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Anthocyanin-Functionalized Contact Lens Sensors for Ocular pH Monitoring

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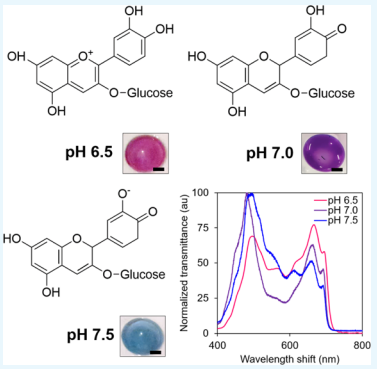
ABSTRACT: Anthocyanins are bioactive compounds naturally found in a variety of leaves, fruits, and vegetables. Anthocyanin pigments undergo a modification in their chemical structure when exposed to different concentrations of hydrogen ions, and they were extensively studied to be used as active elements in biocompatible pH sensors. The ocular pH is a significant parameter to assess the ocular physiology in cases of postocular surgery, keratoconjunctivitis, and ocular rosacea. Contact lenses have the potential to be used as medical diagnostic devices for in situ continuous monitoring of the ocular physiology. Here, anthocyanin-functionalized contact lenses were developed as wearable sensors to monitor the ocular pH. Anthocyanin pigments were extracted from *Brassica oleracea* and used to functionalize the polymeric matrices of commercial soft contact lenses by soaking and drop-casting processes. Contact lenses responded to the physiological ocular pH of 6.5, 7.0, and 7.5, exhibiting a systematic color shift from pink (pH 6.5) to purple (pH 7.0) and blue (pH 7.5). The functionalization of contact lens sensors was evaluated as a function of the dye concentration. Quantitative values were obtained by comparing the RGB triplets of the colors obtained with the naturally extracted dye and with delphinidin chloride dye in 0.0 to 1.5 mmol L^{-1} aqueous solution. The functionalization of contact lenses was studied as a function of the soaking time, resulting in best results when soaking for 24 h. The dye leakage from the contact lenses in deionized water was evaluated, and a negligible leakage after 18 h was observed. Poly-2-hydroxy ethylmethacrylate contact lenses were fabricated and cross-linked with anthocyanin dye, resulting in a slight color shift upon pH changes from 6.5 to 7.4. Contact lens pH sensors may be used to continuously monitor the ocular pH at point-of-care settings.



INTRODUCTION

Anthocyanins are colored water-soluble pigments contained in a range of edible fruits, vegetables, and flowers and are consumed as dietary polyphenols.[1] Primary anthocyanins found in nature include cyanidin, peonidin, delphinidin, and petunidin. The chemical structure of anthocyanins consists of a flavylium nucleus attached to one or more sugars, such as D-glucose, D-galactose, L-rhamnose, and D-arabinose.[2] The chemical stability of anthocyanins is influenced by pH, which induces a color shift from red in acidic conditions to blue in basic conditions. Besides their use as natural dyes, anthocyanins have shown antioxidative and antimicrobial properties. They improve visual and neurological health;[3] they were reported to induce a decrease in coronary heart disease, and they were used as the main components in antidiabetic preparations.[4] Delphinidin chloride is an anthocyanidin, and its antioxidant activity results from its degradation products, such as gallic acid. Anthocyanidins induce a higher secretion of immunosuppressive proteins, suggesting potential applications in the treatment of autoimmune diseases.[5] Other studies showed that anthocyanidins decrease obesity and improve bone density.[6] There is an increasing need for developing technologies to minimize microbial film formation in several fields of application,[7] and anthocyanin-functionalized surfaces were reported to decrease bacterial adhesion.[8]

Anthocyanins were extensively studied in the field of intelligent packaging to provide food preservation and detect food deterioration. Anthocyanin-containing thin films were synthetized with various methods. Thin layers were produced using anthocyanins extracted from corn starch, glycerol, and blueberry powder and casted to obtain colorimetric pH indicators.[9,10] pH-sensitive indicators were also synthetized by electrospinning in the form of membranes for pharmaceutical applications. pH dyes were trapped within ultrafine polymer fibers with a diameter of 510 nm, which exhibited a color change from pink to green when exposed to acidic and alkaline buffers, respectively.[11] Naturally extracted anthocyanins were extensively used as dopants to polymeric complexes, such as polyvinyl alcohol/chitosan, to monitor food product quality in real time

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associated with temperature and pH variations.[12] Anthocyanins may be also immobilized on natural solid matrices. Anthocyanins extracted from *Ipomoea batatas* were immobilized on agar and potato starch to produce pH-sensitive films in the range 2.0−10.0 to be used as meat spoilage sensors.[13] Another study reported the usage of anthocyanins extracted from *Brassica oleracea* as dopants in bacterial cellulose nanofibers. Concentrations of anthocyanins from 32 to 193 mg L^{-1} induced a change in the morphological properties, thus in the colorimetric response, of bacterial cellulose nanofibers as pH probes. This was attributed to the chemical interactions occurring between the bacterial cellulose membrane and anthocyanins, resulting in a decrease of the diffraction intensities of bacterial cellulose upon the addition of anthocyanin concentrates, which induced partial disintegration of cellulose microfibrils. In contrast, the intrinsic morphology of the nanofibers could be preserved by adding diluted anthocyanins, with a clearer response to pH variations.[14]

With regard to the ocular environment, anthocyanins were found to have beneficial effects on the retinal tissue.[15−17] The staining effectiveness of anthocyanin dyes was demonstrated in ex vivo pig eyes and their retinal biocompatibility in in vitro retinal cells cultures.[18] The safety of intravitreal injection of anthocyanin dyes into rat eyes was assessed by electroretinography (ERG) functional test, which measured the electrical activity generated by retinal cells in response to a light stimulus to assess retinal toxicity. ERG waveforms obtained prior and after anthocyanin injection were comparable, suggesting that anthocyanin dyes did not induce ocular toxicity. Additionally, the oral intake of products containing anthocyanins was recently shown to prevent the myopic refractory shift caused by working at visual display terminals.[15] Anthocyanins were also reported to stimulate the regeneration of rhodopsin in the rod outer segment membranes of frogs.[17] Anthocyanins accumulated in the ocular tissue have shown to improve visual function.[16] These studies provide promising insights into the ability of anthocyanins to prevent several oxidative stress-associated diseases and indicate that anthocyanins might also be beneficial in intraocular surgery. Future potential ocular applications of anthocyanin dyes include vitreoretinal surgery and chromovitrectomy.[18]

Monitoring the ocular pH is highly desirable at a point-of-care setting with a range of applications.[19−21] Originally, human tear pH measurements were carried out using glass electrodes in contact with the cornea,[22] using fluorescent probes,[20] glass probes,[19] and microelectrodes.[23] Healthy tear pH values range from 6.5 to 7.6.[19,20] The significance of ocular pH was highlighted in relation to evaluating the tear buffering capacity, associated to the monitoring of keratoconjunctivitis sicca[21] and to estimate the ocular penetration of drugs.[24] Hydrogen ion concentration in the ocular microenvironment was targeted as a biomarker for the early diagnosis of rosacea, which induces corneal melting and stromal scarring.[25,26] Ocular rosacea patients were reported to have an ocular pH of up to 0.9 units higher when compared to healthy controls.[25] The tear pH was found to increase in senile cataract patients, resulting in pH values ranging from 7.26 ± 0.23 on the day before operation to 7.50 ± 0.23 on the first postoperative day.[27] In the increasingly demanding field of wearable sensors for personalized medicine, contact lens sensors are gaining increasing popularity to provide point-of-care continuous monitoring.[28,29]

Here, a pH-sensitive contact lens was developed to aid the monitoring of the ocular physiology. A naturally occurring anthocyanin dye was chosen to target biocompatibility and to ease the readout of the sensors. The anthocyanin dye was extracted from *B. oleracea,* and its colorimetric response was compared to commercial delphinidin chloride dye to quantify the concentration of the dye suitable to functionalize contact lenses. The anthocyanin dye extracted from *B. oleracea* was chosen in quality of being the most stable upon temperature variations because of the acyl protection of the hydroxyl groups within the molecule.[30,31] The presence of the sugar in anthocyanin allows the molecule to remain stable in water.[32] Contact lens sensors exhibited a pH-dependent color change when tested in pH buffer solutions of 6.5, 7.0, and 7.5. The optical response was evaluated as a function of the concentration of dye in the soaking solution and of the soaking time. Leakage tests were conducted by storing dyed contact lenses in deionized (DI) water, and analyzing the transmittance of the storage solution after 1 min to 24 h. After 18 h, saturation of the leakage was observed. Lacreon and lacreon-free contact lenses were tested. Poly-2-hydroxy ethylmethacrylate (HEMA) contact lenses were cross-linked with anthocyanin dye to evaluate the impact of the chemical processes on the color change.

RESULTS AND DISCUSSION

Anthocyanin dye was extracted from *B. oleracea* var *capitata* (red cabbage) and diluted in DI water at different percentages to obtain pH-sensitive solution. Figure 1a shows the chemical structure of the anthocyanin dye exposed to buffer solutions at pH 6.5, 7.0, and 7.5 and the resulting contact lenses obtained

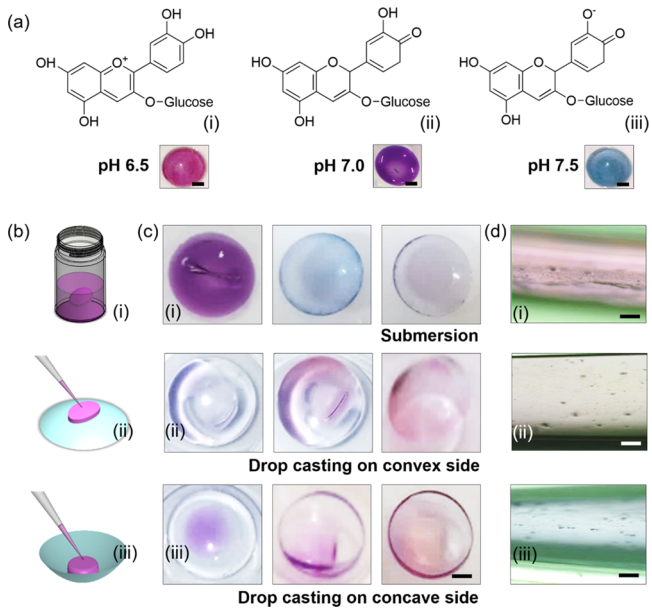

Figure 1. Preparation of the pH-sensing solution and its optimization for dying soft contact lenses. (a) Anthocyanin chemical formulas at pH physiological levels. (i) pH 6.5, (ii) pH 7.0, (iii), and pH 7.5. Inset photographs show tinted contact lenses at different pH values. Scale bars: 5.0 mm. (b) Schematic of the pH-sensing lens preparation methods: (i) soaking and (ii,iii) drop-casting on the convex/concave face of soft contact lenses. (c) Color changes observed in contact lenses tinted with different methods. (i) Submersion method and (ii) drop-casting on convex face. (iii) Drop-casting on the concave face. Scale bars: 5.0 mm. (d) Micrographs showing the cross sections of soaked contact lenses at pH 6.5 (i), pH 7.0 (ii), and pH 7.5 (iii). Scale bars: 200 μm.

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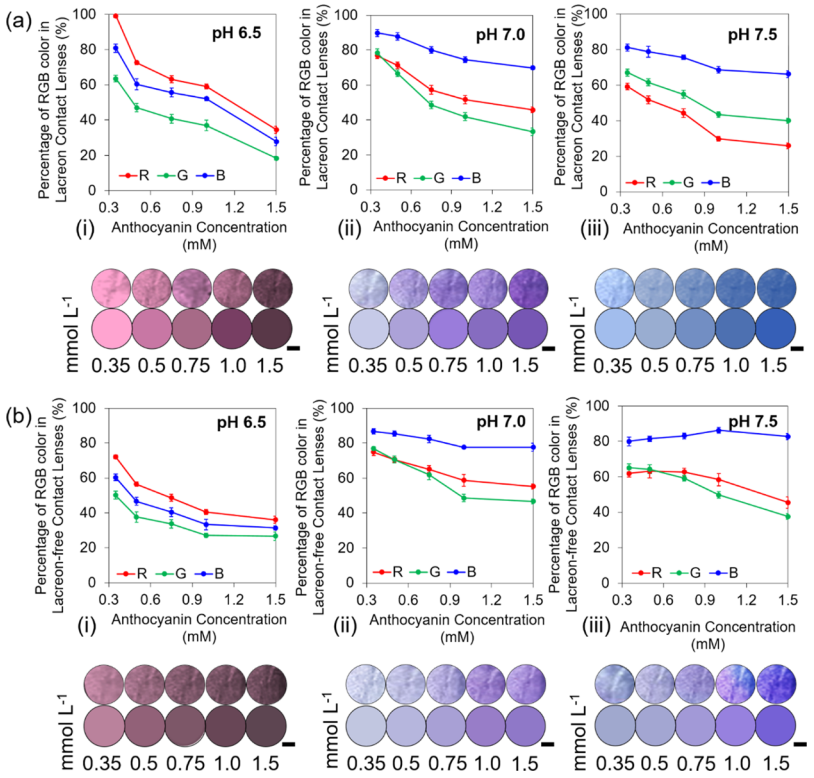

Figure 2. pH-induced colorimetric changes of dyed contact lenses. (a) Percentage of the RGB color of lacreon-containing contact lenses at different pH levels, as a function of the dye concentration in solution. (i) pH 6.5, (ii) pH 7.0, (iii) pH 7.5. Inset micrographs show the color of the contact lens and the normalized color acquired with the smartphone application. Scale bars: 2.0 mm. (b) Percentage of the RGB color of lacreon-free contact lenses at different pH levels, as a function of the dye concentration in solution. (i) pH 6.5, (ii) pH 7.0, and (iii) pH 7.5. Inset micrographs show the color of the contact lens and the normalized color acquired with the smartphone application. Scale bars: 2.0 mm.

by the soaking method. The molecular structure of the anthocyanin dye changed when exposed to different concentrations of hydrogen ions. At acidic pH conditions, the flavylium cation allowed the molecule to absorb light and reflect wavelengths in the red-pink area of the visible spectrum.[33,34] At alkaline pH conditions, the molecule deprotonated because of the hydration of the flavylium cation, and the pigment reflected wavelengths in the blue-green area.[35]

Contact lens pH sensors were obtained by impregnating the polymeric matrices of commercial soft contact lenses with anthocyanin solution by soaking and drop-casting processes, performed on either the concave or the convex face of contact lenses (Figure 1b). Soft contact lenses were chosen over rigid gas permeable lenses because of their higher hydrophilicity.[36] Contact lens sensors were tested in the physiological ocular pH range of 6.5−7.5. Figure 1c shows photographs of contact lenses dyed with different methods. Micrographs of the cross section of contact lenses are presented in Figure 1d. 1-Day ACUVUE Moist lenses with and without lacreon were used and compared to evaluate the impact of lacreon on the dying process toward an efficient colorimetric detection of hydrogen ions. As expected,[37,38] lacreon-containing contact lenses held a higher concentration of dye, which resulted in an enhanced moisture retain, and brighter colors were distinguishable with the naked eye. The equivalent concentration of the extracted dye in solution was calculated by comparing the transmission spectra of contact lenses soaked in aqueous solutions containing the naturally extracted dye at percentages of 25, 33, 50, 75, and 100% (wt/wt) to contact lenses soaked in 0.35, 0.5, 0.75, 1.0, and 1.5 mM delphinidin chloride aqueous solution. In the soaking process, the lens was submerged in 20 mL of dye aqueous solution for 24 h. In the drop-casting method, 500 μL of dye aqueous solution was poured on the convex/concave faces of the lens. The drop-casting method led to limited distribution of the dye across the lens when compared to the soaking method, which in turn resulted in a higher permeation and a homogeneous spatial distribution of the dye. Drop-casting on the concave and convex side of the lens led to a higher concentration in the center and on the sides, respectively, as it was intuitive in the case of curved surfaces.

Quantitative investigation of color changes in dyed contact lenses exposed to pH buffer solutions was carried out by measuring the RGB coordinates associated with the color of the contact lens at pH levels of 6.5, 7.0, and 7.5, using a smartphone camera and a color recognition application at laboratory light levels of 200 lux. Figure 2 shows the percentages of RGB color variation of lacreon (Figure 2a) and lacreon-free (Figure 2b) contact lenses soaked in aqueous solutions containing dye concentrations of 0.35−1.50 mmol L^{-1}. Insets show the imaged lens and the normalized color at different concentrations and pH values. Lacreon-containing contact lenses reported a color variation that was more easily distinguishable with the naked eye for all concentration values tested. At pH 7.5, lacreon-containing contact lenses exhibited a blue color with different intensities and saturations upon variations in the concentration of the dye in solution. Lacreon-free contact lenses exhibited a purple-blue color, often not distinguishable from the color at pH 7.0 with the naked eye. Moreover, lacreon-containing contact lenses exhibited a more homogeneous color. Both contact lenses showed bright colors that

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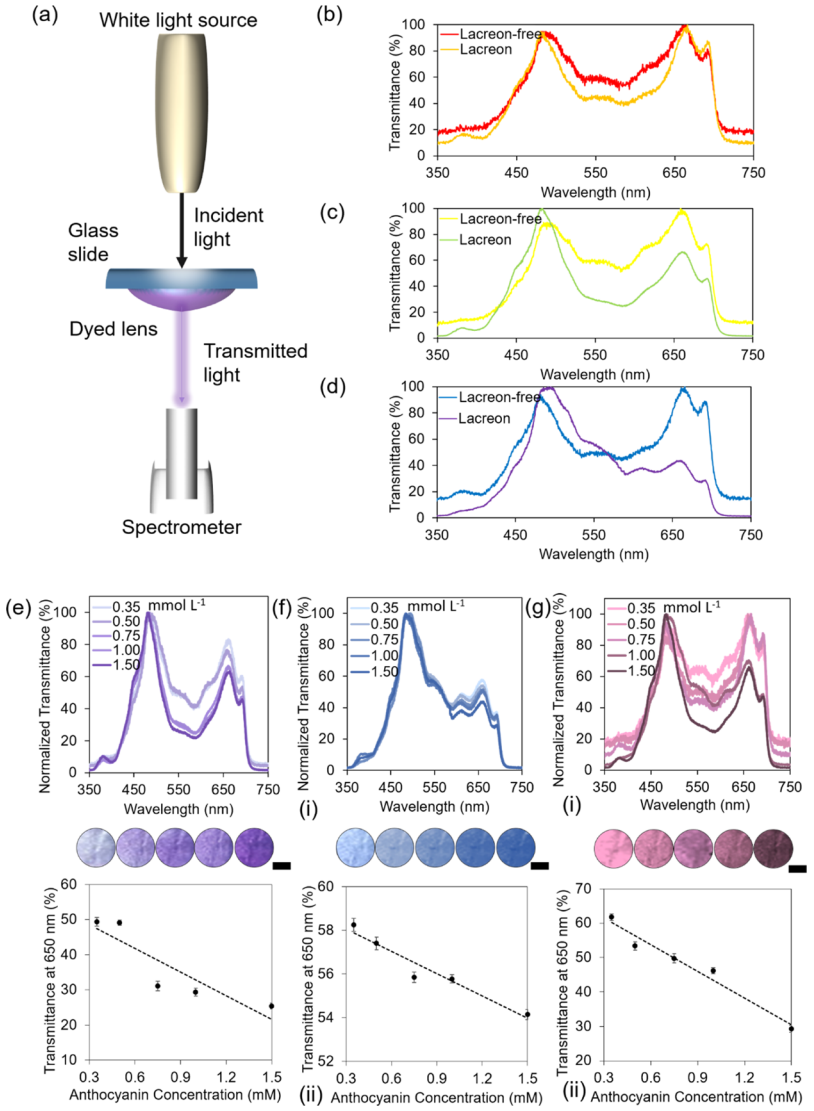

Figure 3. Optical characterization of dyed contact lenses. (a) Schematic of the spectroscopy measurement setup in the transmission mode. (b–d) Comparison between transmission spectra of lacreon-containing and lacreon-free contact lenses dyed in 0.5 mM anthocyanin solution at pH 6.5 (b), pH 7.0 (c), and pH 7.5 (d). (e–g) Transmission spectra of lacreon-containing contact lenses dyed by the soaking method in 0.35–1.5 mM anthocyanin solution, exposed to pH buffers. (e) pH 6.5, (i) transmission spectra and (ii) transmittance trend at 650 nm. (f) pH 7.0, (i) transmission spectra and (ii) transmittance trend at 650 nm. (g) pH 7.5, (i) transmission spectra and (ii) transmittance trend at 650 nm. Insets show photographs of the contact lenses. Scale bars: 2.0 mm.

reached RGB percentages of up to 90% when imaged at a distance of 5.0 cm and at ambient light conditions of 200 lux. Lacreon-containing contact lenses were therefore chosen over lacreon-free contact lenses and prepared by the soaking method for further characterizations.

The spectral characterization was performed in the transmission mode with the setup depicted in Figure 3a. The transmission spectra of dyed contact lenses in 0.5 mM solutions showed two peaks at wavelengths 470 nm (blue) and 660 nm (red) (Figure 3b–d). At pH 6.5, both lacreon-containing and lacreon-free dyed contact lenses exhibited two peaks at 470 and 660 nm, with intensities of 1.03 and 1.02, respectively. The depths of the green-yellow band reported maxima of 60% and 40%, for lacreon-free and lacreon-containing dyed contact lenses, respectively. At pH 7.0, the intensity ratios in the transmission spectra for lenses were 1.13 and 1.66 and the depths of the green-yellow bands yielded maxima of the 50% and the 22%, for lacreon-free and lacreon-containing dyed contact lenses, respectively (Figure 3c). At pH 7.5, the transmission spectra of lacreon-containing lenses showed a suppression of the red band, with an intensity ratio of 2.5. However, lacreon-containing contact lenses showed the highest intensity peak, which reached 100% at 660 nm (Figure 3d). Changes in the intensity ratio of the two peaks and of the depths of the green-yellow band (500–650 nm) indicated the color shift of contact lens sensors. Figure 3e–g shows the transmission spectra of lacreon-containing contact lenses at pH levels of 6.5, 7.0, and 7.5, as a function of the concentration of the dye in solution. A decreasing trend was observed in the depth of the 500–650 nm band and in the peak at 660 nm upon increasing the concentration of the dye in solution.

To test the effect of the soaking time on the dying process, contact lenses were soaked in anthocyanin solution for 1 min, 3, 6, 12, 18, and 24 h. Transmission spectra were acquired at each step (Figure 4a). A systematic increase of the peak intensity at 660 nm was observed in the transmission spectra of

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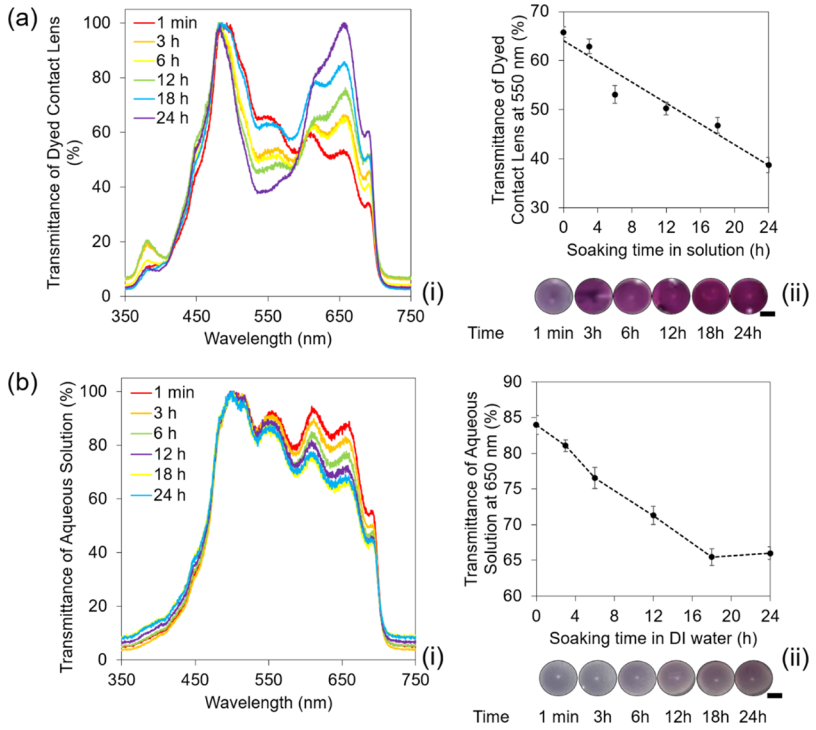

Figure 4. Soaking process over time and dye leakage in storage solution. (a) Soaking time effect on the transmittance of contact lens sensors. (i) Transmission spectra at different soaking times. (ii) Transmittance trend over the soaking time. Insets show photographs of contact lenses soaked for different intervals, from 1 min to 24 h. Scale bar: 2.0 mm. (b) Dye leakage in aqueous solution. (i) Transmission spectra of distilled water upon storing contact lens sensors for 1 min and from 3 to 24 h. (ii) Transmittance trend over soaking time. Insets show photographs of the storage solution after different time intervals. Scale bar: 2.0 mm.

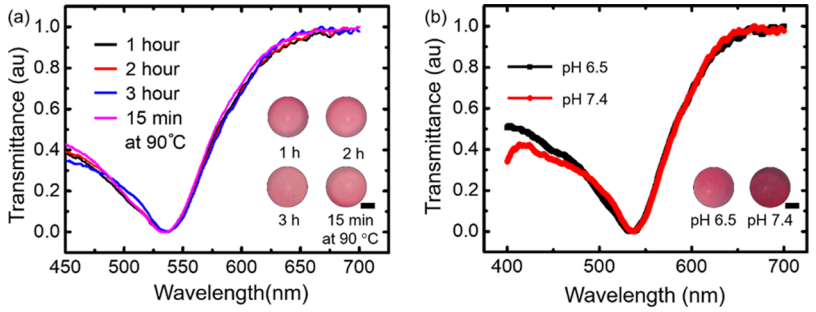

Figure 5. Transmission spectra of custom poly-HEMA contact lenses cross-linked with anthocyanin dye, exposed to buffer solutions at pH 6.5 and 7.4. (a) Transmission spectra of the anthocyanin-cross-linked poly-HEMA contact lenses after immersion in a saline solution for 3 h. The inset shows photographs of the contact lenses at different submersion times. Scale bar: 2.0 mm. (b) Transmission spectra of the lens submerged in buffer solutions at pH 6.5 and 7.4, at ambient temperature. The insets show photographs of contact lenses exposed to different pH values. Scale bar: 2.0 mm.

dyed contact lenses when increasing the soaking time. This resulted in a higher permeation of the dye within the polymer matrix and thus in a brighter color. After 24 h, the transmission intensity at 660 nm saturated. The dye leakage was evaluated by storing contact lenses in distilled water for 1 min, 3, 6, 12, 18, and 24 h. Figure 4b shows the transmission spectra of the aqueous solution upon storing the dyed contact lens for different time intervals. As expected, dye leakage in DI water increased when increasing the storage time, with saturation after 18 h.

To explore alternative methods to fabricate pH-sensitive contact lenses, poly-HEMA soft contact lenses were fabricated and cross-linked with the anthocyanin dye during the photopolymerization process. For studying the dye leakage for the in-house-made contact lens, the lens was immersed in a buffer solution at room temperature and the transmission spectra were acquired after 1, 2, and 3 h. Followed by soaking the lens in a buffer solution at a temperature of 90 °C for 15 min, the transmission spectrum was recorded again. The transmission spectra of the lens over time were comparable, even when it was immersed in a high-temperature buffer, indicating robust polymer-anthocyanin dye cross-linking within the contact lens matrix (Figure 5a).

The transmission spectra of poly-HEMA contact lenses exhibited an absorption peak at 540 nm, while commercial contact lenses dyed by the soaking method presented an absorption peak around 490 nm. The absorption band of poly-HEMA (in-house-made) lens was wider as compared to commercial contact lenses tinted via immersion, which reflect a modification of the chemical structure of the anthocyanin dye

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during the cross-linking process (Figure 5b). Poly-HEMA lenses appeared peach red at pH 6.5 and gradually shifted to darker red shades when pH increased up to 7.4 showing a slight color shift, which is difficult to be recognized easily by the naked eye. Therefore, for developing contact lenses that function as a pH sensor, we expect that cross-linking anthocyanin dye with other hydrogel matrices such as poly vinyl alcohol or polyacrylamide might result in a more significant color change with pH.

CONCLUSIONS

Contact lens sensors were developed for continuous monitoring of ocular pH variations with a minimally invasive approach. Commercial lacreon and lacreon-free contact lenses were functionalized by soaking and drop-casting processes using anthocyanin aqueous solutions. Lacreon contact lenses exhibited brighter and more uniform color distribution, which could be observed with the naked eye in the physiological pH range 6.5−7.5. The color variation was evaluated based on the concentration of the dye in solution, from 0.35 to 1.5 mmol L^{-1}, and of the soaking time (1 min to 24 h). The leakage of contact lens sensors was evaluated by storing DI water for up to 24 h. Poly-HEMA contact lenses were fabricated and cross-linked with anthocyanin dye to evaluate an alternative method for incorporating the dye within the polymeric matrix. Further studies may include in vitro and in vivo biocompatibility tests.

MATERIALS AND METHODS

Materials. 1-Day ACUVUE Moist LACREON and LACREON-free soft contact lenses were purchased from Johnson & Johnson. 2-Hydroxyethyl methacrylate, ethylene glycol dimethacrylate, 2-hydroxy-2-methylpropiophenone, and delphinidin chloride were purchased form Sigma-Aldrich and used without further purification.

Optical Characterization Setup. An optical fiber was coupled into a port of an upright optical microscope (Zeiss). Broadband white light was used to illuminate the contact lens, and the transmission spectrum was obtained in the opposite direction by an optical fiber connected to a spectrometer (Maya Pro-2000, Ocean Optics).

Extraction of the Anthocyanin Dye. Anthocyanin dye was extracted from *B. oleracea*, which was sliced and soaked in DI water (3:2, wt/vol). The mixture was boiled and simmered for 10 min to allow the diffusion of the dye. The slices were removed, and the aqueous solution was filtered and stored at 4 °C until usage. Another dye solution was obtained by dissolving delphinidin chloride in DI water to obtain solution with concentrations 0.35, 0.5, 0.75, 1.0, and 1.5 mmol L^{-1}.

Fabrication of Contact Lens Sensors. Contact lenses were dyed by soaking and drop-casting. In the soaking process, only commercial contact lenses were soaked in 20 mL of dye aqueous solution for 1 min, 3, 6, 12, 18, and 24 h. In the drop-casting method, 500 μL of dye aqueous solution was poured on the convex/concave faces of contact lenses.

Fabrication of Poly-HEMA Contact Lens Sensors. The anthocyanin dye (0.2 wt/vol %) was dissolved in DI water, and HEMA (80 vol/vol %) was mixed with the dye aqueous solution. The photoinitiator, 2-hydroxy-2-methylpropiophenone (1 vol/vol %), and the cross-linker ethylene glycol dimethacrylate (5 vol/vol %) were added to the monomer solution. The mixture was pipetted to the contact lens mold and cured under UV light (λ = 365 nm) for 5 min.

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Author Contributions

R.S.R., M.E., R.M., and M.U.H. performed the experiments. H.B. and A.K.Y. supervised the work. R.M. and M.E. wrote the manuscript. All authors reviewed the manuscript and made intellectual contributions.

Notes

The authors declare no competing financial interest.

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