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Surface Modification of Contact Lenses Using Adsorption of Ethylene Oxide Branched Copolymers

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ABSTRACT: To examine methods for reducing the amount of adsorbed protein on the surface of contact lenses during use, cationic copolymers containing poly(ethylene oxide) units were synthesized and evaluated as surface modifiers. Poly(ethylene oxide) graft-branched copolymers of composition 70 mol % dimethylaminoethyl methacrylate (DM) and 30 mol % methoxy polyethylene glycol methacrylate (M*p*0G; $p = 2, 4, 9$; the average number of the ethylene oxide units) were obtained using nonionic monomers containing poly(ethylene oxide) units. The copolymers very efficiently prevented protein adsorption on a contact lens. Contact angle measurements showed that immersion in tear fluid made the lens surface hydrophobic because of adsorption of proteins with hydrophobic residues. The copolymer pretreatment made the lens surface hydrophilic, even after dipping in artificial tear fluid. These results suggest that adsorption of the poly(ethylene oxide) branched copolymer on the contact lens would make the lens surface hydrophilic and prevent protein adsorption. © 2012 Wiley Periodicals, Inc. J. Appl. Polym. Sci. 000: 000–000, 2012

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INTRODUCTION

Soft contact lenses are made of hydrogels, which are crosslinked nonionic polymers, such as poly(hydroxyethyl methacrylate) copolymerized with methyl methacrylate or methacrylic acid (MAA). The estimated number of contact lens users worldwide is more than 150 million.[1,2] Commercial soft contact lenses are classified into four categories according to their water content and the electrostatic properties of their surface, and these properties can be controlled by the degree of crosslinking and the copolymerization ratio, respectively (Table I).[3,4]

The most popular type of contact lens is Type 4 because of its high water content making the lenses more comfortable. However, in spite of the popularity of Type 4 lenses, more than 75% of users had concerns about lens cloudiness and eye dryness ($n = 116$).[5] This phenomenon could be attributed to adsorbed dirt.[3,6,7] Lysozyme (isoelectric point: pH 11.0 and molecular weight: 14,300), which bears a positive charge in tear fluid (pH 7), would adsorb on the negatively charged lens surface through electrostatic interaction.[8] We thought that the adsorbed lysozyme would act as a base layer for enhancing adsorption of other proteins or lipids.[9–11]

Adsorbed and residual proteins after cleaning contact lenses are thought to cause eye diseases because microorganisms, such as bacteria, propagate by nutritive staining.[3,12] It would be useful to develop a safe additive for contact lens care products that modifies the lens surface, prevents protein adsorption, and helps to remove adsorbed proteins.

Surface-modification technology is very important. In the biological science, development of protein-resistant surfaces is needed because most biomaterials require technology for prevention of protein adsorption.[4] Many researchers have intensively investigated control of the adhesiveness of proteins.[4,13–19] For removable articles, such as contact lenses, surface modification during daily care procedures is an effective method, however, the appropriate technology has not yet been developed.

We have investigated surface modification using adsorbed polymers that can change surface properties. For example, we have

Table I. Food and Drug Administration Categories of Soft Contact Lenses

Electrostatic property	Water content $<50\%$	Water content $\geq 50\%$
Nonionic	Type 1	Type 2
Anionic	Type 3	Type 4

Nonionic: contains <1 mol % anionic monomer in polymer composition, Anionic: contains ≥1 mol % anionic monomer in polymer composition.

developed an amphoteric copolymer containing cationic moieties for adsorption, and anionic moieties for modifying surface hydrophilic properties. When it was used as an additive in a washing agent, the amount of adsorbed hydrophobic stains, such as sebum, on the washed surface decreased.[20–22] From these results, we concluded that the hydrophilic or hydrophobic properties of the surface is an important factor in producing antisoiling surfaces.

The aim of this study was to develop a method of modifying the surface of contact lenses by cationic copolymer adsorption, and the copolymers could be used as additives in soft contact lens care products.

EXPERIMENTAL

Polymer Preparation

All monomers, namely dimethylaminoethyl methacrylate (DM; Tokyo Chemical Industry (TCI) Co., Tokyo, Japan), methoxy polyethylene glycol methacrylate (Shin-Nakamura Kagaku Co., Wakayama, Japan; M*p*0G, the average ethylene oxide length, $p = 2$, 4, 9 units), and vinylpyrrolidone (Kanto Chemical Co., Tokyo, Japan; VP) were used without further purification.

DM/nonionic-monomer (M*p*0G or VP) copolymers were synthesized by free-radical solution polymerization in ethanol as a solvent, with 2,2′-azobis(2-methylbutyronitrile) (Wako Pure Chemical Industries, Osaka, Japan; V-59) as an initiator.[20–22] The obtained copolymer solutions were purified by water dialysis with cellulose tubing (EIDIA Co., Tokyo, Japan; cut-off molecular weight: 14 000, pore size: 50 Å, and UC 36-32-100) and freeze dried.[23] The residual monomer and polymerization compositions were confirmed using nuclear magnetic resonance spectrometry data (^{1}H-NMR) obtained at 400 MHz in D_2O. The polymerization yields were greater than 99%, and the composition ratios were almost the same as the monomer ratios. The molecular weights of each copolymer were confirmed by gel-permeation chromatography (polystyrene standard, 10 mmol/L LiBr in THF, column: TSK gel 5000, 3000, 40°C, 0.5 mL/min, detector: RI, injection rate: 100 µL) to be $2–10 \times 10^4$, no structural irregularities, such as crosslinks, were recognized.

Evaluation of the Amount of Protein Adsorbed on Contact Lens

Direct Measurement of the Amount of Protein Adsorbed on Contact Lens. Artificial tear fluid was prepared according to a method reported in Ref. 9, using 0.12 g of egg-white lysozyme (Wako Pure Chemical Industries, Osaka, Japan), 0.9 g of sodium chloride, and 0.045 g of sodium dihydrogen phosphate dehydrate in 100 mL of ion-exchanged water adjusted to pH 7.[10] The solution used for extracting adsorbed lysozyme from the contact lenses was prepared by adding 1 wt % sodium dodecyl sulfate (Wako Pure Chemical Industries, Osaka, Japan, SDS) to a 1 wt % sodium carbonate (Wako Pure Chemical Industries, Osaka, Japan) solution.

Commercial Type 4 soft contact lenses (Johnson & Johnson, New Brunswick, NJ; Acuvue®) were used in the experiments. A lens was dipped in 5 mL of 1 wt % polymer solution at room temperature for 1 h, and then soaked in 2 mL of the artificial tear fluid, and shaken at 37°C, for 5 h. The lens was placed in 1.5 mL of the SDS solution and shaken at 37°C for 3 h. The extracted lysozyme, colored with bicinchoninic acid, was detected spectrophotometrically at 562 nm. The amount of lysozyme adsorbed on the contact lens was calculated using the standard relationship (the concentration range of calibration curve: 0–2 mg/mL).[24]

Relative Amounts of Protein Adsorbed on Contact Lens. The lenses treated with artificial tear fluid were colored with 2% ninhydrin solution. The color of the lens was measured with a colorimeter and the psychometric lightness (L^* value) was used to calculate the relative lysozyme-adsorption value. The relationship between the amount of adsorbed lysozyme on the lens and the L^* value of the lens dyed with ninhydrin has been known to be proportional.[24] The relative amount of adsorbed lysozyme (A_p) was calculated from L^* using eq. (1); the value for a blank lens (i.e., without polymer treatment) was scaled as 100%.

$$A_p = -2.34L * +205.5 \tag{1}$$

Evaluation of Ability of the Copolymer to Remove Residual Proteins. To evaluate the washing ability of the copolymer, a contact lens previously immersed in artificial tear fluid was washed, using a normal finger rubbing method, with 2 mL of 1% copolymer solution. The amount of residual lysozyme on the lens was determined by the method of direct measurement described above.

Evaluation of Surface Tension of the Copolymer. Surface tension was measured by the droplet method using an automatic surface tension meter PD-Z (Kyowa Interface Science Co., Tokyo, Japan) at 20°C.

Measurement of Contact Angle of Lens Surface in Water

A contact lens was immersed in ion-exchanged water, and an air bubble was attached beneath the lens surface. The shape of the air bubble was captured with a CCD camera, and the contact angle (ϕ) was calculated using the equations shown in Figure 1.

RESULTS AND DISCUSSION

Evaluation of Protein Adsorption on Various Contact Lenses

To study the factors affecting protein adsorption on the contact lens surface, the amount of lysozyme adsorption was measured using commercial contact lenses with different MAA contents (direct measurement).

Figure 2 shows the relationship between the amount of protein adsorbed during dipping in the artificial tear fluid (containing

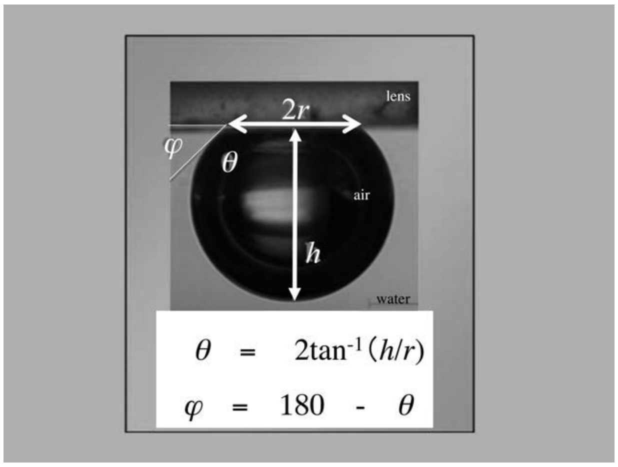

Figure 1. Picture of an air bubble on the lens surface in water, and the equations for calculating the contact angle (φ).

1.2 mg/mL of lysozyme), and the zeta potential of the lens surface, respectively, plotted against the MAA content of the lens material. The zeta potential data are from Refs. 10 and 11.

Figure 2 shows that the zeta potential of the surface decreases in proportion with the MAA content, showing that the surface was negatively charged. A significant amount of lysozyme adsorbed on the negative lens surface. For nonionic lenses, the amount of adsorbed protein was very small (10 μg/lens). Based on the results shown in Figure 2, we think that lysozyme (a cationic protein) targets the anionic sites of the lens surface, and the nonionic surface probably prevents lysozyme adsorption.

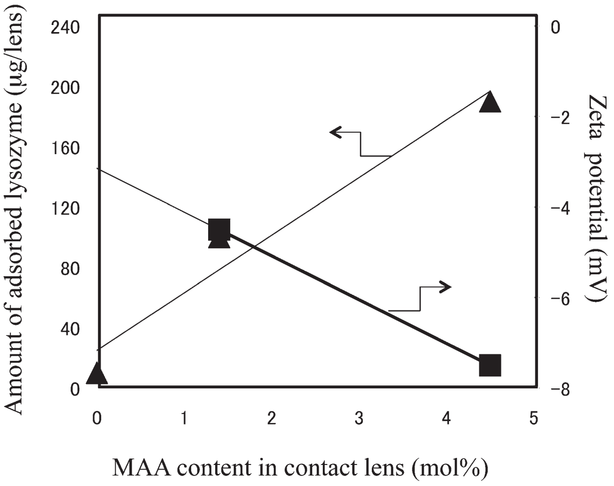

Figure 2. Relationship between MAA content, amount of adsorbed lysozyme (▲, left ordinate), and the zeta potential from Refs. 10 and 11 (■, right ordinate). Left ordinate: direct measurement of lysozyme adsorption in 1.2 μg/mL of lysozyme solution. Right ordinate: reference data measured with ELS-800 [electrophoretic light scattering (laser Doppler)]; conditions: 20°C, pH 7.0, 10×10^{-3} mol/L NaCl solution; reference particle: polystyrene latex (coated with hydroxypropyl methylcellulose for use in an aqueous solution, diameter: $d = 520$ nm).

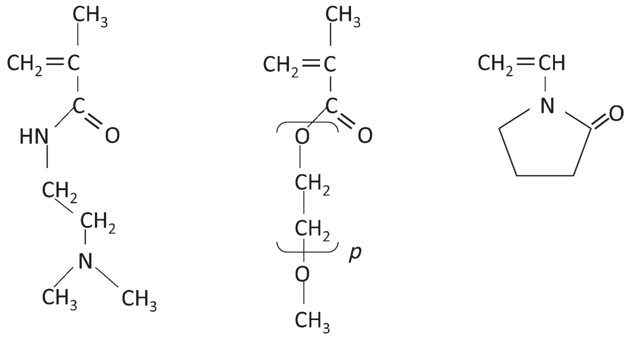

Figure 3. Chemical structures of monomers (left: dimethylaminoethyl methacrylate = DM; center: methoxy polyethylene glycol methacrylate = Mp0G, p indicates the average number of EO units (molecules); and right: vinylpyrrolidone = VP).

Polymer Preparation

To develop a surface modifier for preventing protein adsorption on contact lenses, copolymers with DM and nonionic monomer (M20G, M40G, M90G, and VP) were synthesized.[20–22] The DM moiety will be cationic because its pK_a (8.44 at 25°C) is higher than those of the artificial tear fluid (adjusted to pH 7.0) and natural tears (about pH 7.5).[25] We considered that the cationic moieties would have two important roles: one is to enhance adsorption of the copolymer itself, the other is to cover the anionic sites on the lens surface. Also, polymers with *N*, *N*-dimethylamine groups do not have antibiofouling properties of their own.[26]

The data in Figure 2 suggest that nonionic surfaces are effective in preventing protein adsorption, so two types of nonionic units were introduced into the cationic copolymer to make the lens surface nonionic. To introduce a nonionic-branched structure into the copolymer, we used methoxy polyethylene glycol methacrylate monomers, which have a poly(ethylene oxide) structure (EO; p indicates the average number of EO units; Figure 3). When VP was used, the copolymer contained nonionic moieties on the polymer main-chain.

The copolymers used in this study are shown in Table II.

The vinyl peaks in the NMR spectra showed that the amount of residual monomer was less than 1 mol %. There was a large peak at 3.8 ppm (methylene protons repeating units) from ethylene oxide, and there was no carboxylic acid caused by decomposition of the ester structure. These results confirmed that the poly-EO moiety was maintained in the copolymer structure.[27]

Prevention of Protein Adsorption Using Polymer

The amount of protein adsorbed on the contact lens treated with a 1% polymer solution was determined using the method described Experimental section (direct measurement).

Figure 4 shows the amounts of protein adsorbed on the polymer-treated contact lens surface during dipping in the artificial tear fluid. The purpose of this study is to develop safe surface-modification additives for contact lens care products, so reference polymers were selected from commercial polymers that are used in the medical or personal care fields. The vertical axis shows the polymer used for pretreatment of the contact lens.

Table II. Copolymers Used in This Study

Copolymer	Composition (mol %) DM/Mp0G	Nonionic monomer used in copolymer: Abbreviation	Nonionic monomer used in copolymer: EO chain length (number of EO units)
1	70/30	M90G	9
2	70/30	M40G	4
3	70/30	M20G	2
4	60/40	M20G	2
Reference	Composition (mol %)	Nonionic monomer used in copolymer	
	DM/VP	Abbreviation	EO chain length (number of EO units)
	50/50	VP	–

The horizontal axis is the amount of adsorbed lysozyme on the contact lens for each polymer.

A contact lens pretreated with 0.9% NaCl solution was used as a blank. The result for the blank was 220 μg of lysozyme on the lens.

The amount of lysozyme adsorbed on the contact lens treated with hydroxypropyl methylcellulose (nonionic polymer) was much larger than that adsorbed on the nontreated lens (i.e., the blank). A cationic cellulose (Leoguard® GP (XE511), Lion Corp., Tokyo, Japan) and a commercial nonionic/cationic copolymer (VP/DM copolymer, GAFQUAT® 755N, ISP Japan, Tokyo, Japan) both slightly reduced lysozyme adsorption relative to the blank lens. The amount of adsorbed lysozyme on a contact lens pretreated with a synthesized cationic/nonionic copolymer (DM/M90G copolymer) was less than one-fifth of that adsorbed on the blank lens.

To confirm the effects of the nonionic structures of the copolymers, we synthesized DM/VP and DM/M*p*0G copolymers with different EO lengths (*p* units) and evaluated their ability to prevent lysozyme adsorption.

Figure 5 shows the results for lysozyme adsorption on contact lenses treated with each copolymer, with the blank as 100%. The contact lenses used in the experiment, dyed with ninhydrin solution, are shown in the figure.

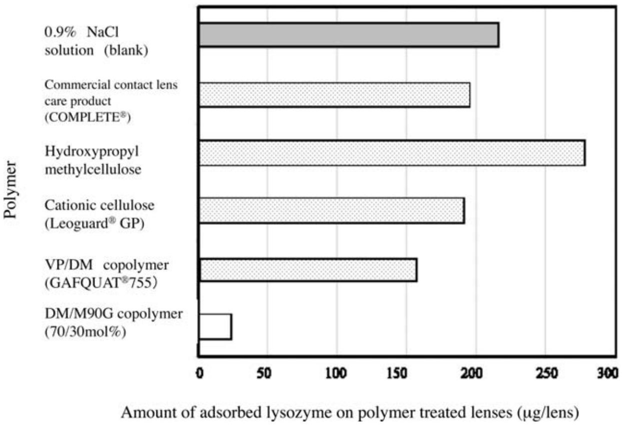

Figure 4. Effects of polymer pretreatment on lysozyme adsorption onto contact lens.

In Figure 5, it can be seen that the copolymers containing EO grafted side-chains prevented lysozyme adsorption on the lens more effectively than did the cationic/nonionic linear copolymer (DM/VP copolymer). Among the M*p*0G monomers, the effect of the EO length in the copolymer was relatively small, and the contact lenses dyed with ninhydrin solution looked almost the same to the naked eye. No other differences in the properties resulting from different EO lengths, such as contact angle, were obtained under these conditions.

The results suggest that the grafted nonionic moiety in the DM/M*p*0G copolymer is very effective in inhibiting protein adsorption. We thought the reason would be that the grafted nonionic moiety acts as a long tail on the adsorbed surface and plays an important role as a steric hindrance barrier.

Washing Ability of the Copolymer

To assess the washing ability of the DM/M*p*0G copolymer, the copolymer solution was used as a cleaning agent, and the amount of residual lysozyme on the lens was measured after

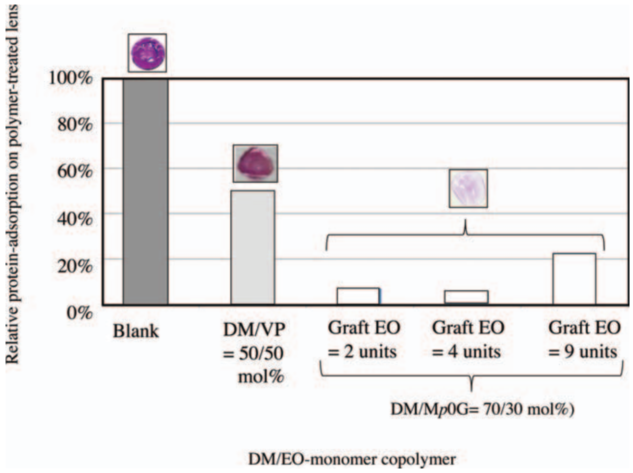

Figure 5. Comparison of pretreatment polymers with respect to ability to prevent lysozyme adsorption (the contact lenses dyed with ninhydrin solution are shown in the squares). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

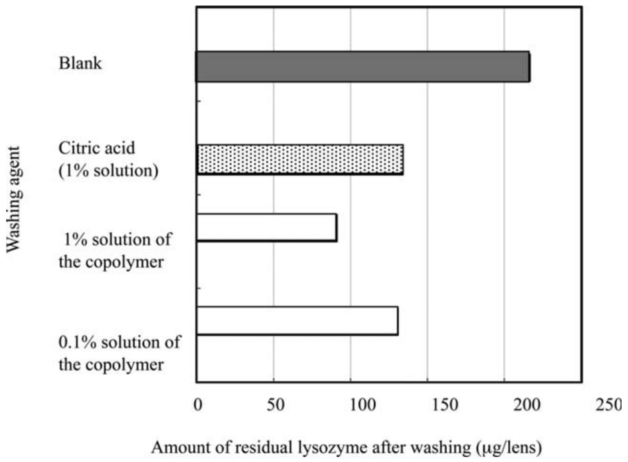

Figure 6. Residual lysozyme on the contact lens after washing with copolymer solution (DM/M20G = 60/40 mol %).

washing. Citric acid solution (1%), which is used as a cleaning agent in commercial contact lens care products, was used as a reference.

Figure 6 shows that a 1% solution of DM/M20G copolymer was much more effective than the citric acid solution, and even a 0.1% solution of the copolymer exhibited the same washing ability as a 1% citric acid solution.

Figure 7 shows the surface tensions of the solutions of DM/M*p*0G copolymers related to the polymer concentration and pH. The results show that the DM/M*p*0G copolymer had surface activity, especially at around pH 7–8. It is supposed that the un-dissociated DM moiety would act as a hydrophobic moiety, so, in higher pH regions, with DM as the hydrophobic moiety and an EO moiety as the hydrophilic moiety, the copolymer would be an amphiphilic polymer and act as a surface active agent. Furthermore, the polymer concentration affected the surface tension, so the washing ability of a 1% copolymer solution was better than that of a 0.1% solution.

The copolymer would therefore not only inhibit protein adsorption on the contact lens but also effectively wash the lens surface.

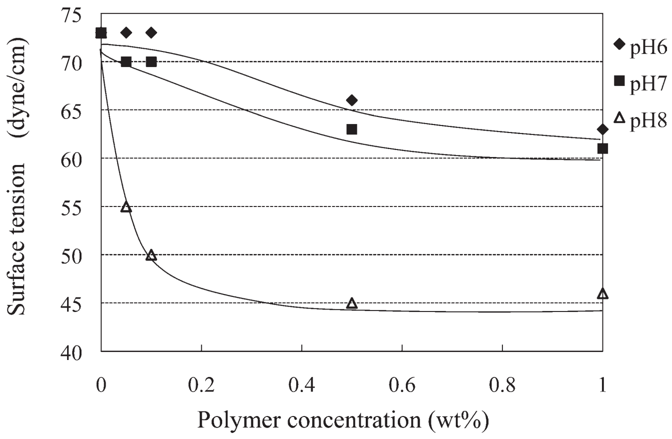

Figure 7. Surface tension of copolymer solution (DM/M40G = 80/20 mol %).

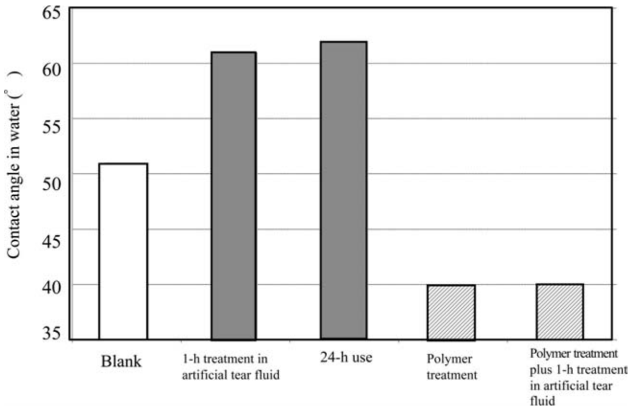

Figure 8. Contact angle of lens after treatment with copolymer solution (DM/M90G = 70/30 mol %, 1%).

Surface Properties After Polymer Treatment or Use of Contact Lenses

The surface contact angle of the contact lens in water was measured to investigate the properties of the contact lens surface; the properties changed following protein adsorption and polymer pretreatment. The results are shown in Figure 8.

The contact angle of the contact lens increased from 51° in the pristine state to 63° after 24-h use, indicating that the surface became significantly more hydrophobic. This increase in hydrophobicity is consistent with the observation that contact lens users typically feel eye dryness after 24 h. The contact angle of a contact lens soaked in artificial tear fluid (containing 1.2 mg/mL of lysozyme) for 1 h was 62°, indicating a similar increase in hydrophobicity of the surface.

These results indicate that when a contact lens is placed on the eye's surface and tear fluid spreads over it, proteins in the fluid are adsorbed on the lens surface and make the lens surface more hydrophobic. After polymer pretreatment with a 1% solution of copolymer DM/M90G, the contact angle of the lens was lower than that of the pristine lens. It is suggested that the lens surface became more hydrophilic as a consequence of the copolymer adsorption. The contact angle of the lens pretreated with copolymer DM/M90G and then soaked in the artificial tear fluid was also 40°, the same as that of the pretreated lens, indicating that the hydrophilicity of the lens kept the surface clean by preventing protein adsorption.

CONCLUSIONS

Our investigation revealed that copolymers containing a cationic moiety and an EO grafted side-chain are very useful in contact lens care products because the copolymer is able to inhibit protein adsorption on the lens and to remove adsorbed proteins when the contact lenses are pretreated or washed with the copolymer solution. These effects were thought to be the result of the ability of the EO side-chains of the adsorbed copolymer to make the lens surface hydrophilic; also, the steric effects of the long tails of the branched structure would prevent the protein from approaching the lens. Further studies of the relationships between copolymer structure and polymer adsorption are in progress.

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