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Nanoscaled Morphology and Mechanical Properties of a Biomimetic Polymer Surface on a Silicone Hydrogel Contact Lens

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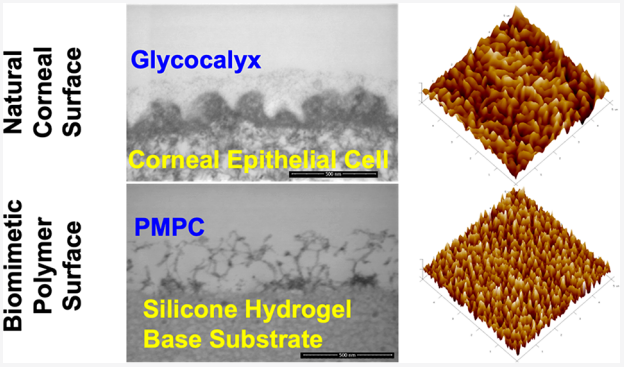
ABSTRACT: Materials taking advantage of the characteristics of biological tissues are strongly sought after in medical science and bioscience. On the natural corneal tissue surface, the highly soft and lubricated surface is maintained by composite structures composed of hydrophilic biomolecules and substrates. To mimic this structure, the surface of a silicone hydrogel contact lens was modified with a biomimetic phospholipid polymer, poly(2-methacryloyloxyethyl phosphorylcholine) (PMPC), and the nanoscaled morphology and mechanical properties of the surface were confirmed with advanced surface characterization and imaging techniques under an aqueous medium. Concavities and convexities on the nanometer order were recognized on the surface. The surface was completely covered with a PMPC layer and remained intact even after 30 days of clinical use in a human ocular environment. The mechanical properties of the natural corneal tissue and the PMPC-modified surface were similar in the living environment, that is, low modulus and frictional properties comparable to natural tissues. These results show the validity of material preparation by biomimetic methods. The methodologies developed in this study may contribute to future development of human-friendly medical devices.



1. INTRODUCTION

In biological tissue, biomolecules are highly complex and organized to express unique functions. They are responsive to the surrounding environment and capable of adapting to changing local conditions. It is clear that elucidating the process by which these complex molecular structures are derived and artificially reproducing it will be useful for creating materials. In particular, medical devices that have contact with a living tissue need to have surface properties similar to those in the living tissue. Biomimetic concepts for material design are predicated on the idea of reproducing the chemical and mechanical characteristics of biomolecules with artificial compounds. Also, since biological tissue has a complex structure and function in an environment where water is present, new methodologies are needed to observe the surface under biological conditions.

The cornea of the eye is transparent to light, wet with tears, exposed to air, and in mechanical contact with the eyelids. The anatomy on the surface of the cornea plays an important role in maintaining a wettable surface, mechanical strength, and dynamic lubricity.[1] On the corneal surface, a soft hydrogel-like matrix called the glycocalyx containing a complex matrix of glycosaminoglycan provides the necessary wettability and lubricity and covers the collagen-rich layers beneath which provide the mechanical strength and optical properties of the cornea.[2] In order to thinly and evenly distribute the tear film on the surface of the cornea, the presence of the membrane-type mucin that binds to the surface is important. However, when a contact lens is placed on the cornea, it divides the tear film into layers above and below the contact lens. Since there is no mucin layer on the surface of the contact lens, the tear film on the contact lens becomes less stable and the lubrication characteristics are also affected. This causes the rigid surface of the contact lens to come into direct contact with the upper eyelid marginal conjunctiva with increased friction and shear stress. This can lead to lid-wiper epitheliopathy and/or a marked decrease in comfort. Disturbance of the tear film on the surface of the contact lens also affects the vision quality as the tear−air interface is the primary light refraction mechanism at the corneal surface. Therefore, construction of a surface that eliminates these adverse effects is essential.

Silicone hydrogel contact lens materials, composed of a polydimethylsiloxane (PDMS) segment, have been developed

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to improve oxygen permeability.[3−5] However, prolonged wear of silicone hydrogel contact lenses induces some problems.[6−8] For example, silicone hydrogels can have poor wettability due to the hydrophobic PDMS segments that can be exposed on the contact lens surface. Proteins and lipids from the tear are adsorbed by the silicone hydrogel contact lens material and may reduce clinical performance over time. In our current research, a new material design concept for contact lenses is proposed for modification of the surface properties using loosely cross-linked poly(2-methacryloyloxyethyl phosphorylcholine (MPC)) (PMPC) to provide a similar hydrophilic nature to the corneal tissue, thereby creating a biomimetic material.[9,10] In this study, first, we proposed fine methodologies for observing the structure of the silicone hydrogel contact lens surface in a hydrated state. In particular, when a thin and swollen hydrophilic polymer layer is formed on the surface of a silicone hydrogel contact lens, the surface comes into contact with the tissue of the eye. Therefore, it is important to know the properties of the polymer layer at the contact interface from the perspective of wearing contact lenses. The morphology and mechanical properties of the PMPC-modified silicone hydrogel contact lens were compared with those of natural corneal tissue.

2. MATERIALS AND METHODS

2.1. Sample Preparation. The PMPC-modified silicone hydrogel contact lens was prepared by a previously reported method.[11,12] Briefly, to prepare the base silicone hydrogel contact lens, reagent-grade PDMS monomethacrylate, glycerol-functionalized polydimethylsiloxane dimethacrylate, *N*-vinylpyrrolidone, tetraethylene glycol dimethacrylate, methyl methacrylate, ethylene glycol methyl ether methacrylate, and 2,2′-azobis(isobutyronitrile) were mixed together and polymerized in polypropylene molds at elevated temperature. After that, the cured silicone hydrogel contact lens was removed from the mold, soaked in a poly(methacrylic acid) solution, immersed into an aqueous solution of PMPC which contains 10 mol % 2-aminoethyl methacrylate units (NOF Co., Tokyo, Japan), and finally autoclaved at 121 °C for 45 min. The sample specimens were stored under the physiological saline conditions.

2.2. Environmental Scanning Electron Microscopy (ESEM). The PMPC-modified contact lens samples were sectioned with a razor blade and then mounted onto a microvice holder with the cross-section exposed on the top.[13] The mounted samples were imaged on an environmental scanning electron microscope (Quanta FEG 250 ESEM, FEI/Thermo Fisher Scientific, Hillsboro, OR, USA) at the ESEM mode with 100% relative humidity in the sample chamber. The images were captured at a 5 kV accelerating voltage and 6−10 mm working distance. The sample stage was rotated and tilted at various angles to orient the lens section for different views of the PMPC layer on the lens surface.

2.3. Scanning Electron Microscopy (SEM). The PMPC-modified contact lens samples were cut into quarters, rinsed with 3 exchanges of deionized water, and then transferred to a 0.25% ruthenium tetroxide (RuO_4) solution (Electron Microscopy Sciences, Hatfield, PA, USA) for 30 min.[14−16] Following RuO_4 treatment, lens pieces were rinsed in 3 exchanges of deionized water, dehydrated in a graded series of ethanol aqueous solutions, and critical point dried in a Samdri 795 critical point dryer (Tousimis, Rockville, MD, USA) using CO_2. Following critical point drying, the samples were imaged on a field emission scanning electron microscope (Quanta FEG 250 ESEM, FEI/Thermo Fisher Scientific, Hillsboro, OR, USA) at the low-vacuum mode and an accelerating voltage of 10 kV.

2.4. Scanning Transmission Electron Microscopy (STEM). All experiments were carried out in accordance with the relevant guidelines and regulations set out by Alcon Research, LLC. Three normal human donor cornea tissues in Optisol-GS (Bausch & Lomb, Rochester, NY, USA) were obtained from the Kansas Eye Bank & Cornea Research Center (Wichita, KS, USA) under established guidelines related to informed consent for research use of human donor corneas.

Human cornea tissue samples were immersed in a fix containing 2.0% paraformaldehyde and 2.5% glutaraldehyde in 0.10 M Cacodylate buffer for 2 h. After initial fixation, samples were rinsed in 0.1 min Cacodylate buffer and then fixed again for 1 h with the same fixative to which 1% tannic acid had been added. Following fixation, the samples were cut into pie-shaped wedges for processing. The samples were then rinsed in 0.10 M Cacodylate buffer and osmicated in a buffered 2.0% osmium solution for 1 h. Contact lens samples were rinsed in a PBS solution and cut into pie-shaped wedges. The samples were then immersed in a 0.10% stabilized RuO_4 solution for 30 min. Both the human cornea and the contact lens samples were subsequently rinsed, dehydrated in an ascending series of ethanol, embedded in an EMBed 812/Araldite epoxy resin mixture, and polymerized overnight at 70 °C. Following polymerization of the resin, the sample blocks were sectioned using a Powertome XL ultramicrotome (Boeckeler Instruments, Tucson, AZ, USA) and then imaged using a FEI Quanta 250 FEG SEM equipped with a STEM imaging detector at the low-vacuum mode and an accelerating voltage of 30 kV.[17,18]

2.5. Atomic Force Microscopy (AFM) Imaging. Morphological evaluation of the corneas and the contact lens samples was conducted using a Dimension FastScan Bio Icon Atomic Force Microscope (Bruker Nano, Santa Barbara, CA, USA).[19−21] The PFQNM-LC-A-CAL probe was used to image the human cornea, the PEAKFORCE-HIRS-F-B probe was used for the rabbit cornea, and all of the other samples were imaged using the PEAKFORCE-HIRS-F-A probe. A custom-designed two-piece sample holder was used to mount the samples. The half-dome-shaped bottom part of the holder kept the form of the samples intact, and the top part served as a fluid reservoir to keep the samples fully hydrated during the imaging experiments. The contact lens samples were imaged in their respective packaging solution, whereas the cornea samples were imaged in a sterile saline solution. All of the imaging experiments were conducted in "PeakForce QNM in Fluid" operating mode in an antivibration enclosure and at room temperature. The AFM images of the corneas were recorded at a 1 Hz scan rate, and for the contact lenses the scan rate was kept at 0.50 Hz. The thickness of the surface features can be estimated from the peak−valley distance after image flattening. In addition, a series of AFM images was also recorded for the human cornea and the PMPC-modified silicone hydrogel contact lens sample using the incremental force set points which were then used to create a video.

2.6. Atomic Force Microscopy (AFM) Indentation. Surface indentation experiments were also conducted for the cornea as well as the contact lens samples to measure the elastic modulus of their respective surfaces.[22−25] The AFM setup and the sample holder were the same as those used for the imaging experiments. A soft cantilever PFQNM-LC-A-CAL probe was used for surface indentations. For each sample, the indentation force curves (FCs) were generated at 1.0 μm/s forward and reverse velocities with a force set point of 300 pN using the "PeakForce QNM in Fluid" operating mode. The background noise with the PFQNM-LC-A-CAL probe was used as the threshold to find the point of contact on the extend curve. The distance between the contact point and the maximum indentation displacement was defined as the indentation depth. The retract curve's linear portion was fitted using the cone−sphere model to calculate the elastic modulus. Three samples were tested for each group, and three indentations on different locations were performed on each sample. The average and standard deviation values of the surface elastic modulus were calculated from the 9 indentation FCs for each group.

2.7. Clinical Samples. Five PMPC-modified silicone hydrogel contact lenses were obtained after 1-month daily wearing and cleaning from Alcon's clinical trials that were conducted in compliance with the Declaration of Helsinki. Informed consent was given and signed by all participants prior to enrollment in the study.

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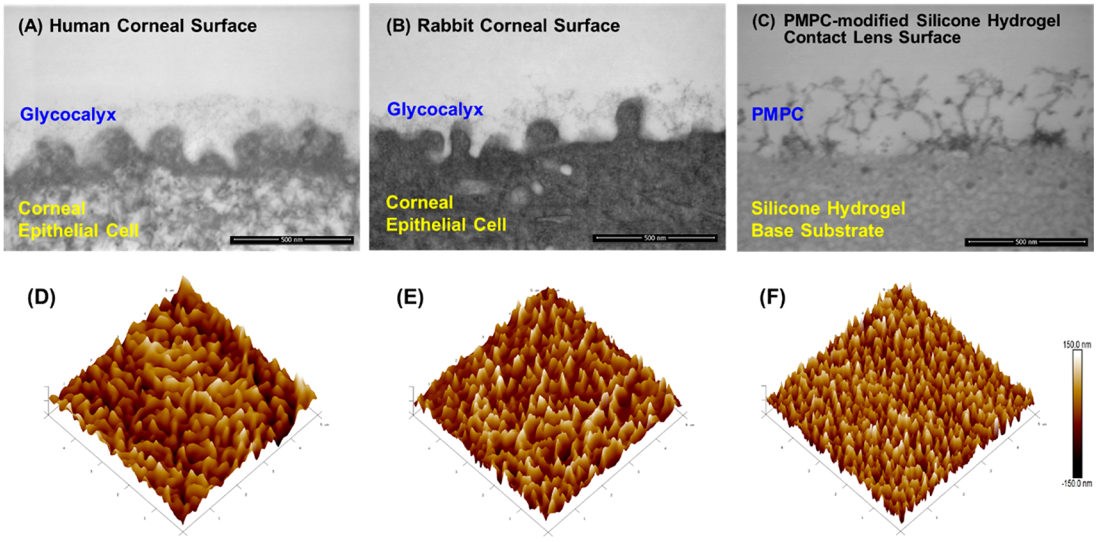

Figure 1. STEM images of the human corneal surface (A), rabbit corneal surface (B), and PMPC-modified silicone hydrogel contact lens surface (C). Scale bars, 500 nm. AFM images (5 μm × 5 μm) of the human corneal surface (D), rabbit corneal surface (E), and PMPC-modified silicone hydrogel contact lens surface (F). All AFM experiments were conducted in aqueous media.

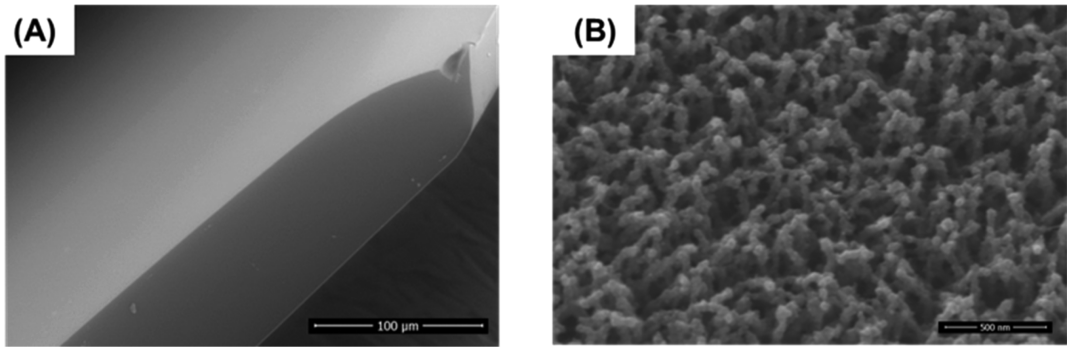

Figure 2. ESEM image of the cross-section of a PMPC-modified silicone hydrogel contact lens (A). Scale bar, 100 μm. SEM image of the PMPC-modified silicone hydrogel contact lens surface (B). Scale bar, 500 nm.

3. RESULTS AND DISCUSSION

3.1. Morphology of PMPC-Graft Silicone Hydrogel Contact Lens. In a previous study, we confirmed that the chemical reaction between PMPC having a small amount of a primary amino group and the silicone hydrogel base material combined with poly(methacrylic acid) is suitable to make a stable PMPC layer on the surface.[11] The chemical structure of PMPC is shown in Figure S1. The thickness of the PMPC layer formed on the surface is in the range from 200 to 500 nm, which is observed using atomic force microscopy in aqueous media. In our previous article, we reported that the contact angle of the air bubble on the surface of the swollen PMPC-modified silicone hydrogel contact lens in aqueous medium is 180°, which corresponds to a water contact angle under atmosphere of 0°. Thus, the surface exhibited superhydrophilicity.[11] In addition, the PMPC-modified silicone hydrogel contact lens can prevent adsorption of biological components such as lipids and proteins from tears.[12] However, the morphology of the PMPC chains at the interface was not clear. In this study, we observed the morphology of the PMPC layer on the silicone hydrogel contact lens surface and clarified its similarity to the natural corneal tissue.

Compared to conventional transmission electron microscopy (TEM), scanning transmission electron microscopy (STEM) is more suitable for polymeric materials because its scanning of the fine electron beam across the sample may decrease the knock-on damage and increase the contrast of weakly scattering objects.[26] We discovered that combining the low chamber pressure of 50 Pa and a low accelerating voltage of 30 kV could minimize the beam damage and achieve nanoscale resolution for both cornea tissues and the biomimetic engineered corneal surface on the PMPC-modified silicone hydrogel samples. This further demonstrated the similarity between the cornea tissues and the PMPC-modified substrate.

As shown in Figure 1A,B, an ultrafine network of glycocalyx was clearly visible on the surface projections, i.e., microvilli and microplicae, of the human and rabbit corneal epithelia. Similarly, a 300−400 nm thick layer of gelatinous PMPC with interpenetrating networks closely mimicking the glycocalyx structures was observed on the surface of the silicone hydrogel base substrate (Figure 1C). This was the first study to clearly visualize the biomimetic morphology of a PMPC hydrogel on the surface of a medical device.

The apical cell membrane of the corneal epithelial layer exhibits microvilli and microplicae, which expresses membrane-associated mucins to form the surface glycocalyx.[2,27] The glycocalyx not only contributes to formation of an optimal tear film but also provides a barrier to the penetration of large

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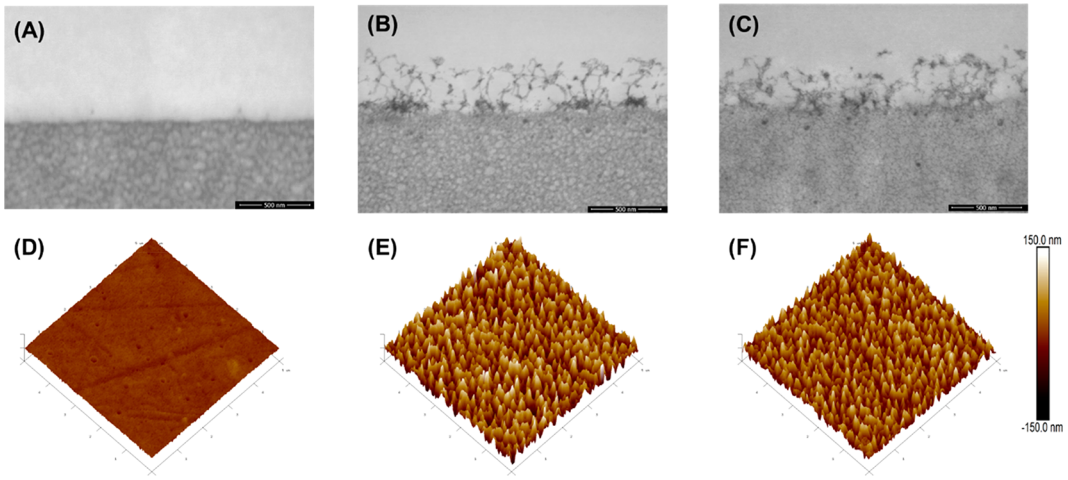

Figure 3. STEM images of the silicone hydrogel base substrate (A) and PMPC-modified silicone hydrogel contact lens surface before (B) and after 30-day wearing on the eye (C). Scale bars, 500 nm. AFM images (5 μm × 5 μm) of the silicone hydrogel base substrate (D) and PMPC-modified silicone hydrogel contact lens surface before (E) and after 30-day wearing on the eye (F).

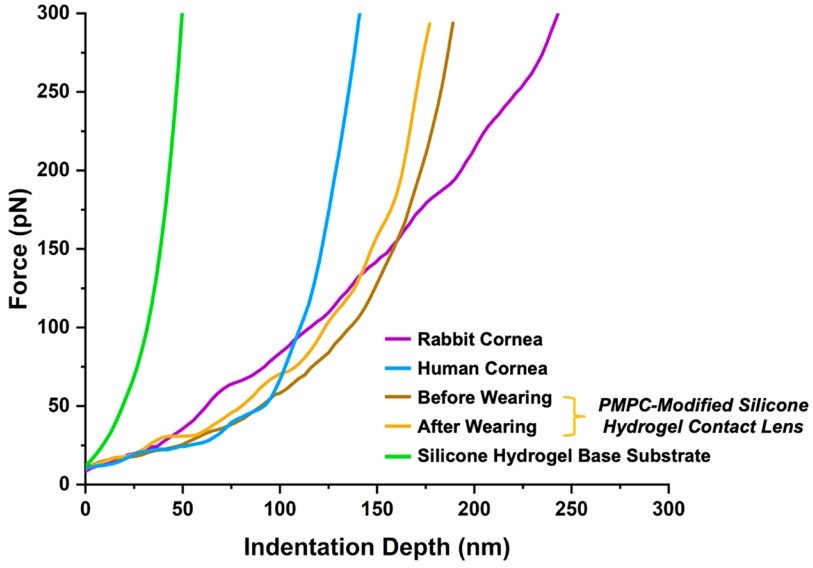

Figure 4. AFM indentation of the silicone hydrogel base substrate, PMPC-modified silicone hydrogel contact lens surface before and after 30-day wearing on the eye, human corneas, and rabbit corneas. Representative force−indentation depth plots.

molecules and pathogens.[1] The corneal epithelial cells with the glycocalyx create a gel-like layer of protection and stabilize the tear film. This allows the tear film to spread across the surface of the cornea and for foreign bodies potentially to be swept away.

As shown in Figure 1D−F, which provide additional AFM images of the human cornea, rabbit cornea, and biomimetic engineered surface on the PMPC-modified silicone hydrogel substrate, the dynamic surface structures of both the glycocalyx and the PMPC-modified substrate are key features for biomimetic ophthalmic materials to enhance the biocompatibility on the cornea surface.

PMPC has valuable properties: it is water soluble, hydrophilic, and electrically neutral as a whole molecule; it has extremely high stability in the biological environment; it is stable even in a sterilization environment such as an autoclave.[10,28] At the surface of the silicone hydrogel contact lens, surface modification with PMPC can suppress biological reactions and deposits as well as provides a soft gel surface interface with corneal tissue that is based on a bioengineered artificial corneal structure.

To mimic these essential corneal surface features, we engineered a glycocalyx-like PMPC grafting layer on the surface of a silicone hydrogel contact lens. At a hydrated or 100% relative humidity environment in an environmental scanning electron microscope (ESEM), the contact lens was saturated with water and its water-rich surface appeared as smooth as the tear-covered corneal surface (Figure 2A). In the ESEM image of the lens cross-section, the dark bulk area was the base silicone hydrogel material with a 55% water content while the bright surface area represented the grafted PMPC layer with a nearly 100% water content, which provides a smooth refractive surface. When water was removed from the contact lens via critical point drying, a dense grafting layer of PMPC in a brush-like structure became visible on the lens surface as shown in the SEM image (Figure 2B). In addition, the high-resolution AFM surface imaging of the fully hydrated contact lens with a grafting layer of PMPC also reveals the

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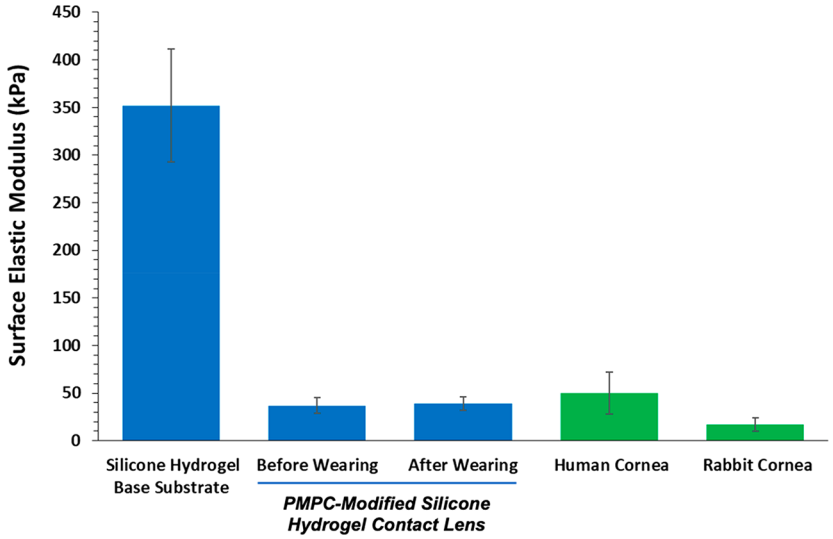

Figure 5. AFM indentation of the silicone hydrogel base substrate, PMPC-modified silicone hydrogel contact lens surface before and after 30-day wearing on the eye, human corneas, and rabbit corneas. Elastic modulus of the surface layer estimated from $n = 3$ samples for each group.

uniform presence of the brush-like structure as shown in Figure 1D. Both the SEM and the AFM images revealed highly branched and interconnected networks of ultrafine polymer gel structures, which covered the surface of the whole contact lens. It is this loose polymer gel structure along with the superhydrophilic nature of PMPC that enables this engineered surface to hold a layer of water, closely resembling the function of the glycocalyx on the human ocular surface.[29] The grafting layer of PMPC on the substrate can stabilize the tear film and reduce adhesion by foreign bodies.[30]

3.2. Effect of Wearing on Morphology of the Surface. In the natural eye system, surface wetting and lubricity are dominant by the characteristics of the hydrated glycocalyx, which binds to the corneal tissue surface and functions at the tear−contact interface. In our biomimetic surface design, a glycocalyx-like structure of PMPC was strongly linked to the silicone hydrogel contact lens as shown in the STEM and AFM images (Figure 3A, 3B, 3D, and 3E).

Such a soft PMPC-modified surface exhibited extended good robustness and could not be removed by mechanical rubbing, surfactant cleaning, or high-temperature treatment such as autoclave sterilization. Even after 30 days of wearing on the eye, with blinking millions of times, 30 cycles of cleaning by finger rubbing, and overnight soaking in surfactant-containing lens care solutions, this PMPC-modified layer remained on the silicone hydrogel contact lens surface with no or little change in the structure as seen in both the STEM and the AFM images of the worn lenses (Figure 3C,F).

3.3. Surface Mechanical Properties of the PMPC-Modified Silicone Hydrogel Contact Lens. AFM indentation technology has been widely utilized to characterize the surface mechanical properties of biological cells and soft materials.[31] For further confirmation of the nature of the PMPC layer, AFM indentation testing was employed to measure the softness of both the corneal and the PMPC-modified silicone hydrogel contact lenses.

Figure 4 shows representative force curves of the natural cornea and PMPC-modified silicone hydrogel contact lens. An indentation force of 300 pN was chosen to generate a contact pressure within the physiological range of the upper eyelid pressure on the human ocular surface.[32,33]

On the basis of the geometry of the AFM probe used for the indentation, a cone−sphere model was employed to estimate the elastic modulus from the indentation force curves of the surface of the silicone hydrogel base substrate, PMPC-modified silicone hydrogel contact lens surface, and cornea samples.

Figure 5 shows the surface elastic modulus of the PMPC-modified silicone hydrogel contact lens before and after 30 days of wearing on the eye. It is clear that the surface elastic modulus did not change significantly, and it were similar to those of human and rabbit cornea surfaces but significantly lower than that of a silicone hydrogel contact lens ($p < 0.01$). Overall, the AFM indentation results show that the hydrated PMPC surface not only mimicked the morphology of the ocular surface but also had a surface softness similar to that of corneal tissue. Such ultrasoft surface properties of both a PMPC-modified silicone hydrogel contact lens and corneal tissues can be attributed to the soft, high water surface structures of both the PMPC chain and the glycocalyx.

In order to capture/record the inherent structural mobility of these ultrasoft surface structures, both engineered and natural corneal surfaces were subjected to varying tapping forces using a sharp AFM probe in a saline solution, and they exhibited very dynamic and mobile flexibility (Supplementary AFM Videos 1 and 2), just like a sea anemone moving freely under water. Such attributes of the corneal surface are believed to facilitate tear film spreading and stabilizing and protect the cornea from foreign bodies.[34,35] A similar mechanism might explain the ultrasoft, lubricious, and antifouling properties of the PMPC-modified layer on the silicone hydrogel contact lens.[29] The PMPC graft chain on the surface moved freely in saline solution, which might be key to the mechanism of the ultrasoft, lubricious, and antifouling properties of the corneal surface as well as this biomimetic engineered surface.

It is a very important that the contact lens complies with the ocular environment. In a living system, free mucin and immobilized mucin play an important role in lubrication during blinking. The PMPC-modified surface having a structure similar to this surface state has high lubricity due to the high hydration property that is also exhibited in the biological environment. It has been reported that the PMPC-modified silicone hydrogel surface can significantly improve

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lubricity,[11] and the PMPC surface grafted on the surface of polyethylene suppresses the wear of the substrate even after 10 million sliding tests in a medium containing bovine serum.[36] Its dynamic friction coefficient is 0.005−0.02 dependent on the load.[37] The lubrication mechanism on the PMPC-modified surface has also been analyzed, and it has been shown that the hydrated PMPC layer provides fluid lubrication.[38,39] The coefficient of friction when sliding between the hydrogel and the human cornea is 0.03.[40] However, the coefficient of friction between the conventional silicone hydrogel contact lens and the cornea is reported to be in the range from 0.04 to 0.08.[41] As the coefficient of friction of human corneal tissue is reported to be 0.015 ± 0.09 in a tear-like fluid in phosphate-buffered saline,[42] it is clear that the PMPC-modified silicone hydrogel contact lens possesses a sufficiently low coefficient of friction against the cornea tissue.

4. CONCLUSIONS

We presented a biomimetic surface with an engineered biomaterial on a widely used medical device. Medical devices used in contact with living tissue need to have a good affinity for the same. This symbiosis between the two reduces the chances of any irritation to the living tissue and maintains the function of the medical device for an extended period of time. At the interface with the living tissue, it is often an environment mediated by body fluids. In other words, many types of ions, lipids, and proteins are present in water media, and in a complex fluid environment related to cell lines and biological tissues, the surface is required to be compatible with the environment, which is extremely important for materials science.

The results in this study demonstrated that the PMPC grafting on the surface of the silicone hydrogel contact lens had a robust nanoscaled morphology similar to the natural corneal surface even after 30 days of daily wearing and cleaning. Also, the mechanical properties of the PMPC-modified surface were comparable to those of human corneal tissue. The dynamic PMPC structure mimicking the glycocalyx at the natural tissue surface is the key feature for producing biomimetic ophthalmic materials to enhance the interfacial compatibility of the contact lens medical device. The imaging and surface characterization methodologies established in this study may be applied to future studies of biomimetic engineered medical devices.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.langmuir.1c02678.

Chemical structure of PMPC (PDF)

AFM video of the surface movement of the human corneal tissue (MP4)

AFM video of the surface movement of the PMPC-modified surface (MP4)

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Author Contributions

J.Y.W. was the principal investigator for this research. J.Y.W., G.Y., and X.S. designed the study and analyzed the data. V.S. developed the AFM imaging and indentation methods and performed surface analysis. D.C.-C. developed and performed the ESEM, SEM, and STEM experiments. K. F. and K. I. contributed to the scientific discussion and data analysis. All authors contributed to the writing of the manuscript.

Notes

The authors declare no competing financial interest.

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