Fig. 2 shows the changes in the gel fraction as a function of the initiator concentration. At less than 0.01% initiator relative to the polymer weight, no hydrogel was formed because the gel frac-

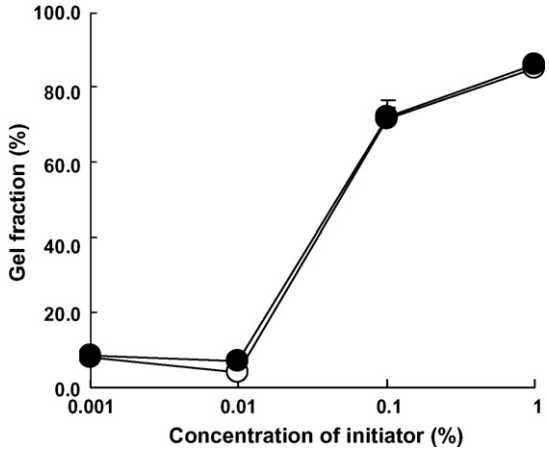

Fig. 2. Gel fraction of the photocrosslinked hydrogel as a function of initiator concentration. The water concentrations of the hydrogels were fixed at 85%. PAA–HEMA (●) and PAA–HEA (◯). Each value represents the mean ± S.D. ($n = 3$).

tion values were very low. By contrast, at above 0.1% initiator, homogeneous hydrogel was prepared and the gel fraction values increased with increasing initiator concentrations. However, there was no difference in the behaviors of the gel fractions of the PAA–HEMA and PAA–HEA hydrogels. Conversely, the polymer composition exerted a significant effect on the degree of swelling, and the values for the PAA–HEA hydrogel were much higher than those for the PAA–HEMA hydrogel (Fig. 3). Since both hydrogels are identical in terms of gel conversion behavior (Fig. 2), it is probably attributed to the hydrophilicity of the polymers rather than to the crosslink density. Because PAA–HEA is a more water-miscible polymer than PAA–HEMA, the PAA–HEA hydrogel interacted with larger amounts of water, resulting in a more swellable hydrogel. Although the degrees of swelling were different, both hydrogels reached a certain limit of swelling, while a commercial product generated by chemical crosslinking swelled infinitely and ultimately became a homogeneous solution (data not shown). This implies that the mechanical strength of photocrosslinked PAA hydrogels is higher than that of the conventional hydrogel. Probe tack measurements were then made (Table 1). Probe tack values represent the adhesiveness of the hydrogels. In a preliminary experiment, the probe tack values of typical commercial products were approximately 200 mN/5 mm Φ, at best (data not shown). In contrast, the probe tack values of the PAA–HEMA and PAA–HEA hydrogels were much higher, at 461.8 ± 71.7 and 371.2 ± 97.9 mN/5 mm Φ, respectively, suggesting that their adhesive properties are superior to those of commercial products. Based on their probe tack values, there was no significant difference in the adhesiveness of the PAA–HEMA and PAA–HEA hydrogels. These results indicated that PAA–HEMA and PAA–HEA hydrogels have great potential as an adhesive for dermatological patch, and their performances are almost the same. So, we conducted the following experiments using PAA–HEMA hydrogel.

Table 1
Probe tack of the PAA–HEMA and PAA–HEA hydrogel

Hydrogel	Probe tack (mN/5 mm Φ)
PAA–HEMA	461.8 ± 71.7
PAA–HEA	371.2 ± 97.9

The water concentration of the hydrogels was fixed at 85%. Each value represents the mean ± S.D. ($n = 8$).

The molecular weight of the polymer is likely to be a crucial factor in the formulation of hydrogel. The entanglement of the polymer chains, which is an important phenomenon in polymer science, depends on the molecular weight of the polymer (Flory, 1953). As the molecular weight of the polymer becomes large, the polymer chains become more tightly entangled with other polymer chains. We assumed that the molecular weight of the polymer would affect various hydrogel characteristics. Fig. 4 shows rheograms of 10% aqueous solutions of photocrosslinkable polymers. It is well known that the viscosity of a polymer solution increases as the molecular weight of the polymer increases (Martin et al., 1970). As we anticipated, the viscosity increased markedly with increases in the molecular weight of the

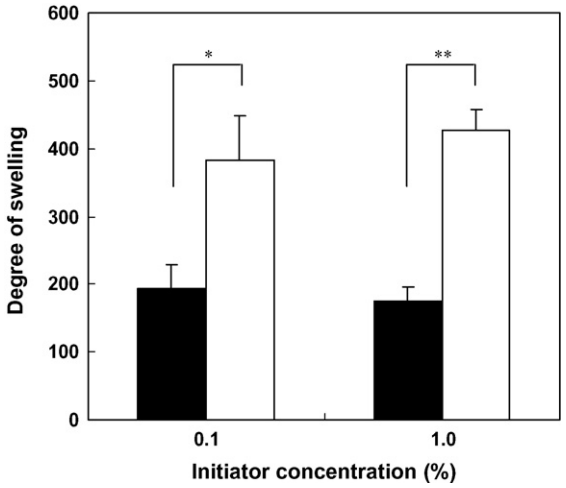

Fig. 3. Comparison of the degree of swelling of the PAA–HEMA hydrogel (■) and the PAA–HEA hydrogel (□). The water concentrations of the hydrogels were fixed at 85%. Each value represents the mean ± S.D. ($n = 3$). $^{*}P < 0.05$, $^{**}P < 0.01$.

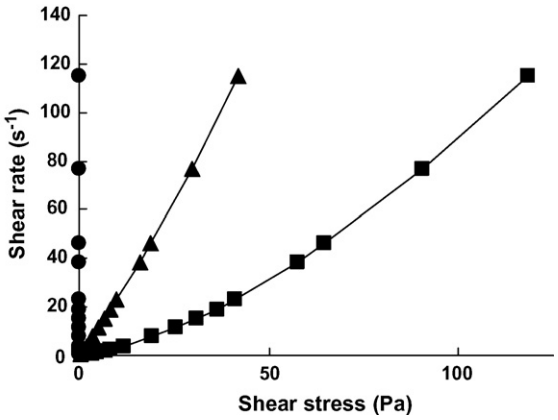

Fig. 4. Shear viscosity of PAA–HEMA aqueous solutions. PAA–HEMAs were composed of PAA of various molecular weights: 5000 (●), 250,000 (▲), or 1,000,000 (■). The polymer concentrations of the aqueous solutions were fixed at 10%.

Table 2
Gel fraction and degree of swelling of the PAA–HEMA hydrogel composed of PAA of different molecular weights

Molecular weight of PAA	Gel fraction (%)	Degree of swelling
5×10^3	0.5 ± 0.2	ND[a]
2.5×10^5	66.4 ± 1.4	734.7 ± 52.2
1.0×10^6	66.8 ± 0.8	567.6 ± 54.0[**]

Water concentration of hydrogels was fixed at 90%. Each value represents the mean ± S.D. ($n = 4$).
[a] Undetectable.
[**] $P < 0.01$ vs. hydrogel made from 2.5×10^5 PAA.

polymer. A wide range of viscosities was observed: 0.17, 41.75, and 118.19 Pa s, at a rate of 114.9 s^{-1}. The viscosity of a reaction solution is a very important characteristic when manufacturing processes are considered. For the easy preparation of hydrogel patches, the viscosity should be adjusted to an appropriate level, which is neither too low nor too high. We confirmed that the viscosity of the reaction solution can be readily controlled by changing the molecular weight of the polymer. The physical properties of the prepared hydrogels were then measured (Table 2). The water concentration of the hydrogels was fixed at 90%. The low-molecular-weight polymer solution (molecular weight of PAA was 5000) became thick with UV irradiation, but it did not form a gel. For hydrogel conversion, the appropriate degrees of crosslinking and entanglement of the polymer chains are required. The low-molecular-weight polymer became negligibly entangled with other polymer chains, and no polymer networks firm enough to generate a hydrogel were formed. Conversely, higher-molecular-weight polymer solutions (molecular weights of PAA were 250,000 or 1,000,000) were successfully converted to hydrogels. However, the prepared hydrogels were distinguishable in terms of their swelling behavior. Whereas their gel fraction values were almost the same (approximately 66%), values for the degree of swelling decreased significantly with increases in the molecular weight of PAA (Table 2), probably because the hydrogels differed in the degree of entanglement of their polymer chains. Entanglement restricts the range of movement of the polymer chains and makes the hydrogel resistant to swelling. Thus, when the polymer chains become tightly entangled with the increasing molecular weight of the polymer, the hydrogel becomes increasingly resistant to swelling.

We confirmed the effects of the composition and molecular weight of the photocrosslinkable polymer on the characteristics of the reaction solution and of the prepared hydrogel. Each formulation factor dramatically affected the response variables in various ways. Therefore, this method allows plenty of room to control the hydrogel characteristics. Although we are often faced with various difficulties and restrictions when developing new pharmaceuticals, evidence so gained can provide profound insights.

3.2. Pharmacological effects of the PAA–HEMA hydrogel

To investigate the pharmacological effects of the hydrogel, we conducted animal experiments using carrageenan-induced edema in rats. The water concentrations of the hydrogels were fixed at 80, 85, or 90%. Fig. 5 shows the changes in the skin surface temperatures after the application of the hydrogels. The skin surface was maintained at a lower temperature than that of the control (nontreatment) group throughout the experimental period by the application of the hydrogels, and this cooling effect was prolonged with increases in the water content of the hydrogel (Fig. 5). The effect of hydrogel containing 90% water was particularly noticeable. It was still hydrated after the 6 h application period and a further cooling effect could be expected. Although differences in water content had no effect on the anti-inflammatory effect of the hydrogel, rat paw edema was significantly reduced by the application of the hydrogel (Fig. 6). Our results confirm that the strong cooling effect of the hydrogel was accompanied by an inhibition of rat paw edema.

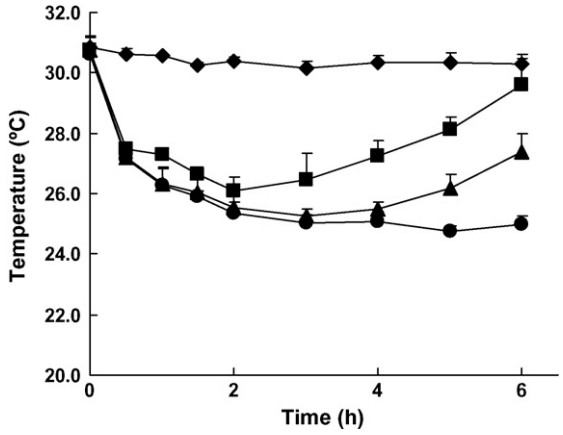

Fig. 5. Surface temperature of carrageenan-induced edema after application of photocrosslinked PAA–HEMA hydrogel with various water contents. Control (♦), water concentration of PAA–HEMA hydrogels: 80% (■), 85% (▲), or 90% (●). Each value represents the mean ± S.D. ($n = 3$ or 4).

The pathophysiology of soft tissue injury, including local inflammation, involves elevated cellular metabolism, hemorrhage, hyperemia, edema, and leukocyte recruitment. Lowering

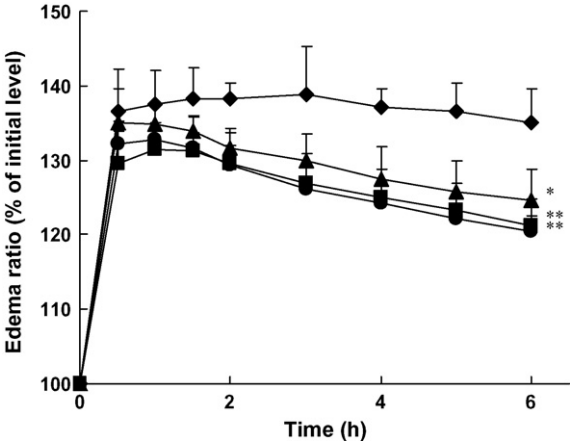

Fig. 6. Inhibition of carrageenan-induced edema after the application of photocrosslinked PAA–HEMA hydrogel with various water contents. Control (♦), water concentrations of PAA–HEMA hydrogels: 80% (■), 85% (▲), or 90% (●). Each value represents the mean ± S.D. ($n = 3$ or 4). [*] $P < 0.05$, [**] $P < 0.01$ vs. the control level at 6 h.

the skin temperature decreases the cutaneous blood supply and reduces the metabolic demands of the tissue (Thorlacius et al., 1998; Amon et al., 2003), thereby preventing edema. The cooling effect also deadens the pain that accompanies the injury. Hydrogels have significant capacity for lowering the temperature of the skin surface because they contain large amounts of water. To achieve a pharmacological effect, we try to incorporate as much water as possible into the hydrogel. However, the inclusion of excessive amounts of water contributes to a reduction in the mechanical strength of the hydrogel. Needless to say, proper adhesion properties are required if the hydrogel is to be used as an adhesive in dermatological patches (Venkatraman and Gale, 1998). As well as sufficient adhesiveness to the skin, the hydrogel must be removable from the skin surface without excessive irritation to the skin or any residue. In conventional hydrogels, the water content has been sacrificed to retain the mechanical strength. The photocrosslinked PAA hydrogel can contain a much larger amount of water, while maintaining adequate mechanical strength. If we try to make a water-rich hydrogel with the conventional method, the polymer solution will not change into hydrogel. We consider that photopolymerization is a sensible solution to the production of a hydrogel suitable for dermatological patches.

In conclusion, we have confirmed that the characteristics of the photocrosslinked PAA hydrogel can be easily controlled by manipulating the factors involved in its formulation, such as the composition and molecular weight of the polymer. We also expect that it will have strong cooling and anti-inflammatory effects compared with those of conventional hydrogels. Thus, photocrosslinked PAA hydrogel is an attractive candidate adhesive for dermatological patches.

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