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Hydrogen Peroxide Mechanosynthesis in Siloxane-Hydrogel Contact Lenses

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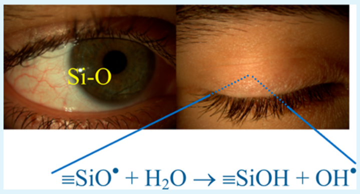

ABSTRACT: Drug-loaded contact lenses are emerging as the preferred treatment method for several ocular diseases, and efforts are being directed to promote extended and controlled delivery. One strategy is based on delivery induced by environmental triggers. One of these triggers can be hydrogen peroxide, since many platforms based on drug-loaded nanoparticles were demonstrated to be hydrogen-peroxide responsive. This is particularly interesting when hydrogen peroxide is the result of a specific pathophysiological condition. Otherwise, an alternative route to induce drug delivery is here proposed, namely the mechano-synthesis. The present work represents the proof-of-concept of the mechanosynthesis of hydrogen peroxide in siloxane-hydrogel contact lenses as a consequence of the cleavage of siloxane bonds at the interface between the polymer and water in aqueous phase. Their spongy morphology makes contact lenses promising systems for mechanical-to-chemical energy conversion, since the amount of hydrogen peroxide is expected to scale with the interfacial area between the polymer and water. The eyelid pressure during wear is sufficient to induce the hydrogen peroxide synthesis with concentrations which are biocompatible and suitable to trigger the drug release through hydrogen-peroxide-responsive platforms. For possible delivery on demand, the integration of piezoelectric polymers in the siloxane-hydrogel contact lenses could be designed, whose mechanical deformation could be induced by an applied wireless-controlled voltage.

KEYWORDS: *hydrogen peroxide, mechanochemistry, water/polymer interface, contact lenses, Fenton reaction*

■ INTRODUCTION

For many clinical applications requiring drug delivery, nanomaterials present several advantages, which are being explored.[1−8] For example, drug-embedded nanomaterials can be formulated to respond to specific environmental triggers, thus making drug delivery responsive to pH, temperature, magnetic fields, specific enzymes, or hydrogen peroxide (H_2O_2).[9−19] These systems hold great potential to reduce drug toxicity and to improve therapeutic efficacy locally at the targeted area. Biocompatible H_2O_2-responsive systems are here of special interest. For example, nanoparticles incorporating a drug and H_2O_2-responsive peroxalate ester group were reported by Lee et al.[10] Geng et al. reported a delivery platform by using a H_2O_2-responsive controlled-release system for therapeutic metal chelator.[11] Broaders et al. reported modified dextran microparticles as H_2O_2-sensitive carrier of ovalbumin.[15] Dextran is a biocompatible polysaccharide. It was modified by arylboronic esters as the triggering groups because of their H_2O_2-mediated degradation at physiological pH and temperature. De Gracia Lux et al. reported biocompatible polymeric capsules consisting of a polymeric backbone and boronic ester groups capable of undergoing backbone degradation and cargo release upon exposure to H_2O_2.[13]

Also, for ocular diseases, such as glaucoma, retinal pathologies, and ocular inflammatory processes, nanomaterials are emerging, and in particular, nanoparticle-loaded contact lenses are often considered as the preferred treatment method.[5,9,12,14,16,19−21] Indeed, they have the advantages of (i) localizing the delivery of drugs to minimize adverse effects caused by systemic administration and (ii) avoiding burst release, which is a limit of eye drops, thus maintaining a local therapeutic dosage for a longer time. A few systems were recently designed. For example, Verestiuc et al. synthesized hybrid polymer networks based on acrylic-acid-functionalized chitosan coupled with 2-hydroxyethyl methacrylate (HEMA) or with *N*-isopropylacrylamide and evaluated the ability of these systems to act as vehicles for ophthalmic drug delivery.[19] Nanodiamond-embedded contact lenses were recently reported by Kim et al.,[9] which are capable of lysozyme-triggered drug release. Nanodiamonds were coated with polyethylenimine and cross-linked with chitosan, which is an enzyme-cleavable polysaccharide. The obtained diamond-nanogel was loaded with timolol maleate and cast into polyHEMA contact lenses.

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Since drug delivery from several biocompatible nanoparticles was demonstrated to be H_2O_2-responsive, synthesis of H_2O_2 during wear of nanoparticle-loaded contact lenses is expected to be a strategic route for continuous and extended drug delivery. If the H_2O_2 synthesis is not induced by a specific pathophysiological ocular condition, in contrast to other examples reported in the literature as for Alzheimer's disease, ischemia/reperfusion injury, etc.,[10,11] a different synthetic route is required. The present work represents the proof-of-concept of the mechanosynthesis of H_2O_2 by siloxane-hydrogel contact lenses (shCLs) as a consequence of the cleavage of siloxane bonds caused by an applied pressure.

ShCLs have been widely used for correction of refractive errors since the late 1990s.[22−24] These systems combine the comfort of the conventional hydrogel contact lenses with the higher oxygen permeability of the siloxane component. New applications are also emerging, which exploit contact lenses as a platform for building remotely controlled integrated circuits.[25−29] Such integrated systems could also be designed to induce a controlled pressure on the lens on demand. Otherwise, a non-negligible pressure applied to shCLs during wear is caused by the eyelid.[30−32] The eyelid pressure on the shCL during wear is sufficient to induce continuous hydrogen peroxide synthesis with concentrations which are biocompatible and suitable to trigger drug release though hydrogen-peroxide-responsive platforms. To our knowledge, no studies were reported on the production of oxidizing agents in the solution/tear hydrating the lens, as a consequence of mechanochemical phenomena. On the contrary, these effects were reported for other polymers used for different applications. The effects of mastication on the mechanical rupture of the constituent macromolecules of polymers have been known for a long time.[33−36] The cleavage of covalent bonds and creation of radicals within stressed polymers were also recently discussed for rubbers or biopolymers.[37−41] When these polymers are in contact with water, the mechanoradicals created within the stressed polymer migrate to the polymer/water interface, where they produce H_2O_2. The amount of H_2O_2 that is produced was demonstrated to scale with the interfacial area. Baytekin et al. took into consideration poly(dimethylsiloxane), Tygon, and poly(vinyl chloride) and reported efficiencies up to 30% for the mechanical-to-chemical energy conversion.[41] In particular, these authors discussed the possibility to use polymeric sponges as solid-state reagents to drive aqueous-phase radical reactions.

■ MATERIALS AND METHODS

ShCLs (−3.00 D) were selected among those available on the market.

UV−vis absorption measurements from 300 to 800 nm were performed by using a Jasco V-650 spectrophotometer.

Scanning electron microscopy (SEM) micrographs were obtained using a LEO 1430 (Carl Zeiss, Oberkochen, Germany) operating at 20 kV and 3×10^{-3} Torr. Samples were first freeze-dried[41] before analyses (−55 °C, 0.63 mbar ×24 h) using an ALPHA 1-2 LDplus freeze-dryer (Martin Christ, Osterode am Harz, Germany) and then sputter-coated with gold to a thickness of approximately 10 nm (to avoid charging the samples) using a Semprep 2 sputter coater (Nanotech Ltd., Prestwick, U.K.) at 10 mA.

■ RESULTS AND DISCUSSION

To detect H_2O_2 in aqueous phase with sensitivity down to 1 nM, 5-sulfosalicylic acid dehydrate ($C_7H_6O_6S$) (Sigma-Aldrich) and $FeSO_4$ were dissolved in water with concentration 165 and 9 μM, respectively, and sufficient H_2SO_4 to adjust the pH to 0.7. The method of H_2O_2 analysis is based on the Fenton reaction $H_2O_2 + Fe^{2+} \rightarrow OH^- + Fe^{3+} + OH^\bullet$,[42,43] which depends on the presence of H_2O_2 and produces Fe^{3+} ions, that complex with $C_7H_6O_6S$. First of all, H_2O_2 aqueous solutions were prepared and mixed with the $C_7H_6O_6S/FeSO_4$ solution with H_2O_2 concentration ranging from 0 to 0.4 μM. The measured absorption spectra showed a band centered at 503 nm (Figure 1, panel a) attributed to the complex formation between the $C_7H_6O_6S$ dye and the Fe^{3+} ion.[43,44] For each H_2O_2 concentration, the spectrum was integrated between 500 and 600 nm, and the integrated values are reported in Figure 1b. The linear regression of the experimental data was obtained with R = 99.69% and represents the calibration curve for the following analyses of H_2O_2 concentration in different solutions.

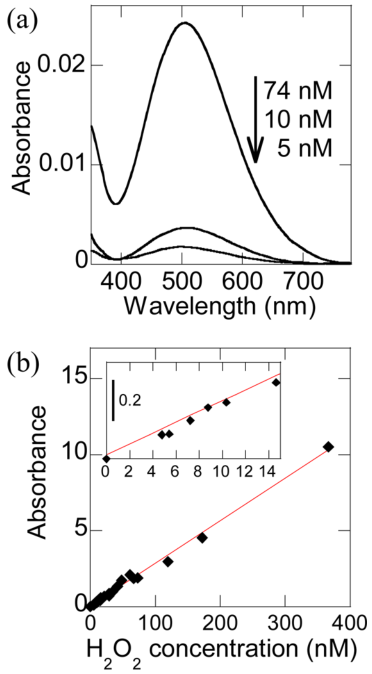

Figure 1. (a) Measured absorption spectra of H_2O_2 $C_7H_6O_6S/FeSO_4$ solutions with H_2O_2 concentrations 74, 10, and 5 nM and (b) measured absorbance of H_2O_2 $C_7H_6O_6S/FeSO_4$ solutions integrated between 500 and 600 nm as a function of the H_2O_2 concentration. Inset of part b shows the same data as in part b on an enlarged scale.

The concentration of oxidizing agents in the preservative solution of different commercial shCLs was measured by adding the blister solution to the $C_7H_6O_6S/FeSO_4$ solution (35% and 65% w/w, respectively, Figure 2, panel a). Among the measured solutions (absorption spectra in Figure 2b), the lowest concentration (mean 0.9 nM; std dev 3.6 nM) of oxidizing agents was found for the blister solution of filcon V shCLs, to be compared with the highest measured value (mean 319.3 nM; std dev 60.6 nM) obtained for delefilcon shCLs. The differences between these two extremes cases were also detectable to the naked eye (blister solution 62% w/w; $C_7H_6O_6S/FeSO_4$ 38% w/w, Figure 2c).

Due to the relatively low concentration of oxidizing agents in their preservative solution, we selected filcon V shCLs to investigate the H_2O_2 mechanosynthesis. Figure 3 shows an image of a worn lens taken by a digital camera mounted on a biomicroscope and an SEM micrograph taken from the surface of an unworn filcon V shCL, where pores are clearly visible.

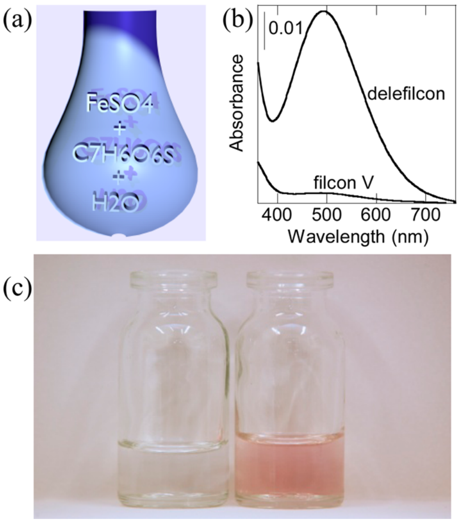

Figure 2. (a) Solution for the analyses based on the Fenton reaction, (b) absorption spectra of solutions obtained by adding the preservative blister solution of either filcon V or delefilcon shCLs to the $C_7H_6O_6S/FeSO_4$ solution (35% and 65% w/w, respectively), and (c) images of vials containing the $C_7H_6O_6S/FeSO_4$ solution (38% w/w) and the preservative blister solution (62% w/w) of either filcon V shCLs (left) or delefilcon shCLs (right).

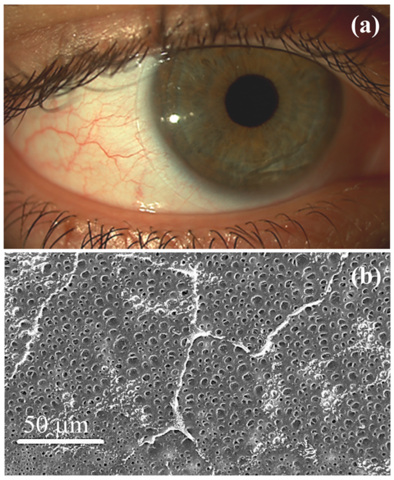

Figure 3. (a) Image of a worn contact lens taken by a digital camera mounted on a biomicroscope and (b) SEM micrograph taken from the surface of unworn filcon V shCLs.

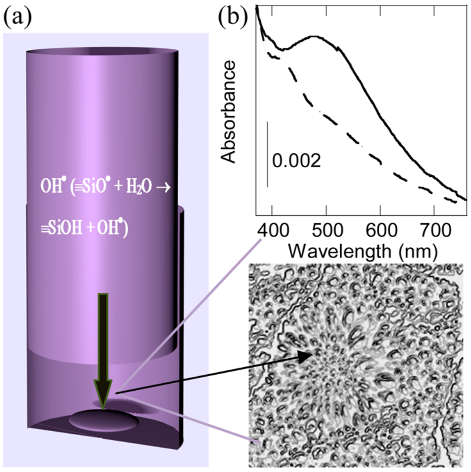

Figure 4. (a) Compression device consisting of a glass syringe enabling 30 N/cm^2 pressure to be applied on the shCLs and schematic illustration of the shCL deformation under the applied pressure (down right side of the figure); (b) absorption spectra of the $C_7H_6O_6S/FeSO_4$ solution, where seven shCLs were immersed after being or not being pressed (continuous and dashed lines, respectively).

Table 1. Volume (pL) of Oxidizing Agents Produced per Filcon V ShCL Either without (w/o) the Applied Pressure or with (w/) Applied Pressure (30 N/cm^2 or 15 N/cm^2)

	volume (pL)		
	w/o pressure	w/pressure 30 N/cm^2	W/pressure 15 N/cm^2
no. samples	35	56	28
mean	0.02	1.32	0.81
std dev	0.30	1.24	0.37
p (stud.)	0.021		
		0.310	
		0.014	

In each experiment, seven hydrated filcon V shCLs taken from their blister were left in a glass syringe in nitrogen atmosphere (~20 mL/min) either under pressure (Figure 4a) or without any applied pressure. When applied, the pressure was either 30 or 15 N/cm^2. After about 3 h, the seven hydrated lenses were removed from the syringe [the content of hydration solution per lens after this procedure was measured to be (14.06 ± 0.70) μL per lens], and they were immersed in 0.6 mL of the $C_7H_6O_6S/FeSO_4$ solution. Absorption measurements on the resulting solution (Figure 4b) allowed to deduce its oxidation level using the calibration curve reported in Figure 1b. The results are reported in Table 1. Statistical significance of differences among measured quantities (with or without applied stress and under 15 or 30 N/cm^2) was obtained by Student's t statistic ($p < 0.05$). Only under the applied pressure of 30 N/cm^2, few measurements were performed by varying the time interval (Δt) during which the shCLs were left under pressure. Also in these cases, the same analytical procedure as described before was followed for the measurement of the volume of oxidizing agents. The results are reported in Figure 5.

To discuss the H_2O_2 mechanosynthesis in shCs, we start from the dissociation energy of one Si−O bond of the siloxane functional groups, which is known to be about 0.67×10^{-18} J.[41] In our first experiment, we applied in a syringe a pressure of 30

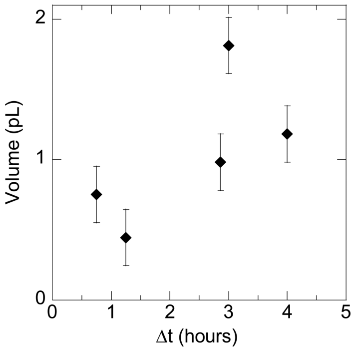

Figure 5. Volume of oxidizing agents produced per filcon V shCL with the applied pressure of 30 N/cm^2 as a function of the time interval Δt during which the shCLs were left under pressure.

N/cm^2 to filcon V shCLs. On the basis of the Young's modulus[45] $[(10^6 \pm 10^5)$ Pa] and the typical thickness of a contact lens $[(100 \pm 10)\ \mu$m], this pressure is expected to produce an energy equal to $(0.92 \pm 0.18) \times 10^{-3}$ J in one compression. Only a few percent of this energy is expected to be used to break Si—O bonds, i.e., $(0.92P \pm 0.18P) \times 10^{-3}$ J, where P is the efficiency of mechanical-to-chemical conversion. The expected number of broken bonds in one compression is therefore $(1.37P \pm 0.27P) \times 10^{15}$. The cleavage of Si—O bonds under stress in a surrounding aqueous phase is expected to generate H_2O_2 through the generation of $\equiv SiO^\bullet$ radicals, which reacted with water to produce $OH^\bullet$ ($\equiv SiO^\bullet + H_2O \rightarrow \equiv SiOH + OH^\bullet$), which, in turn, combined to form H_2O_2.[41] Besides Si—O cleavage, Si—C and C—C bonds (with comparable dissociation energies as for Si—O) could also produce H_2O_2 in air.[41] Each broken bond is expected to produce one H_2O_2 molecule. The expected volume of H_2O_2 produced per shCL in our experiment is therefore deduced $(52.46P \pm 10.34P)$ pL. By matching the calculated volume of synthesized H_2O_2 and the experimental one obtained under pressure (Table 1) it was possible to deduce that the efficiency P of mechanical-to-chemical conversion was (2.62 ± 0.52)%. The order of magnitude for the number of broken bonds in one compression ($(1.37P \pm 0.27P)\ 10^{15}$) is 10^{13}, to be compared with the larger expected number ($\sim 10^{18}$) of Si–O bonds in a shCL with only a few percent of siloxane component in its matrix. The obtained P value is in agreement with the efficiencies reported by Baytekin et al.[41] However, the same authors could reach much larger efficiencies by a proper design of the material up to 30% for spongy poly(dimethylsiloxane) with large interfacial area. The surface morphology of filcon V shCL is shown in Figure 3b. As discussed elsewhere,[46] pores are mainly present in the layer close to the lens surface. Therefore, the efficiency of mechanical-to-chemical energy conversion could be increased by increasing the lens porosity in the core.

In a second experiment, we also applied a lower pressure (15 N/cm^2) to the shCLs (last column, Table 1). At 15 N/cm^2, the obtained value of synthesized H_2O_2 per lens (0.81 pL ± 0.37 pL) is larger than the sensitivity limit of the analytical technique, which is about 0.2 pL, but it is close to this limit. Nevertheless, as in the case of 30 N/cm^2, statistical significance was found for the difference between the volumes of synthesized H_2O_2 without stress or under the applied pressure. No statistical significance was found for the difference between the H_2O_2 volumes under 15 or 30 N/cm^2, due to the large standard deviations of the data for each applied pressure.

The values reported in Table 1 under pressure were obtained by fixing at 3 h the time interval Δt during which the shCLs were left under pressure. The data in Figure 5 show that there is not a *burst* effect in the release of oxidizing agents by the shCLs, while there is a slight tendency to an increase of the release as a function of time. This tendency is in agreement with the results reported by Baytekin et al.[41] They also showed that, after one compression of a tube of poly(dimethylsiloxane) in water, the concentration of H_2O_2 increases with time, up to a few hours. Indeed, the radicals generated in the polymer are expected to migrate toward the polymer/water interface by a radical-driven propagation mechanism. The time dependence is therefore expected to be a consequence of the diffusion of the radicals in the polymer.

During wear, the superior eyelid produces a pressure on the shCLs. The larger pressure is exerted by the eyelid wiper region, which plays the role of redistributing the tear film by "wiping" the ocular surface during blinking. The elastohydrodynamics of the eyelid wiper was recently studied in details by Jones et al.,[32] who reported the forces that the eyelid exerts on the ocular surface during the closing and opening blink cycle. Their model indicates that the highest perpendicular pressure on the ocular surface is generated by the so-called eyelid Marx's line, which is located close to the opening of the Meibomian glands and is about 100 μm in width and about 3 cm in length along the arc length of the eyelid. During wear, at a fixed time, the exposed area of the shCL to the Marx's line is about 100 μm in width and about 1 cm along the arc length (the exposed area of the shCL to the Marx's line is (1.0 ± 0.2) mm^2).[32] The order of magnitude of the Marx's line pressure normal to the ocular surface was reported to be (1.5 ± 0.2) N/cm^2,[32] which corresponds to a force of about $(1.5 \pm 0.2) \times 10^{-2}$ N on the exposed area. On the basis of the shCL Young's modulus[45] ($(10^6 \pm 10^5)$ Pa) and typical thickness ($(100 \pm 10)\ \mu$m), one deduces the energy provided by the pressure attributable to the Marx's line. By assuming that (2.62 ± 0.52)% of this energy is used to break Si–O bonds, the energy transferred by the static pressure of the Marx's line can be found, $(7.8 \pm 5.5) \times 10^{-10}$ J. During the closing and opening blinking, the lid wiper wipes the ocular surface, thus exerting a spanning force on the total 1 cm^2 area of the shCL. The transferred energy is therefore $(1.6 \pm 1.1) \times 10^{-7}$ J, and the cumulative number of broken bonds per blink is about $(2.3 \pm 1.6)\ 10^{11}$. During 1 day of wear, the number of blinks is about 6×10^3.[47] Thus, the number of broken bonds per day is about $(13.8 \pm 9.6)\ 10^{14}$, which is lower than the expected number ($\sim 10^{18}$) of Si–O bonds in a shCL with only a few percent of siloxane component in its matrix. The number of broken bonds per day also corresponds to the cumulative number of synthesized H_2O_2 molecules. The expected amount of H_2O_2 produced per shCL in 1 day of wear is therefore (52.8 ± 36.7) pL. This amount is produced inside the shCL in intimate contact with the shCL polymer, and it is available for small-scale chemical reactions. By considering the typical hydration (10 μL) of worn shCLs, the equivalent cumulative H_2O_2 concentration per day in the shCL is $\sim$4 μM, which is compatible with the H_2O_2 concentration values reported in the literature to obtain drug delivery from H_2O_2-responsive systems.[10−15] We underline that the amount of H_2O_2 produced per shCL in 1 day of wear is expected to be underestimated because (i) the eyelid pressure on the shCL is expected to be larger than the pressure (1.5 N/cm^2) on the ocular surface without any lens, (ii) the contribution of the whole eyelid to the exerted pressure, not only of the Marx's line, was omitted, and (iii) the shear forces exerted by the eyelid were omitted. For example, the shear stress acting on the ocular surface during a blink was calculated by Jones et al.,[32] who reported the drag per unit span acting on ocular surface as a function of time during a blink, with maximum values of the order of about 0.05 N/m. We also stress the fact that both the normal and the shear stresses are expected to be larger if the tear film is thin or incomplete, such as in patients affected by dry-eye syndrome. Moreover, the mechanical-to-chemical conversion could be optimized by the design of the shCL. For example, Baytekin et al. reported an efficiency of 30% for spongy poly(dimethylsiloxane)[41] to be compared with the 2.62% of the commercial shCLs of this study.

As a possible innovative implementation, a very promising approach for the controlled H_2O_2 mechanosynthesis is the exploitation of the properties of piezoelectric polymers, which could be integrated in shCLs, whose mechanical deformation could be controlled by an applied voltage.[48] The flexibility and processability of piezoelectric polymers (processed by molding, casting, spinning, etc.[48,49]) make them suitable for implementation, also in shCLs. Piezoelectric polymer devices may be fabricated with different geometrics, such as thin-film geometry in parallel plate configurations or nanofibers.[50,51] Persano et al. recently reported the procedure to obtain high-density arrays as piezoelectric textile.[51] The conversion factor between applied voltage and pressure was found to be of the order of about 0.5 mV/Pa. The same authors also studied the dynamic bending and reported no significant changes in the piezoelectric properties up to 1000 cycles. In view of the H_2O_2 mechanosynthesis, an applied voltage of 3 V is expected to produce a pressure of 0.6 N/cm^2, which is compatible with the required pressure to break Si−O bonds in shCLs. By a designed capacitor, the voltage could be applied to the material at a fixed frequency, so that the deformation can be iterated. This frequency can be much larger (e.g., 10 Hz or more) than the blinking frequency of the eye (about 0.2 Hz). The recent advantages in the development of circuits on the lenses indicate that the required voltage can be applied by a wireless-powered active contact lens. For example, Stangel et al.[26] powered a chip sensor implanted in a contact lens using a 13.56 MHz inductive link with the external reader unit mounted close to the eye. Also, Puttjer et al.[25] developed a wireless LED display on a contact lens. Pandey et al.[29] incorporated a fully integrated display functionality on a contact lens consisting of a micro-LED, a far-field RF 2.4 GHz wireless energy harvesting, and loop antenna. They demonstrated that sufficient energy was available to power their device and discussed in detail its energetic feasibility. In their specific case, the nominal turn-on voltage was 3 V, and the power consumption of one LED was 12 μW for a total power consumption of hundreds of μW. For their purposes, they used a small on-chip capacitor for energy storage. Since integrated capacitors of the order of 1 nF can be realized, they could also be used to provide energy to a polymeric piezoelectric-shCL. The possible release on demand opens the possibility of innovative platforms, which integrates onto the same active lens two communicating systems: (i) the detection system to monitor wearer's health through biomarkers present in the tear fluid (glucose, cholersterol, etc.) and (ii) a controlled drug-delivery system.

■ CONCLUSIONS

The key point of the present study is the proof of the H_2O_2 mechanosynthesis due to the cleavage of chemical bonds of shCLs in aqueous phase. In our experiment, after applying 30 N/cm^2 pressure (or 15 N/cm^2 in a second experiment) on commercial shCLs, the amount of synthesized H_2O_2 was measured to be (1.32 ± 1.24) pL per lens [or (0.81 ± 0.37) pL under 15 N/cm^2], corresponding to an efficiency of about a few percent for the mechanical-to-chemical energy conversion. This efficiency could be improved by proper design of the shCL with larger interfacial area. The release of oxidizing agents by the shCLs as a function of the time interval of the applied pressure did not show any burst effect, but a tendency to increase, attributable to the diffusion time of the radicals in the polymer toward the polymer/water interface.

On the basis of the eyelid pressure, the amount of synthesized H_2O_2 per lens per day is predicted on the order of 50 pL, a value which is likely to be underestimated because the eyelid pressure on the shCL was assumed equal to the pressure on the ocular surface without any lens, because only the eyelid Marx's line was taken into consideration, neglecting the other areas of the eyelid and neglecting shear forces, and because an ideal tear film was assumed. In this respect, we also underline that a refined experimental setup and a refined model should be developed to better reproduce and simulate the shCL wear.

This amount of synthesized H_2O_2 is available for small-scale chemical reactions, such as those required for possible drug delivery from H_2O_2-responsive embedded nanoparticles. In this respect, in contrast to the cases reported in the literature for H_2O_2-responsive drug delivery, in this case the presence of H_2O_2 is not the result of a pathophysiological condition, but it is the result of the mechanosynthesis induced by an applied pressure. We point out that the experimental evidence of the H_2O_2 mechanosynthesis in CLs over time, not only after the first compression, would be crucial for extended drug delivery. However, in our experiment, after about 10 compressions or more, the shCL hydration was found to be relatively low (<8 μL). Since water is fundamental for the formation of H_2O_2, our experimental method based on an applied pressure was not used to study the H_2O_2 mechanosynthesis over time. However, we mention that Baytekin et al.[41] already demonstrated that consecutive squeezing events on polymeric samples [poly(vinyl chloride and a boronic ester derivative] generate approximately the same amount of H_2O_2 each time the polymer was squeezed for several events and hours.

In our specific case, the mechanosynthesis is produced by the continuous eyelid pressure on a worn shCL. In general, a similar approach could also be applied to other medical devices to obtain drug delivery controlled on demand, through the control of the applied pressure. For example, a promising approach for the controlled H_2O_2 mechanosynthesis is the exploitation of the properties of piezoelectric polymers, which could be integrated in shCLs, whose mechanical deformation could be controlled by an applied wireless-controlled voltage.

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Notes

The authors declare no competing financial interest.

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