Polymer(Korea), Vol. 40, No. 4, pp. 628-634 (2016)
http://dx.doi.org/10.7317/pk.2016.40.4.628

ISSN 0379-153X(Print)
ISSN 2234-8077(Online)

새로운 가교제를 사용한 아크릴 하이드로젤 막의 합성과 약물 방출 특성

강동윤 · 권기완 · 정경혜* · 안성호** · 강인규†

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(2016년 2월 18일 접수, 2016년 3월 30일 수정, 2016년 3월 31일 채택)

Drug-Release Performance of Acrylic Hydrogel Membranes Synthesized Using a Novel Cross-linker

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(Received February 18, 2016; Revised March 30, 2016; Accepted March 31, 2016)

초록: 하이드로젤 콘택트렌즈는 약물 충전과 방출을 조절할 수 있는 형태이기에 안과 약물 전달 점안액의 대체재로 도입되었다. 이 논문에서는 polypropylene 몰드 안에서 새로운 가교제인 ethylaluminium diacrylate(EADA)와 methyl methacrylate(MMA), 2-hydroxyethyl methacrylate(HEMA), *N*-vinyl pyrrolidone(NVP)의 공중합을 통해 아크릴 하이드로젤 막을 제조하였다. 그리고 하이드로젤 막의 팽윤 거동과 기계적 물성을 조사하였다. 약물 방출 성능은 친수성 약물 timolol maleate와 사이크로텍스트린으로 포접한 소수성 약물인 α-tocopherol로 평가하였다. 또한 비교를 위하여 기존의 가교제인 ethylene glycol dimethacrylate(EGDMA)를 사용한 하이드로젤을 제조하였다. 실험결과 EADA 가교제로 제조한 하이드로젤 막의 인장강도(0.168 MPa)는 EGDMA로 제조한 하이드로젤 막의 인장강도(0.136 MPa)보다 훨씬 향상되었다. 0.1mol% EADA로 가교시켜 만든 하이드로젤 막은 30시간 후 66%의 α-tocopherol 약물방출을 나타낸 반면 0.1 mol% EGDMA로 가교시켜 만든 하이드로젤 막은 동일한 시간 동안에 42%의 약물방출을 나타내었다. 한편, 2일간의 섬유아세포 배양실험에서 EADA를 함유하는 하이드로젤 막은 EGDMA를 함유하는 하이드로젤 막보다 훨씬 우수한 생리활성을 나타내었다.

Abstract: Hydrogel soft contact lenses have been introduced as alternatives to eye drops for ophthalmic drug delivery, because of their controllable drug loading and release behavior. In this study, acrylic hydrogel membranes were prepared by copolymerization of the novel cross-linker, ethylaluminium diacrylate (EADA), with methyl methacrylate (MMA), 2-hydroxyethyl methacrylate (HEMA), and *N*-vinylpyrrolidone (NVP) in a polypropylene mold. The swelling behavior and mechanical properties of hydrogels containing the newly designed cross-linker were then investigated. Drug release performance was evaluated using a hydrophilic drug, timolol maleate, and a cyclodextrin inclusion complex of the hydrophobic drug, α-tocopherol. For comparison, hydrogels were also prepared using a conventional cross-linker, ethylene glycol dimethacrylate (EGDMA). As the results, tensile strength of the hydrogel membranes using EADA (0.168 MPa) was significantly improved compared to that of the hydrogels made with EGDMA (0.136 MPa). The hydrogel membrane cross-linked with 0.1 mol% EADA showed 66% α-tocopherol release after 30 h while the hydrogel membrane cross-linked with 0.1 mol% EGDMA showed 42% α-tocopherol release. After 2 days of incubation, human fibroblasts on the hydrogel membrane containing EADA showed significantly greater viability than those on EGDMA-containing hydrogel.

Keywords: hydrogel membrane, cross-linker, ethylaluminium diacrylate, cyclodextrin.

Introduction

More than 90% of eye diseases are treated using eye drops.[1] However, eye drop efficacy is limited by insufficient drug concentration and residence time.[2] Hydrogels are attractive materials among drug delivery carriers such as particles and films, because they facilitate controlled drug loading and residence time, as well as showing excellent wettability and biocompatibility characteristics.[3-6] For ophthalmic applications, hydro-

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gel soft contact lenses make good candidates as drug carriers, because of their high water content and large intermolecular pores, which allow sufficient loading and controlled release of hydrophilic drugs.[7] As a result of these advantageous properties, silicon hydrogel contact lenses are widely used to carry hydrophilic drugs.[8-11] Additional examples of ophthalmic drug delivery have been reported using hydrogel soft contact lenses made of acrylate copolymers, including drugs such as ketotifen fumarate, norfloxacin, and timolol maleate.[12-16]

Cross-linker chemistry is a critical determinant of hydrogel characteristics through its effects on water content and mechanical properties. For example, the cross-linker, glutaraldehyde, affects the water content of poly(vinyl alcohol) (PVA) hydrogels through modulation of chemical structure and hydroxyl group content.[17] Another example is hexamethylene diisocyanate cross-linking in PVA hydrogels, for which the molecular structure significantly affects mechanical properties, such as polymer chain flexibility and crystallinity.[18] In addition, physical cross-linking through ionic interactions and crystallization have also been reported as factors affecting hydrogel performance.[19]

For hydrogel soft contact lenses, cross-linking is also a crucial factor affecting drug release performance. A large number of studies have reported mainly covalent cross-linkers for hydrogel soft contact lenses. The most commonly used are methacrylic cross-linkers, such as ethylene glycol dimethacrylate (EGDMA).[12-14,20] In addition, *N*,*N*′-methylene-bis-acrylamide[21] and 2-methacryloyloxyethyl phosphorylcholine[22] have been evaluated as cross-linkers for drug delivery applications using hydrogel soft contact lenses.

This study focused on the preparation of hydrogels using a novel cross-linker, ethylaluminium diacrylate (EADA), which confers soft contact lenses with unique performance characteristics. For comparison, hydrogels were also synthesized using the conventional cross-linker, EGDMA. The performance of the two cross-linkers was compared by examination of mechanical properties, swelling ratios, optical transmittance, and drug release. Hydrogel membranes were loaded with representative hydrophilic and hydrophobic drugs to evaluate their potential as carriers for the delivery of various types of drugs.

Experimental

Materials. All materials required for the preparation of hydrogel soft contact lenses were purchased from Sigma-Aldrich, and were used after additional purification. The molds used for contact lens production were provided by EnvoyVision Corporation, Korea. The monomers used for hydrogel polymerization were 2-hydroxyethylmethacrylate (HEMA), *n*-vinyl-pyrrolidone (NVP), and methyl methacrylate (MMA). Azobisisobutyronitrile (AIBN) was used as a polymerization initiator, and ethylene glycol dimethacrylate (EGDMA) was used as a cross-linker. The novel cross-linker, ethylaluminium diacrylate (EADA), was chemically synthesized using ethylaluminium dichloride and acrylic acid. For drug release tests, a well-known medicine for glaucoma, timolol maleate, was chosen as a representative hydrophilic drug, while vitamin E (α-tocopherol), prepared as a β-cyclodextrin (β-CD) inclusion complex, was chosen as a representative hydrophobic drug (Sigma-Aldrich).

Synthesis of the Novel Cross-linker, EADA. The novel cross-linker, EADA, was synthesized using ethylaluminium dichloride and acrylic acid at a molar ratio of 1:2. Ethylaluminium dichloride was dissolved in hexane and the solution was purged with nitrogen for 10 min. Acrylic acid was added using a syringe. The mixture was stirred at 60 °C for 10 h. Subsequently, the mixture was sonicated, distilled water was added, and the product was separated from unreacted starting materials by centrifugation, and was then freeze-dried to obtain a white powder.

Analysis of the Cross-linker, EADA. The synthesis of EADA was confirmed through the identification of chemical bonds using Fourier transform infrared spectroscopy (FTIR), using a Spectrum GX spectrometer and AutoImage analysis software (PerkinElmer). Aluminium content was determined by the method of inductively coupled plasma spectroscopy (ICP), using an Optima 7300DV spectrophotometer (PerkinElmer). In addition, Baeyer's reagent was used to confirm the presence of unsaturated chemical bonds in EADA. The relative viscosity in mixtures of monomers and EADA cross-linker was monitored using an Ostwald viscometer, with the viscosity of distilled water at 25 °C as a calibration reference.

Synthesis of Hydrogel Membranes. Mixtures of AIBN, HEMA, NVP, MMA, and cross-linkers were stirred at a speed of 300 rpm for 3 h. Molds containing 0.05-0.1 mL of mixture were then incubated in an oven at 120 °C for 90 min to facilitate polymerization. The concentrations of initiator, monomers, and cross-linkers used in the polymerization mixtures are shown in Table 1.

Swelling Ratios and Mechanical Properties. Hydrogels were prepared using the new cross-linker, and water content (*w*) was measured by immersing the hydrogel membranes in

Table 1. Concentrations of Initiator, Monomers and Cross-linkers Used for Preparation of Hydrogels

Designation of sample \ Composition	HEMA (mol%)	AIBN (mol%)	NVP (mol%)	MMA (mol%)	EADA (mol%)	EGDMA (mol%)	Degree of swelling (%)
A	92.7	0.1	7	0.2	0	0	42.6
B	92.5	0.1	7	0.2	0.2	0	39.4
C	92.5	0.1	7	0.2	0	0.2	39.6
D	92.5	0.1	7	0.2	0.1	0.1	35.7
E	91.7	0.1	7	0.2	1	0	32.2

distilled water for 12 h. The swelling ratio was calculated using the formula w=[(m2-m1)/m1]×100 where m2 and m1 are the masses of the dry and hydrated membranes, respectively.

The mechanical properties of hydrogel membranes were measured in a universal testing machine (model 3343, Instron), using a 1 kgf load cell, at an extension speed of 10 mm/min. The test specimens were fabricated using Teflon molds measuring 1 cm in width and 6 cm in height. Average values of tensile strength, Young's modulus, and elongation at break were obtained from measurements using 10 specimens. Maximum and minimum values were excluded before calculation of the mean values.

Drug Release. Drug-loaded hydrogel soft contact lenses were prepared by the addition of drugs during hydrogel synthesis. Release of the drugs, timolol maleate and α-tocopherol, was determined by absorbance at wavelengths of 294 and 293 nm, respectively, using a UV-VIS spectrophotometer (JASCO V-650). Cumulative drug release was analyzed by quantitation of the absorbance peaks at multiple timepoints.

Cytotoxicity Assays. Cytotoxicity was tested using human dermal fibroblasts purchased from the Korean Cell Line Bank (CCD-986sk). The cells obtained at the passage number of 4-15 were used for the evaluation of cytotoxicity of the hydrogel membranes. For the preparation of cell culture media, Dulbecco's modified Eagle's medium, fetal bovine serum and penicillin G-streptomycin stock solutions, were obtained from GIBCO.

The cytotoxicity of hydrogel soft contact lenses was tested using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT) assay. Fibroblasts were cultured on hydrogel soft contact lenses in Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum and 1% penicillin G-streptomycin. The cultures were then incubated for 4 h with 50 μL of MTT solution, and the resulting dye was solubilized using 0.04 N HCl-isopropanol in the dark. The absorbance was measured at a wavelength of 570 nm using an EL×800 kinetic microplate reader (Bio-T® Instruments, Inc., Highland Park).

Results and Discussion

Analysis of Cross-linker Synthesis. The synthesis of EADA was confirmed using FTIR analysis to detect functional groups, including C=O, C-H, and C=C bonds. As shown in Figure 1, the expected peak for the C-H bond was found at a frequency of 2950 cm^{-1}, while the non-conjugated peak corresponding to C=C and C=O bond stretching was observed at frequencies of 1646 and 1710 cm^{-1}, respectively. In addition, C=O and C-O bonds corresponding to the carboxylate anion, showed strong peaks at frequencies of 1500 and 1450 cm^{-1}, respectively. The presence of Al was confirmed by ICP, thus demonstrating the successful chemical synthesis of EADA. The presence of a C=C bond in EADA was further confirmed using Baeyer's reagent. Unsaturated organic compounds react with potassium permanganate to produce a change in color from pink to brown. This method is widely used to confirm the

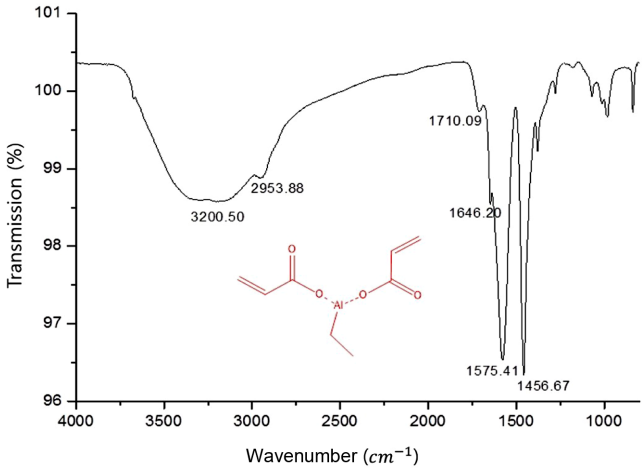

Figure 1. FTIR spectrum of the cross-linker, EADA.

Figure 2. Images of a 0.02 M $KMnO_4$ solution before (pink, left) and after (brown, right) added with 0.01 M EADA solution.

presence of vinyl groups in organic compounds because of its simplicity.[23] Figure 2 shows photographs of the EADA solution before and after adding potassium permanganate, illustrating the color change. Thus, Baeyer's reagent clearly confirmed the presence of a C=C bond after synthesis of EADA.

The functional effect of cross-linking on hydrogel polymers was tested by measuring the relative viscosity, using an Ostwald viscometer. The viscosity of the polymer synthesized using 0.1 mol% AIBN and 99 mol% HEMA, in the absence of EADA, showed a value of 350 cp, while it had a value of 4270 cp when 0.1 mol% EADA was added. Thus, EADA was an effective cross-linker, dramatically increasing the viscosity of the polymer solution.

Mechanical Properties. The effects of the two cross-linkers, EGDMA and EADA, on the mechanical properties of hydrogel soft contact lenses were investigated. As shown in Figure 3, the tensile properties of hydrogel soft contact lenses made using EADA were significantly improved compared to those of the hydrogel made with EGDMA. EADA forms both covalent and ionic bonds, while EGDMA provides only covalent bonds. Due to the strong ionic bonds, EADA creates stronger bridges between polymer chains, resulting in superior mechanical properties. Goda *et al*. reported a phosphorylcholine-based intermolecular cross-linker, which provides superior tensile strength compared to conventional cross-linkers because of its higher reactivity with monomers.[22] Cross-linker structure also affects polymer crystallinity, which

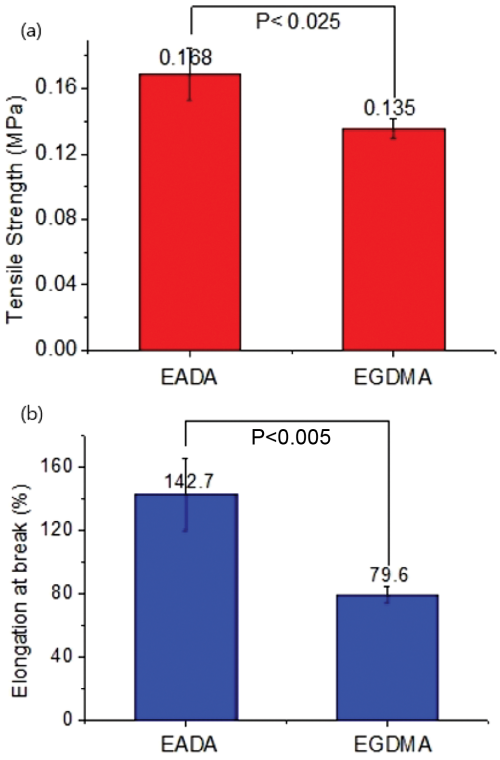

Figure 3. Mechanical properties of the hydrogel membranes made from two types of cross-linker: (a) tensile strength; (b) elongation at break.

can have pronounced effects on mechanical properties.[18,24-26] Therefore, it is worth studying both the effects of cross-linker type and concentration on hydrogel performance by varying the choices of cross-linker structure and reaction conditions.

Swelling Behavior. Swelling behavior is an essential characteristic of hydrogels because it profoundly affects drug loading and diffusivity in drug delivery applications. Swelling behavior is also crucial for user comfort while wearing contact lenses. The swelling ratios determined after soaking hydrogel soft contact lenses in water are summarized in Table 1. The highest swelling ratio, 42.6%, was observed for the hydrogel that had been fabricated without a cross-linker. The swelling ratio was found to decrease as the hydrogel cross-linker content was increased. In addition, no significant difference in the swelling ratios was observed for hydrogels synthesized using EADA or EGDMA. However, in the hydrogel cross-linked with a mixture of both EADA and EGDMA, the swelling ratio was found to be lower. The swelling behavior of hydrogels depends on hydrogen bonding between hydrogel polymer chains and water molecules, and can be strongly affected by cross-linker chemistry.[27] Thus, increased cross-linker reaction

time and concentration typically result in greater cross-linking density, and a decreased swelling ratio.[22,28-30] When two different types of cross-linkers are used simultaneously, this may result in hydrogels containing greater cross-linking density and lower water content.

Optical Transmittance. Figure 4 shows the effect of cross-linker content on transmittance in hydrogel soft contact lenses. Non-cross-linked hydrogel (Figure 4(A)) had low transmittance compared with transmittance in EADA (Figure 4(B), (D),(E)) and EGDMA (Figure 4(C)) hydrogels. Low transmittance would be an unsuitable property for contact lenses. In contrast, the hydrogels containing either of the two cross-linkers, EADA or EGDMA, showed optical transmittance greater than 90% in the visible range (400-800 nm). The type of cross-linker used has little if any effect on the optical properties of hydrogel soft contact lenses. However, there was a slight decrease in transmittance when the cross-linker concentration was greater than 1 mol% (Figure 4(E)), cautioning that cross-linker amounts need to be carefully controlled.

Drug Release. Hydrophilic Drug Release: Hydrophilic drugs are highly compatible with acrylic monomers, thus facilitating the manufacture of drug-loaded hydrogel soft contact lenses. We therefore focused on the effects of the cross-linkers on drug release performance using timolol maleate, a hydrophilic drug widely used for the treatment of glaucoma.[1] Monomer and cross-linker ratios used for hydrogel synthesis are shown in Table 1. The content of timolol maleate was 200 μg per lens. The amount of drug released was determined by spectrophotometry.

Figure 5 shows the cumulative release of timolol maleate over time. When the hydrogel did not contain a cross-linker, drug release was only 36%. However, the release of timolol maleate increased to 64% and 70% in hydrogels cross-linked with EADA or EGDMA, respectively. Thus, by controlling cross-linking, drug release properties can be optimized for the needs of different applications. Moreover, hydrogel chemistry is important because the binding between polymer and drug is a critical factor in drug release performance. Several studies have determined the optimum composition of hydrophobic and hydrophilic components in copolymeric hydrogels, and evaluated the microstructures obtained using different monomers and variation of mixing ratios.[2,9,13,20] It has also been reported that increased cross-linking in chitosan gels, using genipin as a cross-linker, led to delayed release of albumin.[28]

It is noteworthy that the highest levels of drug release, 77%, occurred in the hydrogel that was cross-linked using a combination of both EADA and EGDMA. A potentially irregular pattern of cross-linking bridges, resulting from the cross-linkers combination, may provide more sites for the capture of drug molecules. As shown in Table 1, the hydrogel containing the combination of two cross-linkers showed a lower swelling ratio, compared to hydrogels containing only one type of cross-linker. Thus, hydrogel polymer chains can be more effectively cross-linked using two cross-linkers with different chemical bonding properties and different chain lengths.

Hydrophobic Drug Release: For hydrophobic drugs, the evaluation of drug release behavior is more challenging, because of their lack of solubility in water. Therefore, addi-

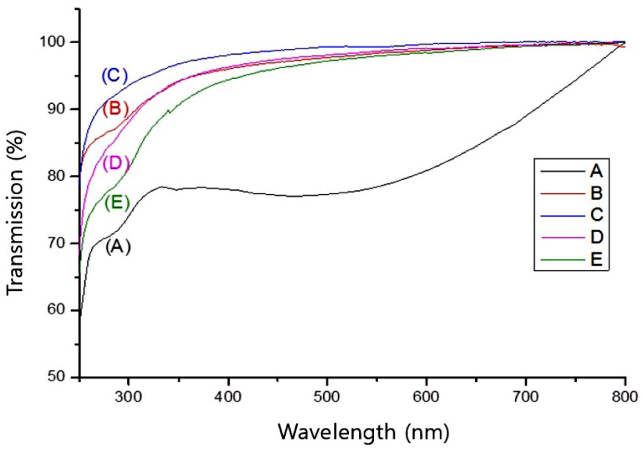

Figure 4. Optical transmittance of soft contact lenses prepared using different cross-linkers. The concentration of cross-linkers: (A) without cross-linker; (B) 0.1 M EADA; (C) 0.1 M EGDMA; (D) 0.1 M EADA+0.1 M EGDMA; (E) 1 M EADA.

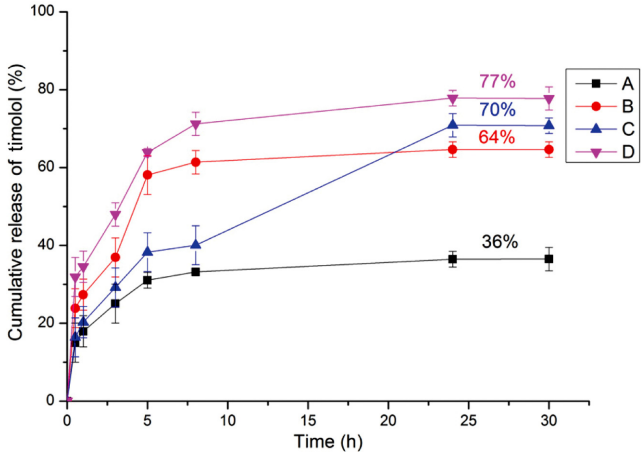

Figure 5. Cumulative amount of timolol maleate released from the hydrogel membranes as function of incubation time. The concentration of cross-linkers: (A) without cross-linker; (B) 0.1 M EADA; (C) 0.1 M EGDMA; (D) 0.1 M EADA+0.1 M EGDMA.

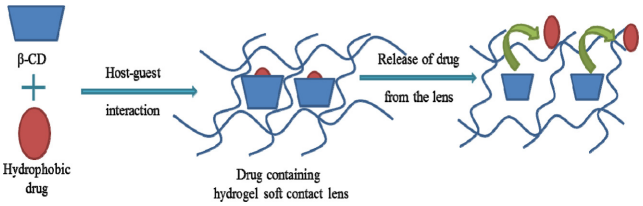

Figure 6. Scheme showing preparation and drug release of β-CD inclusion complex.

tional steps must be taken to enhance drug loading. Cyclodextrins (CDs) have a hydrophilic exterior but contain a hydrophobic interior cavity, which facilitates the formation of host/guest inclusion complexes.[31-33] On account of their non-toxic and biodegradable natures, CDs have frequently been used in biomedical applications, such as drug delivery. β-CD is also used as a co-monomer during hydrogel polymerization, resulting in improved swelling ratio and tensile strength, as well as controlled drug release through the formation of β-CD drug inclusion complexes.[34,35] In this study, a representative hydrophobic drug, α-tocopherol, was prepared as a β-CD inclusion complex. The interior cavity size of β-CD was suitable for a host/guest interaction with α-tocopherol, as illustrated in Figure 6. It was also convenient that α-tocopherol showed an absorption peak at a wavelength of 292 nm, while β-CD did not.

The effect of the β-CD/α-tocopherol complex on optical transmittance was shown in Figure 7. Hydrogel soft contact lenses containing less than 0.01 g of the complex (Figure 7(A), (B), (C)) were highly transparent. However, the transmittance was drastically reduced for lenses containing higher drug content (Figure 7(D), (E)). For optical applications, therefore, this limits the content of the β-CD inclusion complex that can be used.

To investigate the drug release performance of the β-CD inclusion complex, hydrogel soft contact lenses containing different ratios of cross-linkers were fabricated as summarized in Table 1. Cumulative drug release from lenses containing 80 μg of the β-CD-α-tocopherol complex is shown in Figure 8.

The contact lenses fabricated under all four cross-linker conditions released most of the α-tocopherol within 2 h, which therefore differs from the rate of release for the hydrophilic drug, timolol maleate. However, the hydrogel soft contact lens cross-linked with 0.1 mol% EADA (B) showed the best drug release performance among four, thus confirming its potential for ophthalmic drug delivery applications. Further studies will focus on the interaction between the β-CD inclusion complex

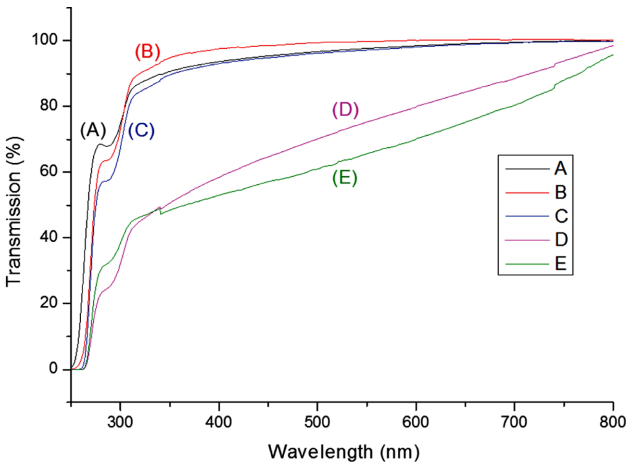

Figure 7. Optical transmittance of the hydrogel membranes containing β-CD/α-tocopherol complex: (A) 0.001 g; (B) 0.005 g; (C) 0.010 g; (D) 0.05 g; (E) 0.1 g in 12 mL of monomer solution.

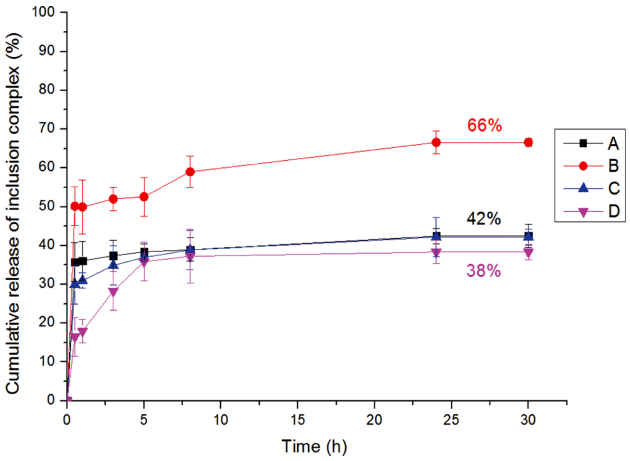

Figure 8. Cumulative release of α-tocopherol from soft contact lenses containing the β-CD inclusion complex. The concentration of cross-linker: (A) without cross-linker; (B) 0.1 M EADA; (C) 0.1 M EGDMA; (D) 0.1 M EADA+0.1 M EGDMA.

and the EADA cross-linker, and this may allow improvements in the efficiency of hydrophobic drug release.

Cytotoxicity. Fibroblasts were cultured on hydrogels cross-linked with EGDMA or EADA, and MTT assays were carried out (Figure 9). After 1 or 2 days of incubation, fibroblasts on the hydrogel containing EADA showed significantly greater viability than those cultured on EGDMA-containing hydrogel. Thus, the hydrogel synthesized with EADA was biocompatible with use in soft contact lenses. Furthermore, after 3 days of incubation, hydrogels containing EGDMA or EADA showed similar levels of fibroblast viability, confirming that both types of hydrogel are safe for use in soft contact lenses.

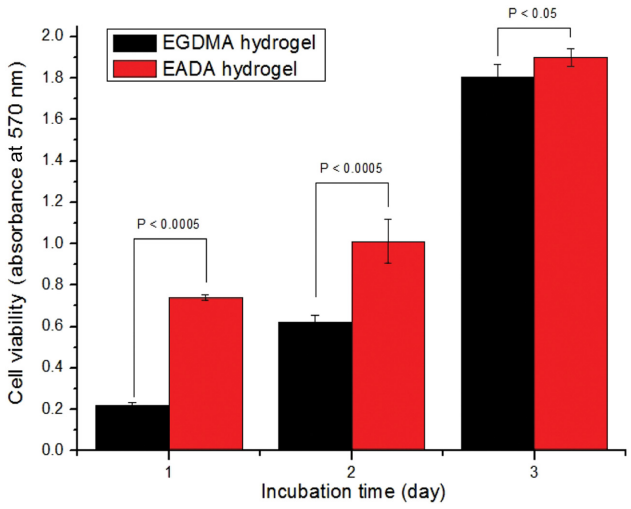

Figure 9. Viability of fibroblasts cultured on the hydrogels synthesized using two different cross-linkers.

Conclusions

Hydrogel soft contact lenses were prepared for ophthalmic drug delivery applications using the novel cross-linker, EADA, which contains Al as part of its chemical structure. The chemical synthesis of EADA was shown to be successful, and the functional characteristics of EADA as a cross-linker were investigated by evaluation of hydrogel viscosity. The presence of the metal ion in the structural backbone of EADA provides hydrogel soft contact lenses with unique properties, including excellent mechanical and swelling characteristics. Furthermore, hydrogel contact lenses prepared using EADA exhibited stable and controlled drug release properties. Finally, the EADA cross-linked hydrogel showed little if any cytotoxicity, confirming its safety for use in the fabrication of soft contact lenses.

Acknowledgements: This research was supported by the Basic Research Laboratory Program (No 2011-0020264), and the General Research Program (2013 R1A1A 2005148), granted by the Ministry of Education, Science and Technology of Korea.

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