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이온성 천연다당류가 다공성 수화젤 콘택트렌즈의 기능 향상에 미치는 영향

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Effect of Ionic Natural Polysaccharides on the Functional Enhancement of Porous Hydrogel Contact Lenses

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초록: 다공성 수화젤 콘택트렌즈를 제작한 후 이온성 천연다당류를 가교시켜 이온성 천연다당류가 콘택트렌즈의 물리적·화학적 성질에 미치는 영향을 알아보고자 하였다. 다공성 수화젤은 발포제로서 sodium carbonate를 사용하였으며 이온성 천연다당류로서 alginate, chitosan, agarose를 사용하였다. 다공성 수화젤은 일반 수화젤보다 함수율, 산소투과율, 습윤성이 매우 향상되었다. 천연다당류가 결합된 콘택트렌즈는 이온성의 종류에 관계없이 모든 다공성 콘택트렌즈에서 습윤성과 항균성을 향상시켰다. 콘택트렌즈의 단백질 흡착은 다당류의 이온성에 영향을 받았다. 이온성 천연다당류가 수화젤 콘택트렌즈에 결합됨으로써 콘택트렌즈의 기능향상에 기여함을 확인하였다.

Abstract: The purpose of this study was to examine the effect of ionic natural polysaccharides on the physico-chemistry properties of contact lenses by cross-linking ionic natural polysaccharides after fabricating porous hydrogel contact lenses. Sodium carbonate was used as a foaming agent in the preparation of porous hydrogels, and ionic natural polysaccharides such as alginate, chitosan, and agarose were used. Porous hydrogels have significantly improved water content, oxygen permeability, and wettability than ordinary hydrogels (polymacon). Natural polysaccharide cross-linked contact lenses have improved wettability and antibacterial properties in all porous contact lenses, regardless of their ionic type. Protein adsorption of contact lenses was affected by the ionicity of polysaccharides. It was confirmed that the ionic natural polysaccharide contributes to the improvement of the function of the contact lens by being bound to the hydrogel contact lens.

Keywords: contact lens, foaming agent, natural polysaccharide, oxygen permeability, porous hydrogel.

Introduction

Superporous hydrogel (SPH) has an ‘open channel’ system interconnected by a 3D hydrophilic polymer network with multiple pores with diameters from μm to mm. Therefore, when a part of the hydrogel is exposed to water or aqueous fluids, the fluids are absorbed immediately through the open space.[1,2] Consequently, SPH has a very fast swelling rate and absorbs a large amount of water compared to general hydrogels. However, because SPH has weak mechanical properties due to the high expansion rate, polysaccharides including hydrophilic polymers such as sodium alginate, pectin, and chitosan or hybrid agents such as polyvinyl and alcohol are added to increase the mechanical strength.[3]

Recently, due to the growing interest in natural polysaccharides, they are being used to develop hydrogels for biomedical and pharmaceutical applications.[4] Natural polysaccharides have various compositions and properties that cannot be easily imitated compared to synthetic polymers. Hydrogels based on natural polysaccharides are being used for various applications due to properties such as biocompatibility, biodegradability, and irritation reaction.[5] The polysaccharides, which are now widely used in biomedical and pharmaceutical fields, include alginate, chitosan, dextran, carrageenan, and agarose.[6,7]

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Alginate is a seaweed polysaccharide which is a natural anionic polymer extracted from brown algae or produced by bacteria and consists of (1-4)-linked β-*D*-mannuronate (M) and its C-5 epimer α-*L*-guluronate (G) residues.[8] Alginate is a natural polysaccharide that is widely used because of its gelling properties due to the interaction between carboxylic groups and metal ions. Hydrogels obtained from alginate have properties similar to the extracellular matrix and are used in tissue engineering and regenerative medicine applications due to their biocompatibility and low toxicity.[9]

Chitosan is a cationic polysaccharide made from alkaline *N*-deacetylation of natural polysaccharide chitin extracted from the outer coverings of crustaceans, and is composed of glucosamine and *N*-acetyl glucosamine.[10] Chitosan is widely studied in the fields of wound dressing, anticoagulants, drug delivery systems, biomedicine, and pharmaceutical research due to properties such as antimicrobial activity,[11] biodegradability,[12] and biocompatibility.[13] In addition, as chitosan contains a large number of hydroxy groups (-OH), which helps hydrophilicity and nucleophilic amine groups (-NH) to facilitate bonding with other functional groups, it is used for various biomedical applications.[14]

Agarose is a linear polysaccharide extracted from red seaweed, and is composed of alternating *D*-galactose and 3,6-anhydro-*L*-galactopyranose linked by α-(1→3) and β-(1→4) glycosidic bonds and includes several ionized sulfate groups. Agarose is widely used as an agar culture medium in gel-type microbiology and in the food industry, and is utilized in biomedical applications, jellification, biocompatibility, and natural biodegradability.[15]

These natural polysaccharides have useful functions but are difficult to apply to hydrogel production because of the limitations in reactivity and processability.[16] To overcome this problem, there is a method of bridging natural polysaccharides to existing polymers by an interpenetrating polymer network (IPN).

An IPN is a polymer comprising two or more networks which are at least partially interlaced on a polymer scale but not covalently bonded to each other. As a polymer chain from one network is physically intertwined with another network, it is difficult to separate each network.[17] An IPN can produce highly incompatible polymers in a homogeneous form, such as organic-inorganic mixtures,[18] and can increase the mechanical strength and toughness of the final product by using the individual properties of each network.[19]

Hydrogel contact lenses are preferred by many because of their flexible and comfortable fit, but low oxygen permeability can cause eye health problems. Silicone hydrogels containing silicone monomers have higher oxygen permeability compared to hydrogel contact lenses, but have limitations such as reduced wettability due to hydrophobic surfaces and easy adsorption of proteins and lipids. Accordingly, there is a need to develop high-performance contact lens materials to overcome problems such as low oxygen permeability of conventional hydrogel contact lenses and reduced surface wettability of silicone hydrogel contact lenses.

The purpose of this study is to prepare a porous contact lens using a foaming agent in order to compensate for the disadvantages of the hydrogel and silicone hydrogel contact lenses and make use of the advantages. In order to improve the function of the porous hydrogel, ionic natural polysaccharides are introduced. In addition, the effects of the ionic properties of natural polysaccharides on the physical properties of contact lenses were also investigated.

Experimental

Reagent and Sample Preparation. This study used 2-hydroxyethylmethacrylate (HEMA, Sigma-Aldrich) which is a basic monomer, methacrylic acid (MAA, JUNSEI) which is a hydrophilic monomer, and styrene (Sigma-Aldrich) which is a hydrophobic monomer as the reagents to make the hydrogel

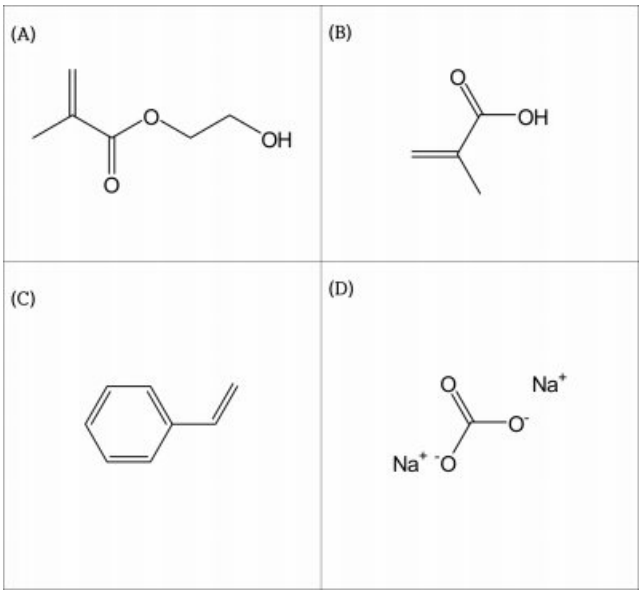

Figure 1. The chemical structure of monomers: (A) 2-hydroxyethylmethacrylate (HEMA); (B) methacrylic acid (MAA); (C) styrene; (D) sodium carbonate (SC).

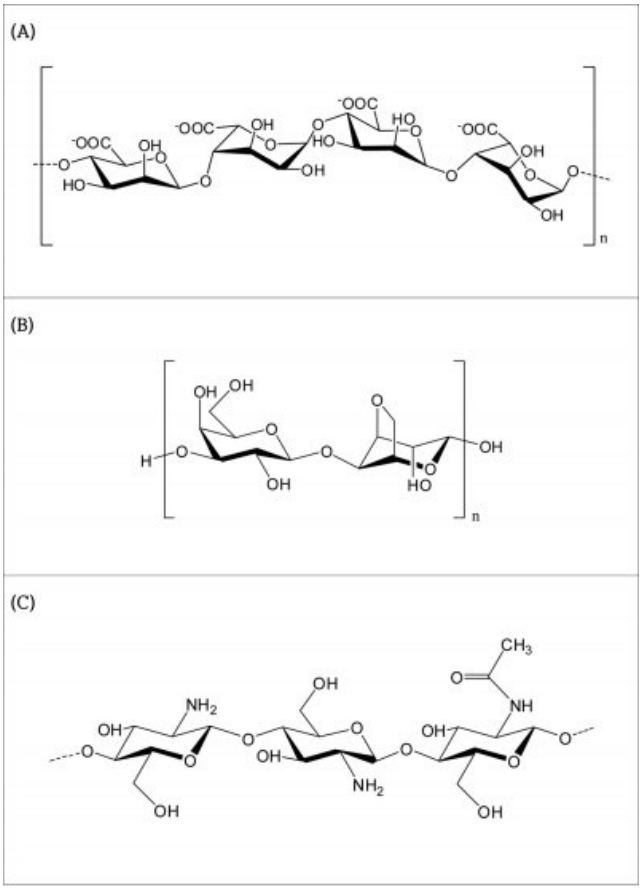

Figure 2. The chemical structure of natural ionic polysaccharides: (A) alginate; (B) agarose; (C) chitosan.

contact lenses. In addition, sodium carbonate (SC, Sigma-Aldrich) was used as the foaming agent, ethylene glycol dimethacrylate (EGDMA, Sigma-Aldrich) as the cross-linking agent, and 2,2-azobis(isobutyronitrile) (AIBN, JUNSEI) as the initiator (Figure 1). Natural polysaccharides such as anionic alginate, neutral agarose, and cationic water-soluble chitosan were used to improve the function of the fabricated porous hydrogel. The water-soluble chitosan was supplied by BIOPOLYTECH Co., Ltd. (Figure 2). In terms of IPN, *N*,*N*'-methylenebisacrylamide (MBAA) was used as the cross-linking agent and ammonium persulfate (APS) as the initiator, which are Sigma-Aldrich products.

Thermal polymerization was performed on the polymacon contact lens without the foaming agent and on the porous

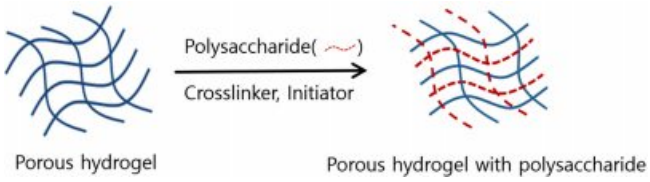

Figure 3. Scheme for preparing a porous hydrogel contact lenses with ionoic polysaccharide such as alginate, agarose, and chitosan.

hydrogel contact lens with the foaming agent at 80 °C for two hours according to the casting mold method. The general hydrogel contact lens without the foaming agent was referred to as Ref, and the contact lens with sodium carbonate as the foaming agent was referred to as Ref-SC (Table 1).

The IPN solutions were prepared by producing alginate, agarose, and water-soluble chitosan as a 1% solution, respectively, and adding 0.3% of MBAA (cross-linking agent) and APS (initiator). The IPN procedure was performed by immersing Ref-SC contact lenses in each IPN solution for 24 h at 37 °C (Figure 3). The samples that were IPN-treated with alginate, agarose, and chitosan were referred to as Alg-SC, Aga-SC, and Chi-SC, respectively.

Physical Properties. The physical and chemical properties of the fabricated samples such as the water content, refractive index, contact angle, light transmittance, and oxygen permeability were measured according to ISO 18369-4:2017. For each measurement item, we averaged five measurements for each sample.

The refractive index was measured by an Abbe Refractometer (ATAGO DR-A1) after washing each IPN-treated sample twice in phosphate-buffered saline (PBS) and removing water with a wiper.

The water content was measured according to ISO 18369-4:2017 and was calculated by using the following eq. (1).

$$\mathrm{WC}(\%) = \frac{W_{\mathrm{swell}} - W_{\mathrm{dry}}}{W_{\mathrm{swell}}} \times 100 \quad (1)$$

WC(%) is the water content in an equilibrium state, W_{swell} is the weight of the sample swelled for 24 h, and W_{dry} is the weight of the sample dried in an oven for 16 h.

The contact angle of the samples hydrated for 24 h was measured by using a DSA30 from Kruss GmbH by the sessile drop

Table 1. Composition of Hydrogel Contact Lens and Nomenclatures of Samples (wt%)

Name	HEMA	10% SC	DW	MAA	Styrene	EGDMA	AIBN
Ref	59.4	-	30	5	5	0.3	0.3
Ref-SC	59.4	30	-	5	5	0.3	0.3

method. We dropped PBS solution 3 μL on the surface of the lens to measure the angle of the water droplet twice per second for 10 s.

The light transmittance was measured in the range of 200~800 nm, and we used Agilent's Cary 60 UV-Vis as the measuring instrument.

The oxygen permeability was measured by the polarographic method and we calculated the DK/t by measuring the current value using Rehder's 201T. The thickness of the samples was measured by using a low-pressure dial gauge (Mitutoyo, VL-50-B). The curvature radius of the polarographic cell was 8.7 mm and the current value was measured after stabilizing at 35±0.5 °C (equal to the temperature of the eye) for at least one hour.

Protein Quantification. In terms of protein, this study used anionic protein bovine serum albumin (BSA) and cationic protein lysozyme, which are similar in shape and chemical properties to human albumin. First, we measured the hydrated weight of each sample to absorb protein and prepared each protein in a solution of 5 mg/mL in PBS. Then, we poured the protein solution into vials and immersed each sample at 37 °C for an incubation time of 24 h to absorb the protein. Next, each sample was washed twice with PBS and added to a solution of 3% sodium dodecyl sulfate (SDS) dissolved in distilled water and heated to 95 °C for 15 min. The proteins attached to the samples were desorbed by shaking the solution gently with a vortex for three minutes. The absorbance was measured by using Agilent's Cary 60 UV-Vis, and we confirmed the absorbance value at 280 nm, which is the maximum absorption wavelength of protein. The molar extinction coefficient ε of BSA is 3.35 (mg-cm/g), and the ε of lysozyme is 13.2 (mg-cm/g), and the amount of protein adsorbed was calculated by using eq. (2) below.[20]

$$Q = \frac{vc}{m} \quad (2)$$

Q is the protein adsorption amount (mg/g)
v is the volume of the solution (mL)
c is the protein concentration in the solution
m is the mass of adsorbent

Antimicrobial Activity. This study used *E. coli* (ATCC 10536) to examine the antimicrobial activity of the natural polysaccharides with ionic properties. The strain was provided by the Korea culture center of microorganisms (KCCM). The liquid medium used for the antimicrobial activity test was prepared by mixing 2 g of peptone and 1.2 g of beef in 40 mL of distilled water and performing an autoclave sterilization treatment at pH 7.0, and the *E. coli* was primary cultured in the liquid medium. Each sample was added to the vial containing the liquid medium, and 1 μL of the cultured *E. coli* was added and incubated at 35 °C for 16 h, and subsequently diluted 10000 times. 1 mL of the diluted solution was smeared to dry film and incubated at 35 °C for 24 h. *E. coli* 3M petrifilm™ was used as the dry film medium. The antibacterial test was repeated three times and expressed as an average value.

Results and Discussion

The Physical Properties of the Porous Contact Lenses. Water Content and Refractive Index: Figure 4 shows the results of measuring the water content and the refractive index of the hydrogel contact lenses polymerized with the composition ratios shown in Table 1. As a result of comparing the water content of Ref (polymacon contact lens) and Ref-SC (porous hydrogel using a foaming agent), the water content of Ref-SC was more than two times higher than that of Ref. This is because SC (the foaming agent) produced carbon dioxide and formed pores in the contact lens, which absorbed a large amount of water.[21]

The water content of Alg-SC cross-linked with alginate was the highest at 78.36%, while that of Aga-SC cross-linked with agarose was the lowest. The water content of Chi-SC and Aga-SC was 44.18 and 31.57%, respectively, which was lower than that of Ref-SC by 41.17 and 57.96%, respectively. Aga-SC even showed a decrease in water content compared to the sample before using the foaming agent. Chavda *et al.*[22]

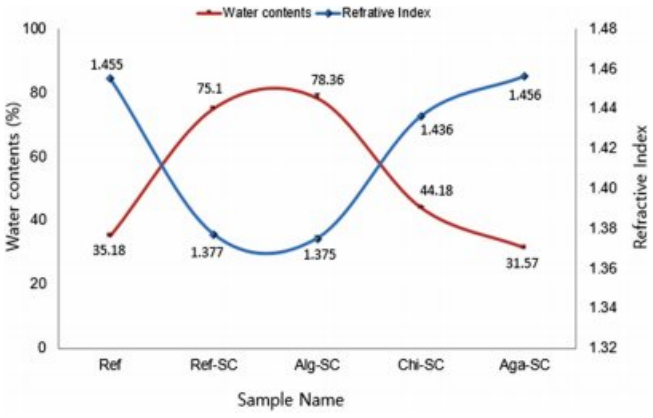

Figure 4. Comparison of water contents (red line) and refractive index (blue line) of porous hydrogels contact lenses with ionic polysaccharide.

reported that the expansion slowed down and the equilibrium expansion rate decreased as the concentration of chitosan increased in superporous hydrogels. It was also reported that the flexibility of the polymer chains was greatly limited by the entanglement with cross-linked chitosan networks. In addition, the water content is lowered as the expansion rate decreases[23] due to the cross-link between the amino groups of chitosan and the carboxyl groups of MAA of adjacent chains. According to the study by Vardar *et al*.,[24] agarose exhibited a relatively lower water content compared with IPNs with alginate and chitosan, which is probably due to the absence of electric charge and low polarity.

The refractive index of Aga-SC was highest at 1.456, which is similar to Ref, while that of Alg-SC was the lowest at 1.375. The refractive index is related to structural aspects such as the molecular arrangement and density in the contact lens and is generally inversely related to the water content. In cross-links with high substitution rates, swelling hardly occurs because of the high density.[25] Therefore, the refractive index of Aga-SC with the lowest water content was high and the refractive index of Alg-SC with the highest water content was the lowest.

Light Transmittance: The light transmittance is one of the most important conditions that must be satisfied for optical lenses. Figure 5 shows the results of measuring the light transmittance in this study. The light transmittance is classified into UV-B (280~315 nm), UV-A (315~380 nm), and visible light (380~780 nm) according to ISO standards. In terms of the light transmittance of the visible light spectrum for each sample, the transmittance of Ref-SC without cross-linking polysaccharides was 93.85%, and the visible light transmittance of Alg-SC, Chi-SC, and Aga-SC cross-linked with natural polysaccharides were 90.49, 91.72, and 88.55%, respectively. The transmittance of all of the samples with polysaccharides slightly decreased, but satisfied a transparency of more than 88%, which is the basic requirement for contact lenses according to ANSI Z80.20: 2004.

Oxygen Permeability: Since the cornea has no blood vessels, most of the oxygen to the eye is supplied from the external environment. Consequently, wearing contact lenses acts as a barrier which reduces the oxygen transfer rate to the eye.[26] As low oxygen permeability causes side effects such as hypoxia, neovascularization, corneal edema, and endothelial polymegethism,[27] contact lenses should have a high oxygen permeability to offer a higher level of safety and comfort.[28] The oxygen transmissibility of the lens is expressed by DK ($(cm^2/sec)\cdot(mLO_2/mL\cdot mmHg)\cdot10^{-11}$)) and the oxygen permeability (transmissibility level) is expressed as the DK per thickness of the lens, DK/t ($(cm/mLO_2)/(sec\cdot mL\cdot mmHg)\cdot10^{-9}$)).

As shown in Figure 6, the DK/t of Ref-SC with the foaming agent was 28.95×10^{-9}, which increased significantly by 74.8%, compared to Ref without the foaming agent. This shows that using the foaming agent increased the oxygen permeability in addition to the water content. Among the samples that were IPN-treated with polysaccharides, the DK/t of Alg-SC cross-linked with alginate were the highest at 30.43×10^{-9}. In the case of hydrogel contact lenses, oxygen is transferred by the water contained in the lens. Consequently, the oxygen permeability is mainly determined by the water content and the thickness.[29] Therefore, if the water content is high, the oxygen permeability also increases exponentially. The porous hydrogel contact lenses showed higher oxygen permeability than the non-porous

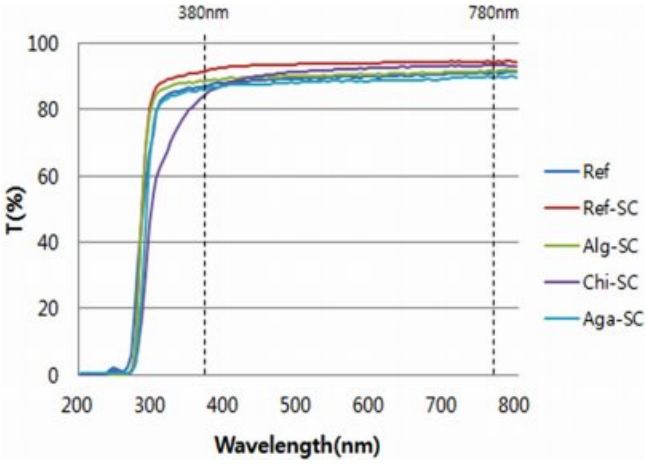

Figure 5. Transmittance of porous hydrogel contact lenses with ionic polysaccharides.

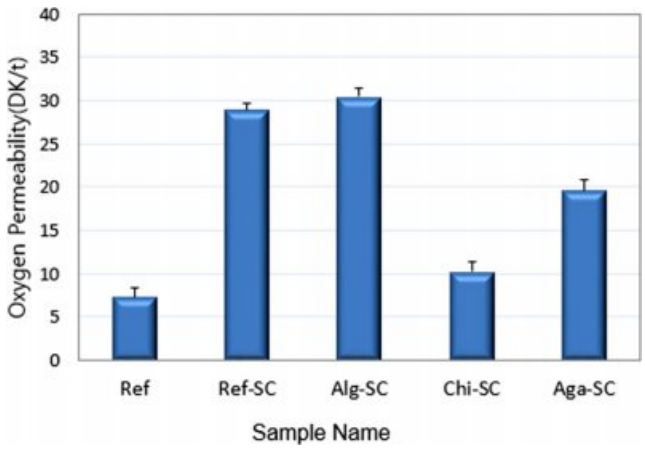

Figure 6. Comparison of oxygen transmissibility and oxygen permeability of porous hydrogel contact lenses.

contact lenses because of the higher water content. In addition, we confirmed that the hydrogels cross-linked with natural polysaccharides were significantly influenced by the water content. The DK/t of Chi-SC were the lowest at 10.28×10^{-9}, which were 64.5% lower than that of Ref-SC. Consistent with previous studies that report the low oxygen and carbon dioxide permeability of chitosan and that the oxygen permeability depends on the water content,[30] the oxygen permeability of Chi-SC cross-linked with chitosan was also reported as low in this study due to the low water content.

Wettability: As contact lenses are directly affected by the wettability of the hydrogel because they are in close contact with the tear film, the stability of the tear film is also affected by the wettability. If the stability of the tear film is destroyed by the use of contact lenses, symptoms such as dry eyes will occur.[31] Therefore, contact lenses need to maintain a hydrophilic surface to maintain a stable tear film. The contact angle is the angle that is formed when a liquid comes into contact with a solid surface. Large contact angles lead to hydrophobic properties and small contact angles lead to hydrophilic properties and better wettability. Contact lenses with good wettability tend to reduce dehydration and cause fewer tears.[32]

As a result of measuring the contact angles in this study, the contact angle of Ref was highest at 60.8° and the contact angle of Ref-SC was 51.0°, which is about 16% lower than that of Ref. This shows that adding the foaming agent increased the wettability. The contact angles of Alg-SC, Chi-SC, and Aga-SC cross-linked with natural polysaccharides were 42.0°, 36.3°, and 30.1°, respectively, which were about 17.6%, 28.8%, and 41.0% lower, respectively, than that of Ref-SC. In particular, Aga-SC exhibited the highest wettability (Figure 7). The chitosan used for cross-linking contains a large number of hydroxy groups (-OH) and amine groups ($-NH_2$), and shows hydrophilicity due to strong hydrogen bonds with water. In addition, the hydrophilicity of agarose is composed of excessive hydroxy groups with 3 hydroxyl radicals per unit of agarose. Therefore, the covalent bond between the atoms of the -OH group becomes extremely high due to the significant difference between hydrogen and oxygen, and this polarity is reported to interact with polar water molecules through hydrogen bonds to impart strong hydrophilicity to the compound.[33]

The Antimicrobial Activity of Contact Lenses with Ionic Natural Polysaccharides. The contact lens surface is a suitable substrate for bacterial adhesion and biofilm formation.[34] Contact lenses are biomaterials that are in direct contact with the eyes, and bacterial contamination which leads to biofilm formation on the surface due to long-term wear is a major problem.[35] Organic materials and bacteria quickly

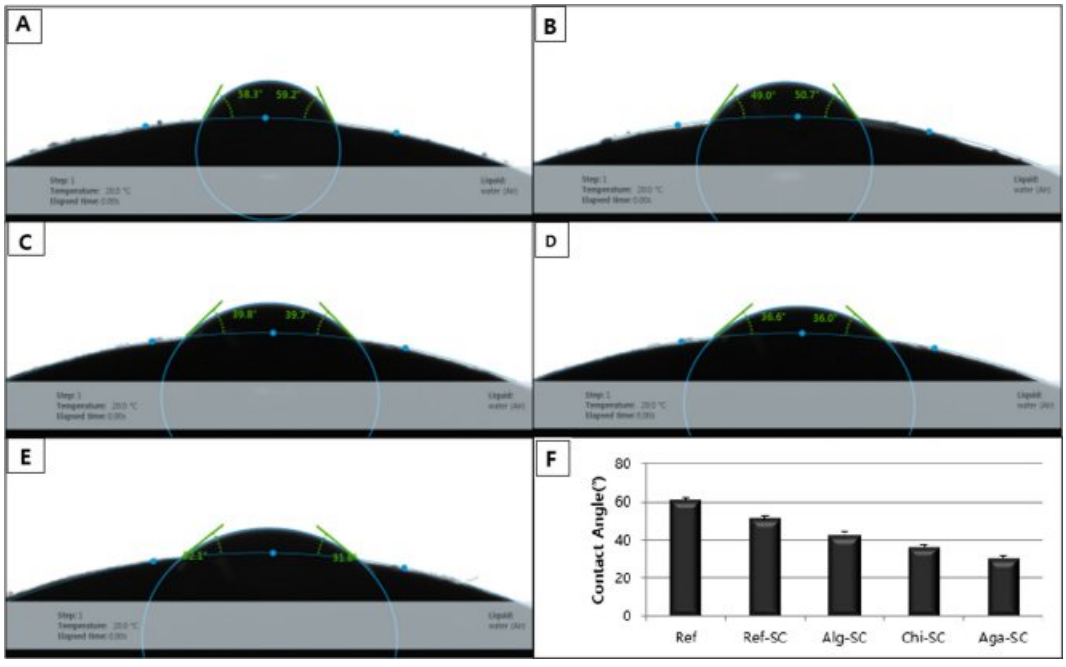

Figure 7. Contact angle image of nonporous and porous hydrogels: (A) Ref; (B) Ref-SC; (C) Alg-SC; (D) Chi-SC; (E) Aga-SC; (F) contact angle graph of porous hydrogel contact lenses.

spread toward the contact lens surface immediately after contact with lens care solutions or body fluids.[36] Typical eye-related bacteria include *E. coli*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*, and these pathogens cause bacterial conjunctivitis and corneal ulcers.[37]

This study found that all of the samples cultured with contact lenses had more antimicrobial activity compared to the Base cultured without contact lenses (Figure 8). The introduction of charged moieties into the polymer network by copolymerizing HEMA with anionic monomers such as MMA improves cell adhesion and proliferation and enhances the biological performance of the material.[38] Based on this, the increase of antimicrobial activity in all of the samples containing MMA has been considered to be enhanced under the presence of MMA. In addition, the hydrogels with SC exhibited antimicrobial activity, and research results have shown that increasing the amount of SC enhances the antimicrobial activity.[39] The number of *E. coli* in Ref, a normal hydrogel lens, is 138 CFU, and the porous hydrogel lens is reduced to 47 CFU. Porous hydrogel lenses cross-linked with natural polysaccharides have significantly improved antibacterial properties (Figure 8). The porous hydrogel contact lenses containing chitosan exhibit more antimicrobial activity than those containing alginic acid and agarose.

Surface treatment by natural polysaccharides or polysaccharides has been used as a promising means to cope with implant-related biofilm infections and many natural polymers exhibit antibiotic properties.[35] Alginic acid has been proven to have antibacterial effects against *S. aureus* and *E. coli*,[38] and chitosan is well known for its superior antibacterial properties.[39] It has been reported that the *D*-glucosamine of chitosan exhibits immune activities by increasing the activity of natural killer cells involved in the defense of the immune system. Moreover, positively charged chitosan oligosaccharide molecules selectively destroy only the bacterial cell membranes without destroying neutral normal cell membranes due to the electrostatic interaction with negatively charged bacterial membranes.[40] The antimicrobial activity of water-soluble chitosan was higher than that of chitosan, and the antimicrobial activity against *E. coli* of *N*–*N*-propyl-*N* and *N*-dimethyl chitosan was reported to be 20 times than that of chitosan.[41]

Protein Adsorption of Contact Lenses According to Ionic Properties of Natural Polysaccharides. The human tear film contains many proteins and lipids. Contact lenses are highly affected by tears and cause various side effects such as decreased comfort and visual acuity due to the adsorption of proteins contained in the tear components.[42] Hydrogel lenses consist of hydrophobic or hydrophilic, negatively charged or positively charged monomers and have a significant effect on the amount of protein deposition.[43]

In the case of anionic Alg-SC, the adsorption of negatively charged BSA was the least and the adsorption of positively charged lysozyme was the most. In addition, cationic Chi-SC showed the most adsorption of BSA, while nonionic Aga-SC showed the least adsorption of lysozyme (Figure 9). Albumin, a protein in tears, is negatively charged and has a high molecular weight. Therefore, the protein adhesion is reduced by the charge repulsion effect when penetrating into the negatively charged hydrogel matrix. On the other hand, lysozyme has a low molecular weight and has a positive charge at physiological pH, which facilitates penetration into hydrogels containing negatively charged monomers.[44] The

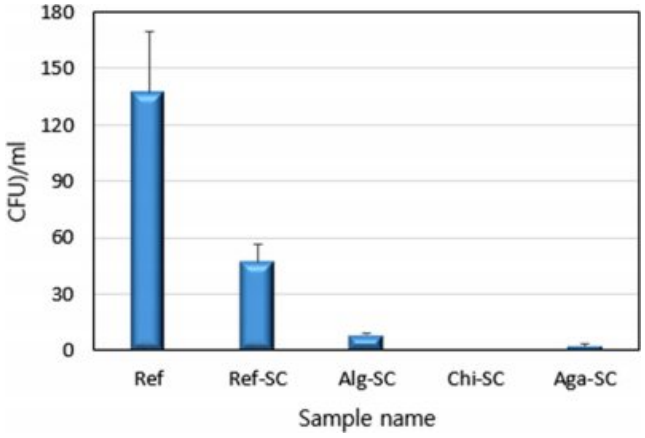

Figure 8. Antibacterial activities for *E. coli* of porous hydrogel contact lenses.

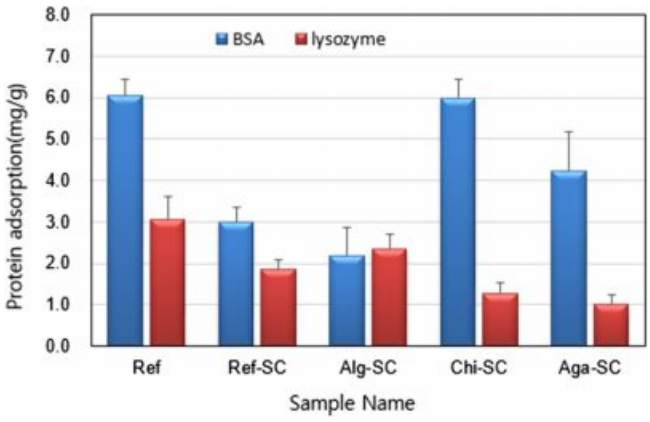

Figure 9. Protein adsorption of BSA (blue) and lysozyme (red) to porous hydrogel contact lenses.

negatively charged BSA protein is highly adsorbed on the cationic Chic-SC, and the negatively charged Alg-SC has the lowest adsorption amount. On the other hand, the positively charged lysozyme protein is highly adsorbed to anionic Alg-SC and less adsorbed to Chi-SC and Aga-SC. BSA adsorbed more than lysozyme in all samples except Alg-SC. Therefore, we confirmed that the ionic properties of natural polysaccharides affect the type and amount of proteins adsorbed in porous hydrogel contact lenses.

Conclusions

Porous hydrogels cross-linked with natural polysaccharides have better contact lens properties than non-porous hydrogels. In addition, the wettability and antimicrobial activities were significantly improved regardless of the type of ionic polysaccharide. Protein adhesion is highly affected by the type of ionic polysaccharide. In conclusion, this study found that natural polysaccharides have a significant contribution to the functional enhancement of porous hydrogel contact lenses.

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