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Electrochemical sensing in contact lenses

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Abstract

Electrochemical sensors embedded in hydrogel-based contact lenses provide valuable health-related information, enabling non-invasive and real-time continuous monitoring. Recently, considerable progress has been made in tear based electrochemical sensors. The scope of the reported analytes is continuously expanding. This review identifies key chemical biomarkers (including metabolites, ions, proteins) that can be electrochemically detected in tears. The working principles of i) amperometric enzymatic biosensors, ii) ion-selective sensors for pH and ions, iii) voltammetric sensors and iv) affinity sensors are summarized. This review provides guidelines for the future development of contact lens based electrochemical sensors.

Keywords: Contact lens; Point-of-care; Electrochemical sensor; Enzymatic biosensor.

1. Introduction

The scope of diagnostics nowadays is expanding to healthcare decentralisation, driven by the huge demanding for improved efficiency and the rapid development of inexpensive point-of-care technologies. Wearable biodevices feature non-invasive and continuous monitoring health status, finding applications not only for patients, but also for healthy people especially athletes and exercise enthusiasts. Wearable biodevices constitute an important sector of the fascinating concept of "bodyNET" [1]. Among them, smart contact lenses emerge as wearable biodevices for next-generation point-of-care diagnostic platform [2]. The primary function of contact lens is to correct vison astigmatism, which was proposed by da Vinci over 500 years ago and became a reality in 1887 (Fig. 1). The past 130 years' development sees the evolution of contact lens material from hard glass and plastic, to soft hydrogel based on poly(hydroxyethyl methacrylate) (polyHEMA) and to more gas permeable silicone hydrogel. New functions, including therapeutic and cosmetic purposes, have been endowed to the contact lens. The last decade experiences the transition to the era of "smart" contact lens embracing new abilities, such as digital display [3], drug delivery and sensing (Scheme 1). Nowadays, contact lenses are daily worn by over 150 million people all around the world [4], with a global market of $7.2 billion annually[5].

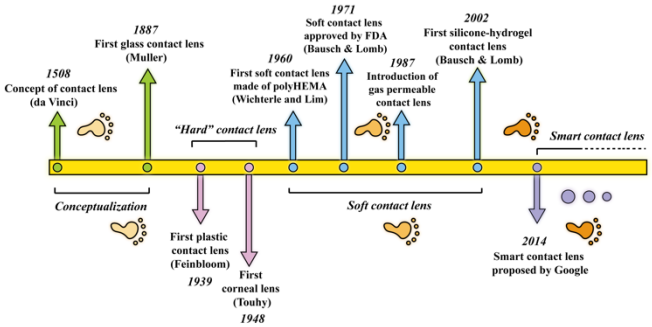
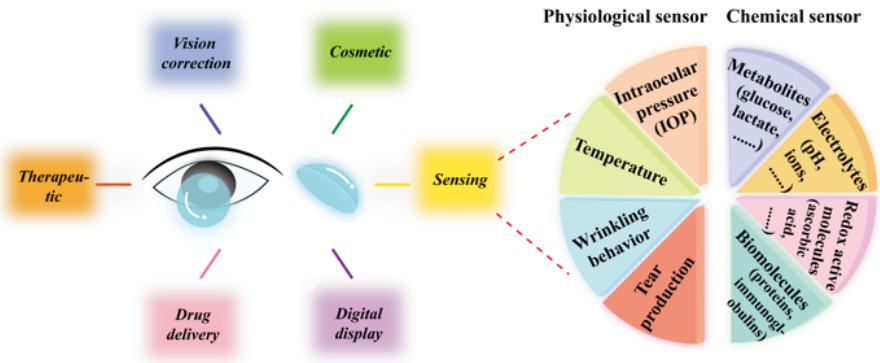
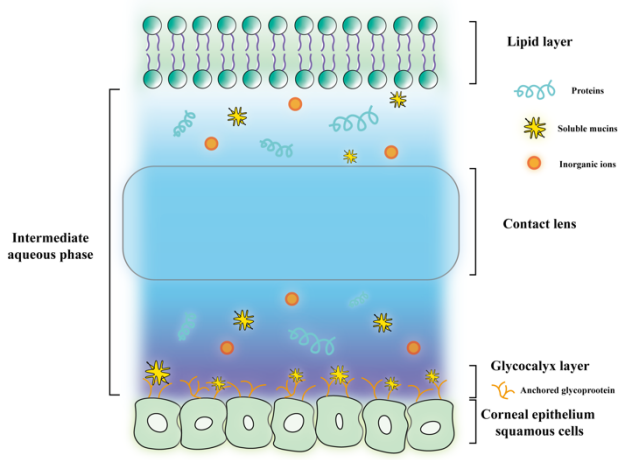


Fig. 1. An overview on the development of contact lens (partially adapted from ref. [5]).



Scheme 1. A summary of functions of contact lenses highlighting the sensing capability.

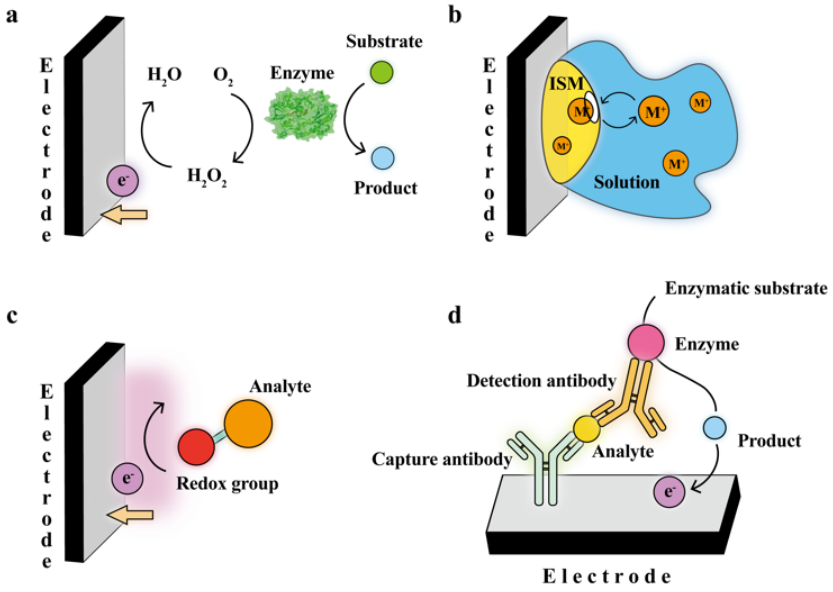
The basal tear film, in a trilaminar configuration composed of a very thin outer lipid layer, an innermost gel-like glycocalyx layer, and an aqueous layer in between, forms a liquid barrier between the air and the proximal ocular tissue (Scheme 2) [6]. It keeps the cornea moist and maintains the ocular antibacterial system [6]. Basal tear, containing a range of species such as glucose, lactate, peptides, proteins, saturated air, etc., reflects the ocular and systemic physiological conditions [4]. Together with saliva and sweat, the tear fluid represents an easily-accessible biofluid [7]. For example, dry eye syndrome (DES), a frequently-encountered complication for diabetic patients [8], is clinically diagnosed by the Schirimer's test that measures the tear production by inserting a paper strip into the lower eyelid for 5 min [4]. Schirimer's test is used to collect tear samples for off-line examination, for example, by mass spectrometry technique. However, it often induces inevitable stress and thus extra tear secretion [9]. Alternatively, contact lenses, floating on the cornea with the direct contact to the tear film, offer the possibility for real-time monitoring (Scheme 2). Tear production rate for DES can be measured by colorimetric using microfluidic cells with a visualization dye, similar to the one for sweat rate [10], if embedded in contact lenses.



Scheme 2. Schematic illustration of precorneal tear film, and the interaction between a contact lens and the tear fluid.

There are excellent reviews [2a, 4] in smart contact lens for a wide scope of applications such as ocular diagnostic [2c, 11], drug release [2b, 12], self-powering bioelectronics [13] etc. Regarding to sensing in tear, two major groups, including physiological sensors (intraocular pressure (IOP) [14], wrinkling behavior [15], temperature [16] and tear production) and chemical sensors (metabolites, electrolytes, and biomolecules), can provide considerable health information of ocular and systemic conditions (Scheme 1). As one type of non-invasive and wearable sensors, the major advantage of sensing in contact lenses is the steady availability of basal tears. Disadvantages are inevitable adverse effects alongside with wearing contact lenses such as discomfort and allergies [4]. In comparison to fluorescence-based sensing with

colorimetric assays [17], electrochemical sensing enjoys greater sensitivity and temporal resolution. In this review, we try to identify the critical biomarkers in the tear fluid that are worthy to be monitored in real-time. We emphasize on electrochemical sensors that can be embedded in hydrogel-based contact lenses, which are still far away from commercial maturity. We describe the working principles of i) amperometric enzymatic biosensors for metabolites, ii) ion-selective sensors for pH and cations, iii) voltammetric sensors and iv) affinity sensors (Scheme 3). This review aims to stimulate the future development of contact lens based electrochemical sensors.



Scheme 3. Schematic illustration of different types of electrochemical sensors: (a) enzymatic biosensors, (b) ion-selective sensors, (c) voltammetric sensors based on direct oxidation/reduction and (d) affinity sensors.

2. Amperometric enzymatic biosensors

2.1. Glucose biosensors

The most frequently reported sensor on contact lens is the glucose sensor for diabetes management. Tear glucose, whose concentration is about thirty-fold lower than that in serum, is revealed to be correlated to blood glucose across the concentration range of interest [18], but with the concerns on the time delay between tear and blood glucose. Different techniques, such as near-infrared glucose-sensitive photonic crystals [19], photonic microstructures [20], and fluorescent sensors [21], on contact lenses have been exploited to measure tear glucose. Electrochemical biosensor for glucose relies on the specifically selective enzymes, including glucose oxidase (GOx) (Fig. 2) and glucose dehydrogenase. GOx, using flavin adenine dinucleotide (FAD) as the redox centre, is the most studied enzyme, initially isolated from *Aspergillus niger* by Prof. Detlev Müller [22]. GOx catalyses the two-electron oxidation of glucose with FAD reduced to $FADH_2$, which is recovered to FAD using dissolved oxygen as the natural electron acceptor with H_2O_2 production [23]. The generated H_2O_2 can thus be electrochemically detected by the direct oxidation on a certain electrode (such as Pt [24]) or the electro-catalysed reduction on a Prussian blue (PB) modified electrode [25]. To circumvent the dissolved oxygen with limited solubility, artificial redox mediators (such as ferrocene [26] and osmium complex modified redox polymer [27])

undergoing fast self-redox process and rapid electron exchange with the FAD cofactor have been developed for so-called mediated electron transfer (MET) based bioelectrode (Scheme 3a).

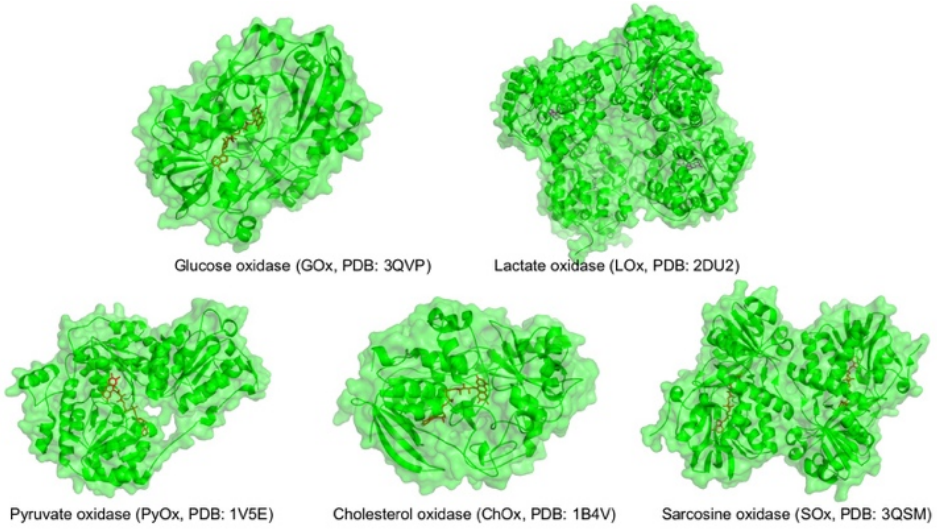


Fig. 2. Flavoproteins that could be used for electrochemical biosensors.

An early attempt to fabricate a flexible and wearable tear glucose using "Soft-MEMS" techniques by Iguchi et al. who immobilised GOx on a Pt working electrode, demonstrating a good linear range up to ca. 1.5 mM [28]. The earliest report of a contact lens consisting of an electrochemical glucose biosensor we can find was by Lähdesmäki et al. in 2010 [29] , although without disclosing substantial parameters. Pt electrodes with immobilised GOx was patterned into a prototype polyethylene terephthalate (PET) based contact lens. In a subsequent report from the same group (Fig. 3) [30], more detailed description of the glucose biosensor is presented with a good linearity towards to the tear glucose range of 0.1-0.6 mM. The parallel work by Chu et al. employed an additional polydimethylsiloxane (PDMS) based flexible GOx modified electrode, which was longer than the contact lens thus limited the wearability, to a PDMS contact lens [31]. A major step forward is to make the glucose monitoring contact lens leadless by coupling with an antenna and a wireless RF power, which was achieved by Liao et al. in 2012 [32].

The headline announcement of the Google smart contact lens in 2014 is appealing [33]. It's envisioned to be a lens with a tiny wireless chip, a miniaturized glucose sensor and an embedded micro-battery, allowing the measured tear glucose levels to be transmitted to a smartphone. However, the exciting project was on hold in 2018, as consistently accurate results in clinical tests couldn't be obtained. The possible reason could be the uncertain correlation between glucose in blood and tears. It could also be due to the glucose sensor itself suffering insufficient sensitivity and selectivity. For example, the tear glucose is typically less than 1 mM, requiring an enzyme, rather than mainstream *Aspergillus niger* GOx, with a low K_M and high catalytic efficiency to afford considerable current signals [34]. It should also be noted that the excess H_2O_2 generated by GOx immobilized electrodes may pose oxidative stress and toxic effect to ocular tissues, although there are different protection pathways in the ocular system [6]. Oxygen-insensitive glucose hydrogenases could be good candidate enzymes, which is however not reported yet for contact lens based glucose biosensors. More reliable glucose sensors can be obtained with MET based bioelectrodes that are more tolerant to oxygen-depletion and interference.

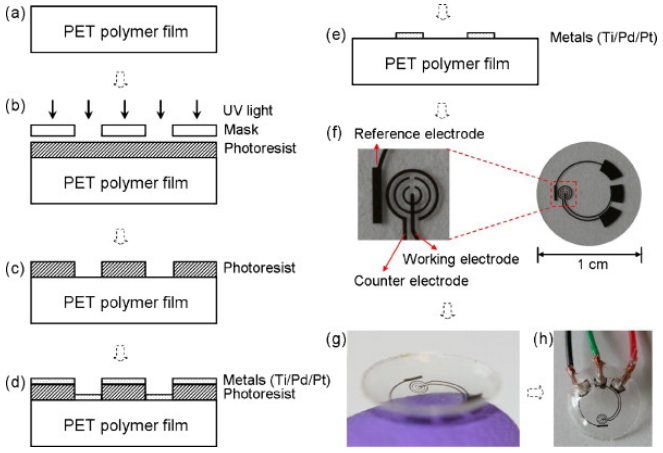


Fig. 3. The sensor microfabrication process (a-g) and (h) the sensor is hardwired for connecting and testing. Reprinted with permission from Ref. [30].

2.2. Lactate and other enzymatic biosensors

Lactate is another important metabolite with a relatively high concentration of 2-5 mM, ca. 4-10 folds higher than that in serum [6], making it an interesting fuel for contact lens based enzymatic biofuel cell (EBFC) that could power tear bioelectronics [35]. Very high lactate levels could reflect oxygen deficiency and indicative of ischemia, sepsis, liver disease and cancer [11a]. Lactate oxidase (LOx) is a flavin mononucleotide (FMN)-dependent enzyme [36] that catalyses the two-electron oxidation of L-lactate into pyruvate. LOx also uses O_2 as the natural electron acceptor (Fig. 3), which could be the reason why some reports mistakenly described LOx as a FAD enzyme [35c, 37]. Thomas et al. reported a contact lens with integrated Pt/LOx biosensor, registering an excellent tolerance to glucose and urea [38]. However, ascorbic acid rendered considerable interference signal due to its simultaneous oxidation on the modified electrode working at a relatively high working potential. It's suggested that Os complex modified redox polymer encapsulated LOx can avoid the oxidation of ascorbic acid [35c], due to i) the low operation potential and ii) the insulating effect of the redox polymer that prevents the direct contact of ascorbic acid from the underling current collecting electrode.

Other metabolites in the tear can also be tracked with the corresponding enzymes (Fig. 3), although not found in literature on the topic of contact lens. Pyruvate, the product of the two-electron oxidation of L-lactate, presents in the tear with a similar level as that in serum and could be a discriminant of metabolism disorders [11a]. FAD dependent pyruvate oxidase (PyOx) modified bioelectrodes can be used for selective pyruvate determination [39]. Cholesterol is a major sterol in tears, secreted primarily from the meibomian gland, and could be associated with hyper-/hypo-cholesterolaemia. Flavoprotein cholesterol oxidase (ChOx) is the enzyme catalysing the degradation of cholesterol, and thus can be used as a biosensor [40]. Moreover, creatinine is a metabolic waste, whose levels are connected to overall kidney function. It has been suggested that tear creatinine could be a less-invasive alternative for serum creatinine [41]. To develop an amperometric biosensor, an enzyme cascade consisting of three enzymes including creatinine amidohydrolase (CA), creatine amidinohydrolase (CAH) and sarcosine oxidase (SOx) can be used [42]. Hydrolysis of

creatinine is first catalysed by CA, generating creatine, which is then hydrolysed into sarcosine and urea. Sarcosine can then be oxidised catalysed by the flavoprotein SOx and measured with the amperometric technique.

Amperometric enzyme biosensors are attractive and can be easily integrated with low-energy circuits. A relatively large scope of redox enzymes is commercially accessible. The relatively poor operational stability due to enzyme leakage or denaturisation is a problem that can be tackled with a series of strategies, such as more robust enzyme immobilization and utilizing extremophile enzymes [23a]. Furthermore, nanozymes are inorganic nanomaterials exhibiting enzyme-like catalytic activity and high stability [43]. Nanozyme based electrochemical biosensors may find applications in contact lenses.

3. Potentiometric ion-selective sensors

Tears have a considerable pH buffering capacity, with a normal range from 6.5 to 7.6 [6, 44], which could be altered due to certain diseases. Thanking to the presence of bicarbonate, as a result of the equilibration with CO_2 in the surrounding air, and other components, tears are especially competent to buffer acidic changes. Alkaline pH values are correlated to ocular rosacea [11a], a chronic dermatosis with an early sign of pH over 8 in the tear [45]. pH-sensitive fluorescent prober can be used to determine tear pH with a fluorometer[46], which has been reported on contact lenses [17b]. Simple colorimetric pH monitoring poly-HEMA contact lenses with cross-linked with anthocyanin dye have been demonstrated [47]. Tear pH has also been measured electrochemically by a micro pH meter [48]. The pH electrode is typically an ion-selective sensor (ISE), which is sensitive to H^+. It's a potentiometric sensor recording the potential difference between the reference electrode and the working electrode (both are generally Ag/AgCl). The later electrode is encapsulated in a pH-sensitive silicate glass that undergoes ion-exchange equilibria of H^+ between the inner filling solution and the sampling solution. To greatly enhance sensor miniaturisation, all-solid-state ISE has been developed to eliminate the usage of inner filling solution (Scheme 3b). Wearable all-solid-state ISE based potentiometric pH sensors, such as the one utilising conductive polymer film of polyaniline, with a underling balance between protonated (doped) polyaniline emeraldine salt and deprotonated (dedoped) emeraldine base, have been reported [49]. Further, potentiometric sensors are in a two-electrode system, leading to considerable simplified setup.

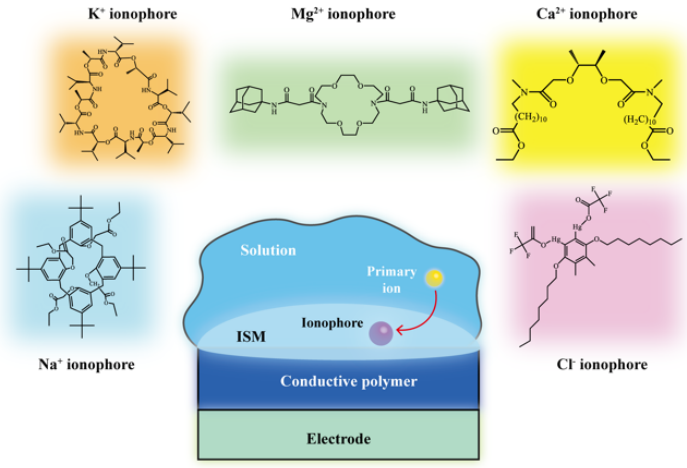


Fig. 4. Common ionophores used in ISE for various ions.

In comparison to those in serum, the concentrations of Na^+, Mg^{2+} and Cl^- in tears are similar [6]. While tear K^+ levels are six-fold higher over serum, with tear Ca^{2+} five-fold lower. These ions in tear electrolytes could also be important manifestations, for example, of DES. The average tear Na^+ levels in thirty-one DES patients were found to be obviously higher over those of twenty-three normal subjects [50]. Quantitative analysis of electrolytes in tears is thus crucial to determine disorders of ion levels. Fluorescent sensing agents with crown ethers have been incorporated in microfluidic devices for direct readout of Na^+, K^+ and Ca^{2+} levels with a smartphone application [51], which was later achieved on a contact lens [52]. Holographic nanostructures have been fabricated with direct laser-writing on a contact lens for sensing the concentration of Na^+ [53]. All-solid-state ISE has been very recently demonstrated in a contact lens for potentiometric Na^+ sensing [54]. The typical configuration is a bilayer on a conducting substrate [55]. The outer ion-selective membrane

(ISM) layer is a composite of polymer matrix, plasticiser, ionic site and ionophore that reduces the free energy of the transfer of target ion from the electrolyte to the ISM. The inner transduction layer, i.e. solid-contact layer, is typically a conductive polymer layer, such as poly(3,4-ethylenedioxythiophene) (PEDOT) and poly(3-octylthiophene) (POT) [56], undergoing the ion-to-electron process. Concentration sensitive potential differences between a reliable reference electrode and the all-solid-state ISE can thus be established and tracked. A wide range of ionophores is available for detecting variable ions (Fig. 4) [57], holding the potential to be embedded into soft contact lenses. The existing issues are the potential drift upon repeat usage due to the undefined redox potential of the inner conductive polymer layer and the competition from the interfering ions that can also interact with the ionophore.

Tear osmolarity is a measure of the electric conductivity all fluids not limited to the ions. A rise in osmolarity of the tear fluid was also observed for DES, related to the low tear production rate [58]. Hyperosmolarity has been identified as a sign of DES[59]. Although not an ISE, we would like to briefly mention in this section that tear osmolarity can be measured with electrochemistry, i.e. electric impedance [60]. A handheld sampler product is already commercially available [61]. A contact lens supported analogue can be possible.

4. Voltammetric sensors

There are many redox active molecules present in tears, which can be directly oxidise or reduced by electrochemistry without involving catalytic enzymes (Scheme 3c). Voltammetric sensors, which register redox current signal upon a potential scan, can be used to correlate the current with the analyte concentration. Depending on the potential ramp method, various voltammetric techniques such as cyclic voltammetry (CV), linear scanning voltammetry (LSV), differential pulse voltammetry (DPV) and square wave voltammetry (SWV) etc., can be used. The latter two techniques feature high sensitivity and minimal background current due to capacitance contribution, suitable for quantitative interpretation. While CV can provide most explorative information, including directly readable information such as peak potential and altitude, as well as the derived information such as reversibility of the redox reaction and number of electrons transferred.

Ascorbic acid is a reduction species which is related to antioxidation protection and displays a high level in ocular tissues and tears during the inflammatory process [62]. Elevated levels of urea, which generally exists in tears at 3-6 mM[6] and similar to that in serum, have been found in the tears of DES patients [63]. Nitric oxide plays an important role in homeostatic processes in the eye, with a declined trend in the eyes of Behcet's patients [64]. The levels of ascorbic acid and nitric oxide can be measured by a contact lens with exclusively designed colorimetric sensors [17]. These compounds are electrochemical active and thus expected to be measured with voltammetric sensors. For example, ascorbic acid exhibits a well-defined oxidation peak at 0.064 V vs. Ag/AgCl on an oxidised glassy carbon electrode, with urea at 0.354 V vs. Ag/AgCl [65]. Sempionatto et al. employed SWV to distinguish different vitamins (B2, B6 and ascorbic acid) in tears that oxidised at a series of potentials [66]. Nitric oxide displays irreversible oxidation on an electrochemically treated carbon fibre electrode with an onset potential of ca. 0.7 V vs. Ag/AgCl in pH 7.4 buffer [67].

Dopamine and norepinephrine are the principal neurotransmitters that modulate biological activities in the retina. Tear dopamine is associated with neurovascular disorders in glaucoma patients and its concentration drop is a sign of neurodegenerative processes [68]. These neurotransmitters can be measured by voltammetric since they can be directly oxidised on the unmodified carbon nanomaterial based electrodes [69]. Such miniaturised electrochemical sensors are expected to be incorporated onto contact lenses in the future. However, the challenges for this type sensor are interfered from coexisting compounds, electrode fouling and contamination after long-term operation.

Other molecules, such as H_2O_2 whose significant levels could be from tumour cells, can also been measured with voltammetric sensors. Some therapeutic drugs, if they are redox active, for ophthalmic treatment could be monitored by voltammetric sensors for the drug management. Although not a biomarker, the redox prober ferrocenemethanol (FeMeOH) has been used by Donora et al. as a model compound to perform spatiotemporal electrochemistry in a contact lens with four working electrodes (Figure 5a-d) to provide the information of biomarker levels across the cornea surface [70], rather than single-point measurement. As shown in Figure 5e, when the redox probe was precisely introduced to a position analogous to the lachrymal ducts close to that of working electrode 1 (W1), FeMeOH was first electrochemically found at W1, then W4 at the lower eyelid section of the eye model. While negligible FeMeOH was observed at W2 and W3. Such an investigation is expected to be expanded to map useful biomarkers with both spatial and temporal resolution.

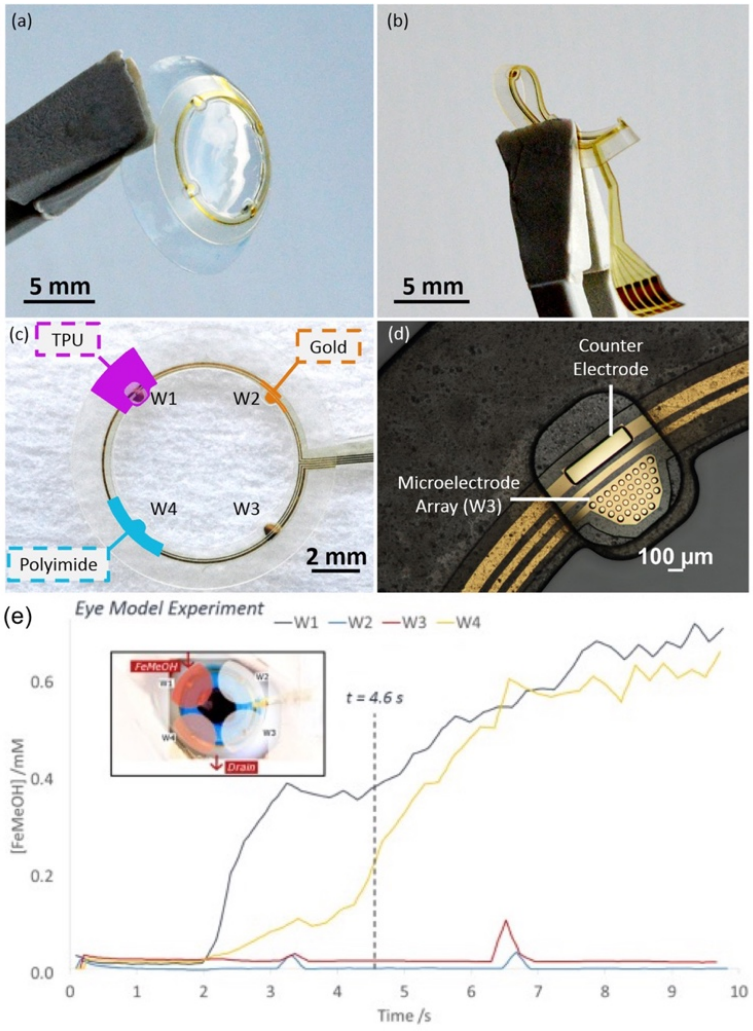


Fig. 5. Digital photos of a contact lens with gold layer based electrodes (thickness: 100 nm) (a), its flexibility (b), illustrated four working electrodes (W1-W4) (c) and zoom in of working electrode 3 (W3). (e) Real-time concentration profile of FeMeOH measured by electrochemistry at the four working electrodes during a 10 s eye model experiment, in which FeMeOH was introduced at a position close to W1. Inset: visual representation of the concentration at each working electrode. Reprinted with permission from Ref. [70].

5. Affinity sensors

Tear proteins include lysozyme, lactoferrin, tear-specific pre-albumin, secretory immunoglobin A (sIgA), mucin, albumin and other immunoglobulins etc. [6] Tear proteomics can provide sufficient information for various ocular disorders [71]. Mucins are glycoproteins secreted by epithelial cells and have been proposed to be a key biomarker for ocular surface microbial infections and DES [72]. Mucins are directly related to mucin deficiency diseases. Total protein levels, including lactoferrin and sIgA, in tears of keratoconus patients are much lower than the normal subjects [73]. Contact lens wear is unlikely to affect the total tear protein changes. Moreover, matrix metalloproteinase 9 (MMP-9) is an important diagnostic indicator of DES and ocular surface disease [74]. Increased levels of serum in tears are found in DES patients [75]. Total tear protein concentration can be determined by bicinchoninic acid (BCA) protein assay [76]. A contact lens with a specific colorimetric indicator, which donates H^+ to proteins with more amino groups, for reporting total protein levels has been recently demonstrated [17]. However, this method cannot distinguish individual proteins as lacking selectivity. Instead, the concentration of specific protein can be measured by enzyme-linked immunosorbent assay (ELISA) [73]. Antibodies are the crucial bio-recognition element in ELISA for immunoassays based on the high affinity antibody-antigen binding. Electrochemical immunosensors, which measure the changes of potential, current,

impedance and capacitance upon immunoreactions [77], can be powerful tools for analysing tear proteins (Scheme 3d). With the progress of body-worn electrochemical immunosensors in sweat [78], similar sensors on contact lenses can also be feasible. A contact lens supported graphene field-effect transistor (FET) with monoclonal antibody has been developed for immunosensing cortisol [79], which is an important steroid hormone for neurological activities. The specific binding event causes electrostatic change at the graphene surface, inducing a change of the electrical signals. A similar wireless FET sensor for sensing MMP-9 on a contact lens has also been recently reported [80]. The electrical perturbation occurring at the graphene surface, due to the biological recognition event, is recorded.

Drawbacks of the immunosensor are expensive, slow recognition, poor stability and tough regeneration. Other inexpensive bioaffinity units, such as molecularly-imprinted polymers (MIPs) and aptamers, have been proposed. Aptamers are artificial oligonucleotide sequences, with a smaller size than that of antibodies. Aptamer can be remarkably specific to a wide range of analytes, such as metal ions, amino acids, peptides and proteins etc. Aptamer shows high stability. Recently, Wang et al. fabricated an ultraflexible FET with aptamer modified graphene on a prototype contact lens (Fig. 6) [81], allowing the detection of a typical inflammatory cytokine biomarker. Their findings reveal the great potential of using versatile aptamer in tear sensing.

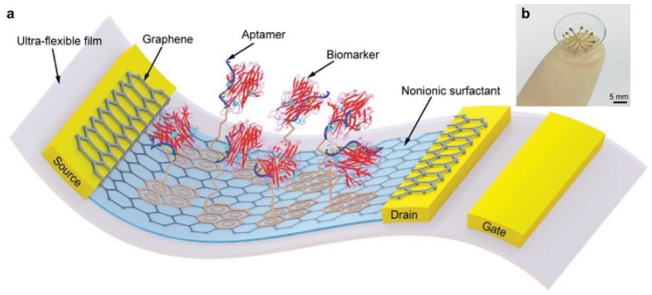


Fig. 6. (a) Ultraflexible aptameric FET sensor consisting of the source, drain, and gate electrodes. (b) Photograph of the sensor mounted a contact lens. Reprinted with permission from Ref. [81].

Table 1. Key biomarkers in tear fluid that can be measured by electrochemical sensors.

Biomarker	Disease/condition[11a]	Sensor type
Glucose	DES; diabetes	Enzymatic biosensor; amperometric
Lactate	Ischemia; sepsis; liver disease; cancer	Enzymatic biosensor; amperometric
Pyruvate	Metabolism disorders	Enzymatic biosensor; amperometric
Cholesterol	Hyper-/hypo-cholesterolaemia	Enzymatic biosensor; amperometric
Creatinine	Renal function	Enzymatic biosensor; amperometric
pH	Ocular rosacea	Potentiometric
Na^+; K^+; Ca^{2+}; Mg^{2+}; Cl^-	Disorders of ion levels	ISE; Potentiometric
Osmolarity	DES	Impedimetric
Ascorbic acid	Cornea inflammatory	Voltammetric
Urea	DES	Voltammetric
Nitric oxide	Behcet's syndrome	Voltammetric
Dopamine	Glaucoma	Voltammetric
H_2O_2	Cancer	Voltammetric
Mucin	Ocular microbial infections; DES; mucin deficiency diseases	Electrochemical immunosensors
Lactoferrin	Keratoconus	Electrochemical immunosensors
sIgA	Keratoconus	Electrochemical immunosensors
MMP-9	DES	Electrochemical immunosensors
Serum	DES	Electrochemical immunosensors
Cortisol	Neurological activities	Electrochemical immunosensors
TNF-α	Sjögren's syndrome	Electrochemical aptamer sensor

6. Conclusions

In this review, we have identified key biomarkers that can be detected with electrochemistry (Table 1). As discussed, contact lens imbedded electrochemical sensors hold the great potential to be widespread in point-of-care settings, being an important part of ongoing campaign of non-invasive and wearable biodevices. Several prototypes have been successfully demonstrated in the literature. Electrochemical sensors can be integrated with different sensors/components in the same lens, leading to the ability for multiplex analysis [17a, 82]. It's certain that the current advanced technologies can enable a compact smart contact lens with all microelectronics encapsulated. In the context of the coronavirus disease 2019 (COVID-19) outbreak, related biomarkers in tears such as cytokine profiles have been proposed for early diagnosis [83]. We can envision smart contact lenses may play an important role in addressing the pandemic.

Challenges remain to reach the research maturity for tear based electrochemical sensing. In contrast to the physical sensors, chemical sensors typically lack of wearability by suffering from limited reproducibility and durability, deserving particular attention. Technological barriers, such as complicated device architecture for wireless-powering and communication, should be overcome. It's expected that advances in microelectronics such as miniaturisation, highly integration, low-energy consumption and ultrasensitive transduction would considerably advance the field of electrochemical sensing in contact lenses. Furthermore, scientific innovations can drive the further development of this filed. An important example is the self-powered biosensor which will greatly simplify the sensor configuration. New biocompatible, transparent and flexible electrode materials are highly desired.

Acknowledgments

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Conflict of Interest

The authors declare no conflict of interest.

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