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Recent advances in smart contact lenses

Zahra Adibag [a,1], Mahsa Ghanbarzadeh [a,1], Mohammad Amin Salati [a,1], Monireh Esmaeili Rad [b], Rais Ansari [c], Christopher N. Ta [d], Daddi Fadel [e], Mohammad Mofidfar [f,g,*], Farhang Abbasi [a,**]

[a] Institute of Polymeric Materials (IPM) and Faculty of Polymer Engineering, Sahand University of Technology, Tabriz, Iran
[b] Faculty of Engineering and Natural Sciences, Sabanci University, Istanbul, Turkey
[c] Department of Pharmaceutical Sciences, Barry and Judy Silverman College of Pharmacy, Nova Southeastern University, Fort Lauderdale, FL, USA
[d] Department of Ophthalmology, Stanford University School of Medicine, Stanford, CA, USA
[e] Centre for Ocular Research & Education, School of Optometry & Vision Science, University of Waterloo, Waterloo, ON, Canada
[f] Department of Chemistry, Stanford University, Stanford, CA, USA
[g] Department of Civil and Environmental Engineering, Florida International University, Miami, FL, USA

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ABSTRACT

The growing demand for healthcare services and recent advances in materials and biosensing technologies have accelerated the development of point-of-care (POC) diagnostics, with smart contact lenses (SmCLs) emerging as a promising platform. This review systematically evaluates the role of tear fluid as a noninvasive diagnostic medium, highlighting its biochemical composition and challenges in sample collection. We examine the design parameters essential for functional SmCLs, including biocompatibility, oxygen permeability, wettability, and mechanical properties, which collectively determine long-term comfort and device performance. SmCLs can significantly improve the bioavailability of drug delivery while addressing the limitations of traditional ocular treatments, such as the rapid dissipation of eye medications through the nasolacrimal duct. Furthermore, the potential of SmCLs in disease diagnosis through chemical and physical biomarker detection is highlighted, showcasing their ability to monitor glucose levels and intraocular pressure in real-time. Overall, current evidence supports SmCLs as multifunctional devices capable of combining diagnostics and therapy in real time. However, large-scale validation studies are required to establish clinical accuracy, patient adherence, and cost-effectiveness. This review concludes that SmCLs represents an innovative direction in personalized healthcare, integrating materials science, biosensing, and drug delivery for noninvasive, continuous health monitoring of ocular and system diseases.

1. Introduction

The increasing need for access to healthcare with advanced technology creates opportunities for point-of-care (POC) diagnostic platforms (Tania et al., 2019). POC diagnostics provide real-time results at the local laboratory, eliminating delays in specimen preparation and transportation, which can improve medical outcomes (Luppa et al., 2011). In POC products, wearable devices have gained significant public interest for their role in preventive and personalized medical care, due to their convenience, exceptional flexibility, and capacity for extended monitoring. Wearable devices offer rapid screening, cost-effective tests with minimal sample requirements, and efficient tools for detecting and monitoring diseases (Andreu-Perez et al., 2015). Modern wearable devices utilize body fluids such as sweat, saliva, and interstitial fluid, along with electrochemical processes, for on-the-spot health assessment (Tseng et al., 2018). The eyes are uniquely positioned for monitoring biological signals (Kim et al., 2017; Park et al., 2018) because of their continuous contact with tear fluid and plasma leakage through the blood-tear barrier (Kim et al., 2020b). Tear fluid, which is easily accessible and rich in proteins similar to those in blood, offers significant potential for tracking and personalizing treatments for ocular diseases, diabetes, and cancer (Tseng et al., 2018; Mitsubayashi and Arakawa,

* Corresponding author. Department of Chemistry, Stanford University, Stanford, CA, USA.
** Corresponding author.
E-mail addresses: mxm801@case.edu (M. Mofidfar), f.abbasi@sut.ac.ir (F. Abbasi).
[1] Zahra Adibag, Mahsa Ghanbarzadeh, and Mohammad Amin Salati have made equal contributions.

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2016). Unlike the conventional blood-based liquid biopsy method, collecting tear fluid non-invasively has the potential for preliminary clinical assessments (Enríquez-de-Salamanca et al., 2010; March et al., 2004; Sambursky et al., 2014). The tear fluid's unique characteristics have made contact lenses (CLs) a valuable platform for medical diagnosis and treatment (Farandos et al., 2015a).

1.1. Tear fluid

Tear fluid is an intricate mixture of salts, proteins, lipids, and enzymes. It also has various biomarkers for disease screening (und Hohenstein-Blaul et al., 2013). The tri-layer structure of tear film acts as a lubricant with an antimicrobial property (Fig. 1) (Murube, 2009). Tear fluid and blood have compositional similarities due to plasma leakage through the blood-tear barrier. It has been shown that common elements such as glucose, Na^+, K^+, and Cl^- ions are present in both blood and tear fluid. Nevertheless, tear fluid is generally regarded as less intricate than serum or plasma due to the existence of the blood-tear barrier (Kim et al., 2020b; Tseng et al., 2018). Studies have demonstrated that there are between 54 and 1543 different types of proteins present in tears. This range depends on the tear collection and the protein separation techniques (Zhou and Beuerman, 2012). The composition of tears varies depending on the types of tears: (1) basal tears (baseline tear production without stimulation); (2) reflex tears (response to irritants); and (3) psychic tears (emotion-induced with elevated hormone levels) (Murube, 2009). Therefore, tear collection circumstances greatly affect its composition (Baca et al., 2007).

Minimally invasive techniques can be utilized to obtain tear fluid (Fig. 2) (Masmali et al., 2014). The Schirmer's test involves inserting a paper strip, called Schirmer's strip, in the inferior fornix adjacent to the lower eyelid for a 5-min duration (Hagan et al., 2016; Ohashi et al., 2006). Glass or plastic capillary tubes can also be used to obtain tears (Rentka et al., 2017). Although tear fluid is easily accessible, there are some challenges in obtaining a reliable sample. Schirmer strips can stimulate reflex tear production when they encounter the ocular surface, whereas microcapillary tubes can be time-consuming (Markoulli et al., 2011; Pankratov et al., 2016).

1.2. Consideration factors in fabricating smart contact lenses (SmCLs)

When designing SmCLs, several key factors need to be carefully considered. Biocompatibility of CLs is critical for many years of vision correction (Chaudhari et al., 2021). Improved biocompatibility allows for long duration of CL wear without discomfort or hypersensitivity reaction to the material (Musgrave and Fang, 2019). Additionally, optimizing the physical properties and mechanical stability will improve the comfort and safety of CLs wear. The following sections will delve into these properties.

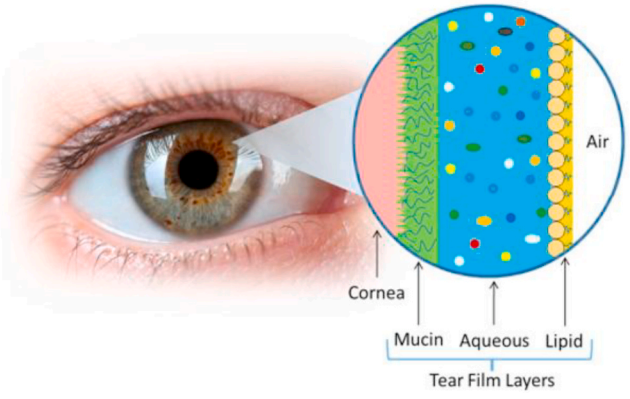

Fig. 1. Schematic of the general structure of the human tear film. Reproduced by permission of ref (Tseng et al., 2018).

1.2.1. Physical properties

Physical properties such as transparency, oxygen permeability, and water diffusion are crucial for the performance and safety of CLs. It is essential to understand and optimize these properties in lens manufacturing, given the intimate interaction between CL and tear fluid (Moreddu et al., 2019b).

1.2.1.1. Oxygen permeability. Cornea cells require atmospheric oxygen in the tear film for normal physiological function. Diffusing oxygen through the CL to the cornea is commonly known as oxygen permeability (Dk). Low oxygen permeability CLs, resulting in limited Dk, can lead to various clinical complications such as corneal edema, corneal acidosis, and epithelial keratitis (Lee et al., 2015). For extended wear, silicone hydrogel CLs (SiHCLs) have high Dk due to the presence of Si-O bonds in the backbone of SiHCLs (Chaudhari et al., 2021). These lenses provide approximately 5–10 times the Dk of traditional hydrogels.

1.2.1.2. Wettability. Wettability refers to maintaining the tear fluid on the CLs' surface, a parameter that is closely associated with the wearer's comfort during prolonged wear (Cheng et al., 2004; Maldonado-Codina and Efron, 2006; Maulvi et al., 2020; Svitova and Lin, 2011). Indeed, CLs divide the tear fluid into two distinct compartments - post-lens and pre-lens (Cheng et al., 2004). CLs tend to disrupt the stability of the precorneal tear film, leading to a thinner tear film due to evaporation. Therefore, lenses' wettability enhancement is essential. Hydrophilic lenses can efficiently disperse water, and this hydrophilicity can be evaluated by analyzing the contact angle between liquid-solid interfaces (Svitova and Lin, 2011). Lowering the contact angle corresponds to high wettability, promoting a stable tear film (Cheng et al., 2004). CL wettability is determined by the pre-lens tear film, as the posterior side of the lens is entirely in contact with the tear film. Additionally, the CL surface is exposed to tear proteins, allowing for protein absorption into the lens material and causing an immune response to the CL.

1.2.1.3. Water content. The quantity of water represented in a given substance is commonly referred to the water content. The waters content of SCLs is a significant characteristic that impacts their performance and oxygen transmissibility attributes. Tranoudis et al. (Tranoudis and Efron, 2004) discovered a positive association between the water content of a SCL and its oxygen transmissibility, free water content, and free-to-bound water ratio. The findings demonstrateed that the higher water content of a CL resulted in an elevation of the free-to-bound water ratio and increased oxygen transmissibility and free water content. High bulk water content lenses tend to have compromised interfacial water content, which can negatively impact the performance and comfort of the lens, highlighting the need for developing new methods to retain surface wettability and biocompatibility (Koffas et al., 2003).

1.3. Mechanical properties

The daily handling of CLs (Bhamra and Tighe, 2017) and their interaction with the ocular environment over an extended period (Opdahl et al., 2003) necessitate an understanding of their mechanical properties, including modulus, tensile strength (Mutlu et al., 2019), and elongation to break (Bhamra and Tighe, 2017). A variety of tests like compression, tension, and dynamic mechanical tests reveal lens mechanical properties. The compression test assesses the CL materials' elastic recovery under eyelid-like deformation (Mutlu et al., 2019). Furthermore, the relationship between mechanical properties and patient comfort has been recognized, resulting in reduced tensile modulus of second and third-generation silicone hydrogel materials (Bhamra and Tighe, 2017). Suitable lenses need high tensile strength and elongation-at-break to resist damage and provide flexibility to prevent

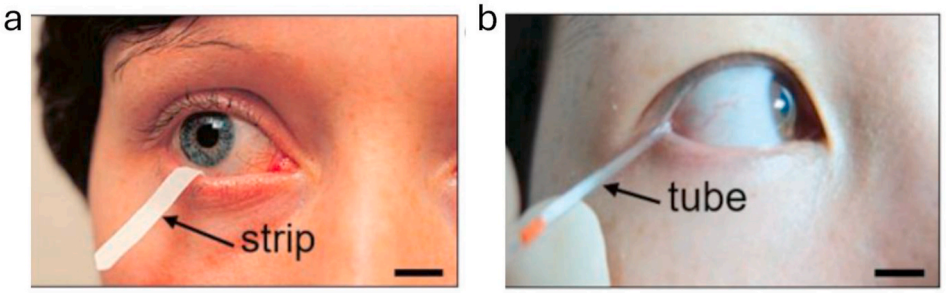

Fig. 2. Tear collecting techniques. (a) The Schirmer's test. Reproduced by permission of ref (Galloway et al., 1999). (b) Capillary tube. Reproduced by permission of ref (Chao et al., 2017).

fracture, respectively. Additionally, moderate Young's modulus of these lenses allows for balanced flexibility and stability.

2. Fabrication technologies of SmCLs lenses

Conventional techniques, namely lathe cutting, spin casting, and cast molding, are widely used for manufacturing CLs, as shown in Fig. 3 and Supplementary (Section S1) (Abdi et al., 2023; Efron and Maldonado-Codina, 2011; Maldonado-Codina et al., 2004; Maldonado-Codina and Efron, 2006). In the cast molding technique, a monomer solution with photoinitiator fills the desired lens shape mold. Subsequently, the solution is subjected to UV light to initiate the curing process. Finally, the cured lens undergoes polishing and grinding to achieve its final configuration (Alam et al., 2021; Aravind et al., 2022; Guryča et al., 2007). In spin casting, rotation facilitates the uniform dispersion of a liquid monomer and a photoinitiator within a rotating mold. The subsequent steps are similar to the cast molding technique, where after UV polymerization, the desired smoothness of the lenses is achieved by polishing the final product (Alam et al., 2021; Moreddu et al., 2019b). The lathe-cutting method involves using a lathe machine to cut cylindrical lens material into the desired shape and dimensions (Alam et al., 2021; Lovrec-Krstič et al., 2023). Currently, advanced fabrication techniques, including 3D printing, microfluidics, lithography, and laser ablation, have enabled of the integration of functional microscale components into SmCLs based on microelectromechanical systems, such as sensors, drug reservoirs, and microchannels (Ma et al., 2021).

3. Various applications of SmCLs

Recent materials and nano-science developments introduce SmCLs with various therapeutic and diagnosis applications beyond vision correction. For instance, soft contact lenses (SCLs) can be designed for drug delivery. SCLs currently dominate the clinical lens market, accounting for 87 % of all lenses. In comparison, rigid gas permeable (RGP) lenses make up only 13 % of the market share (Guzman-Aranguez et al., 2013). Comprehensive discussion of recent advances in these fields is outlined in the following sections.

3.1. Smart contact lenses in drug delivery

Widely used eye drops suffer from low bioavailability due to physiological barriers, tear drainage, and continued tear turnover, where more than 95 % of the ophthalmic drugs are eliminated before absorption and penetration into the eye. Recently, there has been active research on SmCLs as a promising tool for controlled drug delivery to the eye with optimum bioavailability for eye disease treatment (Xu et al., 2018). Originally conceived as visual corrective tools, CLs are currently being explored as an alternative for treating several eye disorders, including glaucoma, dry eye, diabetic retinopathy, cataracts, and inflammation, has been reported.

An ideal drug-loaded lens should enhance the drug retention time on the ocular surface, and prevent drug burst-release and any fluctuations in drug concentration with a sustained medication release to keep the

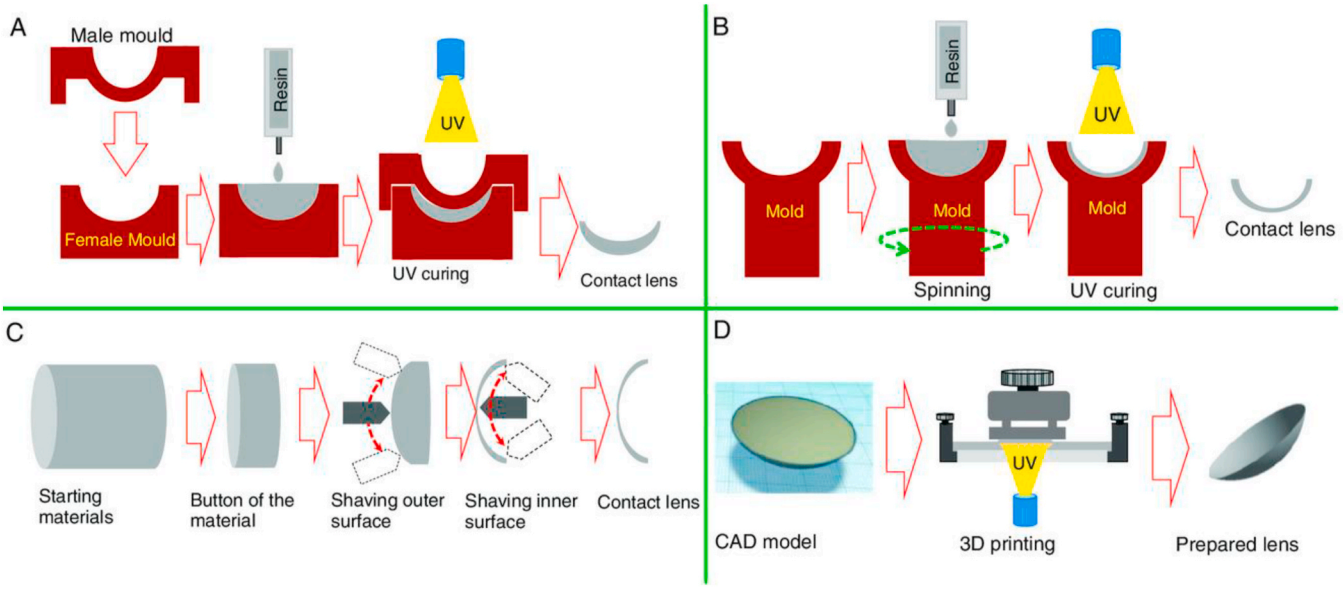

Fig. 3. Different techniques for manufacturing CLs. (a) Cast molding, (b) spin casting, (c) lathe cutting, and (d) 3D printing. Reproduced by permission of ref (Alam et al., 2021).

therapeutic dose at an optimum level while minimizing side effects. Different techniques are reported to design drug-loaded SmCLs for these purposes, including soaking in drug solution, copolymerizing the CLs with functional monomers, molecular imprinting, incorporating drug-loaded colloidal nanoparticles with CLs, and supercritical fluid (Abdi et al., 2023). Some of studies related to application of SmCLs in drug delivery are reviewed in section S2.1 of Supplementary.

3.2. Smart contact lenses in disease diagnosis

The recent advancements in manufacturing integrated circuits (ICs) have resulted in their integration with SmCLs to seamlessly connect with smart devices and medical centers via wireless communication. Electronic contact lenses (E-CLs) are an innovative technology that has transformed the field of vision technology and greatly enhanced human comfort by preserving the size and shape of traditional CLs (Mirzajani et al., 2022).

CLs are powerful tools for health monitoring, augmented reality (AR) (Blum et al., 2014; Chen et al., 2019; Takamatsu et al., 2020), virtual reality experience, and Internet of Things (IoT) technology (Baek et al., 2022; Xiang et al., 2021). A sensor is the fundamental component of IoT technology devices, serving as the sensor layer in the IoT.

3.2.1. Electronic-contact lens

E-CLs can monitor the human eye by detecting chemical and physical alterations. They may transmit the collected data from the lens to doctors and patients. These E-CLs enable continuous collection and delivery of real-time data on a mobile device, screen, or even in virtual reality without interfering with the patient's daily activities (Shaker et al., 2023). In SmCLs, it is customary to use sensors for disease diagnosis, which can change color according to the disease condition. This enables continuous use of the lens (Moreddu et al., 2020; Riaz et al., 2019). In E-CLs, it is possible to check a person's health level without requiring constant lens change, and even by utilizing IoT technology. Fig. 4 offers a bird's-eye view on E-CLs by drawing both their basic building blocks and practical applications. Fig. 4a highlights the onboard micro-systems, in the form of sensors, wireless comms modules, processing circuits, and power modules—incorporated into a soft, biocompatible lens. Fig. 4b illustrates the full range of applications enabled by the on-lens micro-systems in Fig. 4a, spanning non-invasive sensing of tear glucose and intraocular pressure (IOP) to more advanced functions such as drug delivery, IoT integration, augmented reality (AR), and cancer-biomarker sensing. The materials utilized in E-CLs for different applications are summarized in Table S1, section S2.2 of Supplementary.

Combining E-CLs with sophisticated sensing capabilities offers the possibility to identify biomarkers associated with different disorders, including diabetes and glaucoma. The lens with a microelectrode array can detect changes in tear glucose levels, as shown in Table S1. This provides a non-invasive and continuous monitoring approach for managing diabetes. In addition, the lens's IoT connectivity allows for the immediate transmission of data to healthcare professionals, facilitating timely intervention for the patients.

3.2.2. Biosensing capabilities of SmCLs

SmCLs offer a non-invasive platform to monitor various physiological biomarkers directly from the ocular surface. Two key diagnostic applications are glucose detection for diabetes management and IOP monitoring for glaucoma care.

Glucose detection in tear fluid is promising due to the high correlation between tear and blood glucose levels. This approach reduces the need for frequent poking of fingers with needles in diabetic patients (Oliver et al., 2009). Glucose sensors can be integrated into SmCLs to enable continuous, real-time monitoring of the glucose concentration in the tear film. However, incorporating electronic components into contact lenses presents challenges due to the brittle, opaque materials that could cause discomfort and blurry vision. To address these issues, transparent nanostructures and wireless components have been developed without the bulky electronic components (Park et al., 2018). For

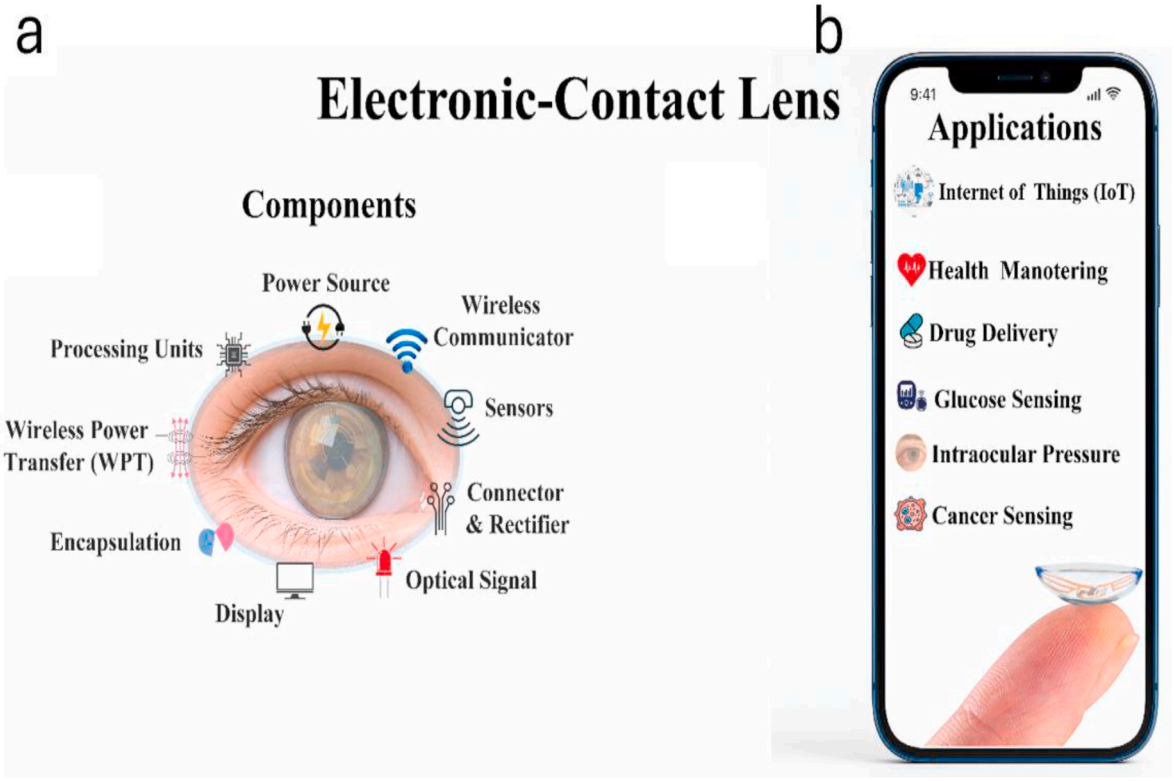

Fig. 4. Electronic-contact lens (E-CL) concept showing hardware architecture and envisioned use-cases. (a) Schematic of a soft contact lens, with identifying the main hardware blocks and (b) representative applications unlocked by these components.

instance, glucose oxidase (Gox) has been immobilized on the graphene surface via a pyrene linker, allowing detection through changes in carrier density related to glucose concentration. In another design, glucose oxidase is integrated with cerium oxide (III) nanoparticles enabling biocompatible biosensor (Kim et al., 2020). Spectroscopic analysis is used to detect changes in glucose levels, which cause shifts in the reflection spectrum. These shifts then establish a correlation curve for measuring glucose levels.

IOP monitoring is another significant application. SmCLs embedded with strain sensors, including strain gauges, piezoresistive, micro inductors, and capacitance sensors, offer a more convenient method. These sensors detect subtle corneal deformations of the meridional angle of juncture between the cornea and sclera, enabling continuous IOP monitoring (Quigley and Maumenee, 1979).

Beyond glucose and IOP measurement, SmCLs can detect biomarkers like enzymes, hormones, ion concentration, and pH value. For example, increased tear pH and sodium ion (Na^+) concentration can indicate dry eye syndrome (DES). With the appropriate biosensor integration, SmCLs have the potential to facilitate diagnosis of several diseases, such as cardiovascular complications and anxiety disorders (Yetisen et al., 2017)' (Sunwoo et al., 2019).

3.3. Eye as a sensory organ

The human eye is a complicated sensory organ responsible for vision. This sophisticated organ faces many disorders and diseases that can lead to loss of vision. Most of these diseases are more prevalent in older populations, including age-related macular degeneration, glaucoma, and cataracts (Lorenzo-Veiga et al., 2021). In contrast, other eye conditions may occur due to injury, infection, inflammation, and rarely congenital defects (Chen et al., 2021; Yaylacioglu Tuncay et al., 2020).

The human eye is a complex sphere surrounded by three concentric layers. The fibrous tunic is the outer substrate divided into sclera and cornea segments. The choroid, iris, and ciliary body are the midsections, called the vascular tunic. The inner layer is the retina, responsible for many ocular diseases, including DR and macular degeneration (Durak et al., 2020). In a broader classification, the human eye comprises of two parts: the anterior and posterior segments. The anterior segment, which consists of the ciliary body, lens, iris, aqueous humor, cornea, and conjunctiva, makes up about one-third of the globe and is located towards the front of the eye. The posterior segment, which accounts for the remaining two-thirds of the eye, includes the choroid, posterior sclera, vitreous humor, and retina and is located towards the back of the eye (Sunita et al., 2021).

4. Eyes' biomarkers for disease diagnosis

Physical and chemical biomarkers are two main types of biomarkers that can be used to identify or monitor various diseases. Physical biomarkers involve changes such as variations in IOP, eye movement, and eye temperature, whereas chemical biomarkers include types and concentrations of proteins or ions, such as lactate and glucose, in tear fluids (Kim et al., 2020b).

4.1. Physical biomarkers

Analyzing physical biomarkers is essential in the early detection and management of ocular diseases, providing critical insights into eye health (Kim et al., 2020b). IOP (Wang et al., 2018), ocular surface temperature (OST) (Shah and Galor, 2021), and eye movement patterns as physical biomarkers (Samadani et al., 2015a) provide a suitable platform for diagnosing glaucoma (Chen et al., 2013), DR (Chandrasekar et al., 2021), and neurological function in concussion syndrome (Samadani et al., 2015b). Using advanced technologies in sensor-embedded SmCLs, allows for continuous monitoring of these biomarkers, enhancing diagnostic accuracy and facilitating timely interventions to improve patient outcomes in ocular health (Khaldi et al., 2020; Moreddu et al., 2019a; Seo et al., 2023).

4.1.1. Intraocular pressure

IOP is the physical indicator that can be measured using the CL sensor platform. Elevated IOP leads to glaucoma, a common disorder that causes irreversible vision loss. The normal IOP is between 10 and 21 mmHg (Wang et al., 2018). The only known modifiable risk factor for glaucoma is IOP (Casson et al., 2012; Chen et al., 2013). Measuring IOP requires using a tonometer, a medical device that can only be performed with an in-person exam. Due to the clinic-based testing requirement, this process does not allow for continuous monitoring of IOP. For this reason, sensor-equipped CLs can offer a non-invasive method for continuous IOP measurement.

The five forces that affect the eye are the atmospheric pressure, the hydrostatic pressure of the tear film posterior to the CL, gravity, the force of the eyelid on the CL, and the surface tension of the tears (Farandos et al., 2015a). Variations in IOP lead to a change in the hydrostatic pressure, which can alter the cornea's radius of curvature (Kim et al., 2020b). In the human ocular system, a 1 mmHg change in IOP causes a 3 μm variation in the cornea radius of curvature. CLs with embedded IOP sensors can monitor this physical change, which can facilitate individualized medicine in the glaucoma treatment (Seo et al., 2023). Recent clinical trials employing the Sensimed Triggerfish® SmCL have reported sensitivity of approximately 80–90 % in detecting IOP variations in glaucoma patients. The specificity of these sensors can be influenced by physiological factors such as corneal thickness, eyelid pressure on blinking, and individualized biomechanical characteristics of the eye. Therefore, patient-specific calibration is thus required to account for these factors and improve accuracy. Despite these limitations, SmCLs demonstrate significant clinical potential for improved early detection, continuous monitoring, and individualized treatment planning in glaucoma treatment (Dunbar et al., 2017).

4.1.2. Temperature

OST can vary depending on blinking, aging, ambient, and body temperature. The OST may be measured efficiently and directly using SmCLs. A temperature-sensitive cholesteric liquid crystal (CLC) implanted in an SmCL was developed by Moreddu et al. The CLC is made up of four sensors that are placed on the OSL, opposing different regions of the cornea to track variations in the OST (Fig. 5a). The molecules in the CLC are arranged in a helical shape that is temperature sensitive. Temperature-sensitive color variations arise from wavelength shifts in the reflected light caused by the helical structure. Using a smartphone to automatically standardize the color photos, the researchers obtained color pictures of the CLC inside the SmCLs. They could generate normalized color images of the CLC by applying temperatures ranging from 29 to 40 °C (Fig. 5b). Additionally, the SmCL colorimetric technique was evaluated on an *ex vivo* porcine eye (Fig. 5c) (Moreddu et al., 2019a). Clinical reliability of OST as a biomarker is demonstrated by the precision in the detection of temperature variations with ±0.5 °C accuracy in *ex vivo* models (Shah and Galor, 2021). In humans, there are few clinical trials, and ambient temperature fluctuations or individual variation in tear film composition may affect clinical significance of measurements.

4.1.3. Eye movement

Eye movement is indicative of human consciousness, which is the outcome of an intricate brain process that involves sophisticated levels of control (Seo et al., 2023). Tracking eye movement is another physical biomarker that can be evaluated. Observing unusual eye movements can provide valuable information on neurological functions. This is particularly helpful when diagnosing concussion syndrome, a challenging brain injury that may manifest symptoms like headaches, disorientation, and slurred speech, all of which can appear days after the initial injury (Samadani et al., 2015). The technique of tracking eye movements has

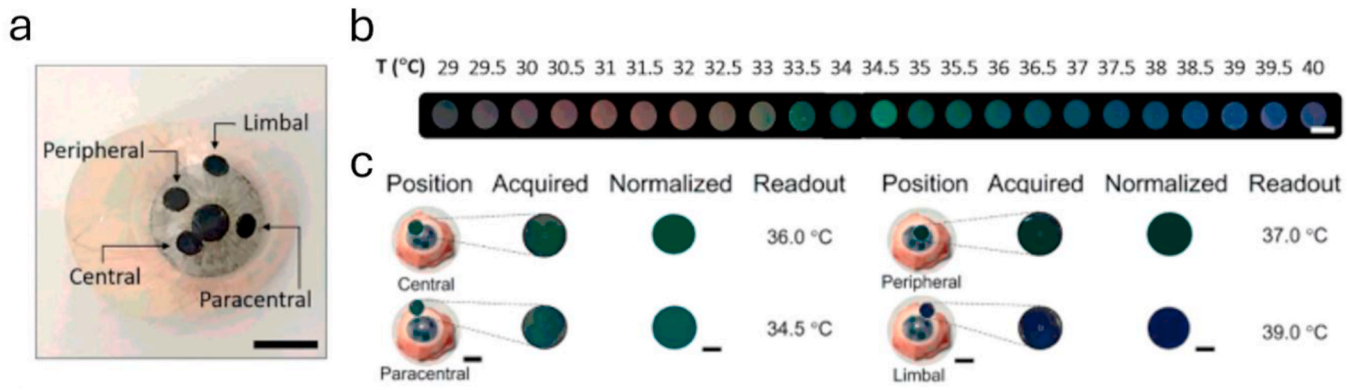

Fig. 5. Physical diagnostic SmCLs are used to monitor OST and eye movement. (a) Image of an SmCL equipped with four CLC temperature sensors. The scale bar measures 1 cm. (b) The screenshot shows normalized color images of CLC at various temperatures. The scale bar measures 2 mm. (c) CLC color readouts from smartphones at four different sensing locations. The scale bars measure 2 mm. Figures (a)–(c) Reproduced by permission of ref (Moreddu et al., 2019a). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

been well-researched, and Purkinje eye imaging is a commonly used method (Kim et al., 2020b). Shining light directly onto the eye produces reflected light. Understanding the direction and motion of the eye is possible by examining the movement of this reflected light. Delays or abnormalities in eye movement can help in the diagnosis of concussion (Kim et al., 2020b). Khaldi et al. developed a prototype eye-tracking lens, which involved encapsulating the integrated electronics and components, such as the primary and secondary antenna and optoelectronic circuitry, within the CL using Loctite glue (Fig. 6a and b). The electronics circuit, as shown in Fig. 6c, emits an infrared (IR) beam to indicate eye gaze direction. This IR beam is combined with a secondary antenna embedded in the eye-tracking lens to receive power from an eyewear power source. This system involves a primary antenna transferring power from an external generator to the lens's secondary antenna via magnetic coupling. To conduct the eye tracking test, a camera was mounted on the eyewear, and the IR beam emitted by the eye tracking lens, placed on an artificial eye, was reflected by a beam splitter towards the camera. The artificial eye facilitates tracking eye movements within a specific angular range, ensuring the system's efficacy in the real world (Fig. 6b). The camera effectively recorded five different gaze directions (Fig. 6d). The coordinates of the vertical cavity surface emitting laser spot corresponding to these five orientations are depicted in Fig. 6e. However, there were too many electronic parts, causing the lens to be too heavy to fit comfortably on the eye (Khaldi et al., 2020; Young et al., 2012).

4.2. Chemical biomarkers

Due to the permeability of the blood vessels, tears contain blood ions, metabolites like lactate and ascorbate, and other proteins from plasma (Table S2, section S3 in the Supplementary) (Baca et al., 2007; Buzanovskii, 2017; Murube, 2009; Paterson and O'Rourke, 1987). Various metabolites and proteins present in tear fluids can serve as surrogates for those found in the serum and, therefore, may detect diseases and respond to treatment (Table S3) (Balasubramanian et al., 2012; Suetrong and Walley, 2016; Thomas et al., 2012). Clinical validity of chemical biomarkers in tear fluid is constrained by variability in composition of tears induced by environmental and physiological status, limiting their reliability as diagnostic markers (Bruszel et al., 2024). Large-scale human clinical studies are required to validate their sensitivity, specificity, and practicality in detecting disease (Buzanovskii, 2017).

4.2.1. Identification of various diseases via eye biomarkers

Tear fluid contains a diverse range of proteins that make it useful for detecting ocular and systemic disorders. Various biomarkers are related to specific diseases or conditions, which can alter the tear fluid's proteomic profile. By detecting certain proteins or metabolites through liquid biopsy, the progression of the related diseases can be effectively analyzed and assessed (und Hohenstein-Blaul et al., 2013).

4.2.1.1. Dry eye syndrome. Many research efforts concerning tear fluid have concentrated on DES, a complicated condition that can lead to discomfort, blurred vision, and inflammation that adversely affects the ocular surface health. DES can manifest as either evaporative dry eye or aqueous tear-deficient dry eye. Target biomarkers for the DES have been identified by analyzing a variety of cytokines, chemokines, growth factors, mucins, neuromediators, and lipid profiles.

Aluru et al. (2012) discovered associations between multiple forms of DES and the decreased expression of lysozyme proline-rich protein 4. Thus, they proposed this protein as a potential DES biomarker. In addition, identifying the inflammatory biomarker matrix, metalloproteinase 9 (MMP-9), in tear fluid is another method of diagnosing dry eye disease because patients with dry eyes have elevated levels of MMP-9. Typically, symptoms of dry eye syndrome can be present if the concentration of MMP-9 in the tear glands exceeds 40 ng mL^{-1}, and a diagnosis of the condition is confirmed if the concentration surpasses 200 ng mL^{-1} (Tsubota et al., 2020). Moreover, given the longstanding evidence linking allergies to dry eye syndrome, biomarkers such as lactoferrin and immunoglobulin E in the tear fluid can be diagnostic indicators for allergic conjunctivitis (Zeev et al., 2014).

4.2.1.2. Diabetes. Diabetes mellitus is diagnosed by measuring the glucose concentration in the blood. Fasting plasma glucose level higher than 126 mg dl^{-1} or non-fasting plasma glucose concentration higher than 200 mg dl^{-1} is diagnostic of diabetes mellitus (Committee, 2023). Many studies have been conducted to diagnose diabetes by measuring glucose concentration in tear fluids. Furthermore, the glucose content of tears can be measured to track how well diabetes are controlled (Kim et al., 2020b).

DR is a common and serious ocular illness that may eventually result in intraocular hemorrhage, retinal edema, glaucoma, retinal detachment, and blindness if not treated (Teo et al., 2021; Vujosevic et al., 2020). Zhang et al. discovered twenty differentially expressed proteins in the tear fluid of patients suffering from non-proliferative diabetic retinopathy (NPDR) (Zhang et al., 2025). Among them, three proteins, such as lipocalin 1 (LCN-1), heat shock protein 27 (HSP27), and beta-2 microglobulin (B2M), reduced progressively in their levels, showing that they can be used as biomarkers to diagnose diabetic retinopathy at an early stage. Subsequently, Costagliola et al. (2013) revealed that patients with DR exhibited elevated levels of tumor necrosis factor-alpha (TNF-α), confirming the potential association between TNF-α and the

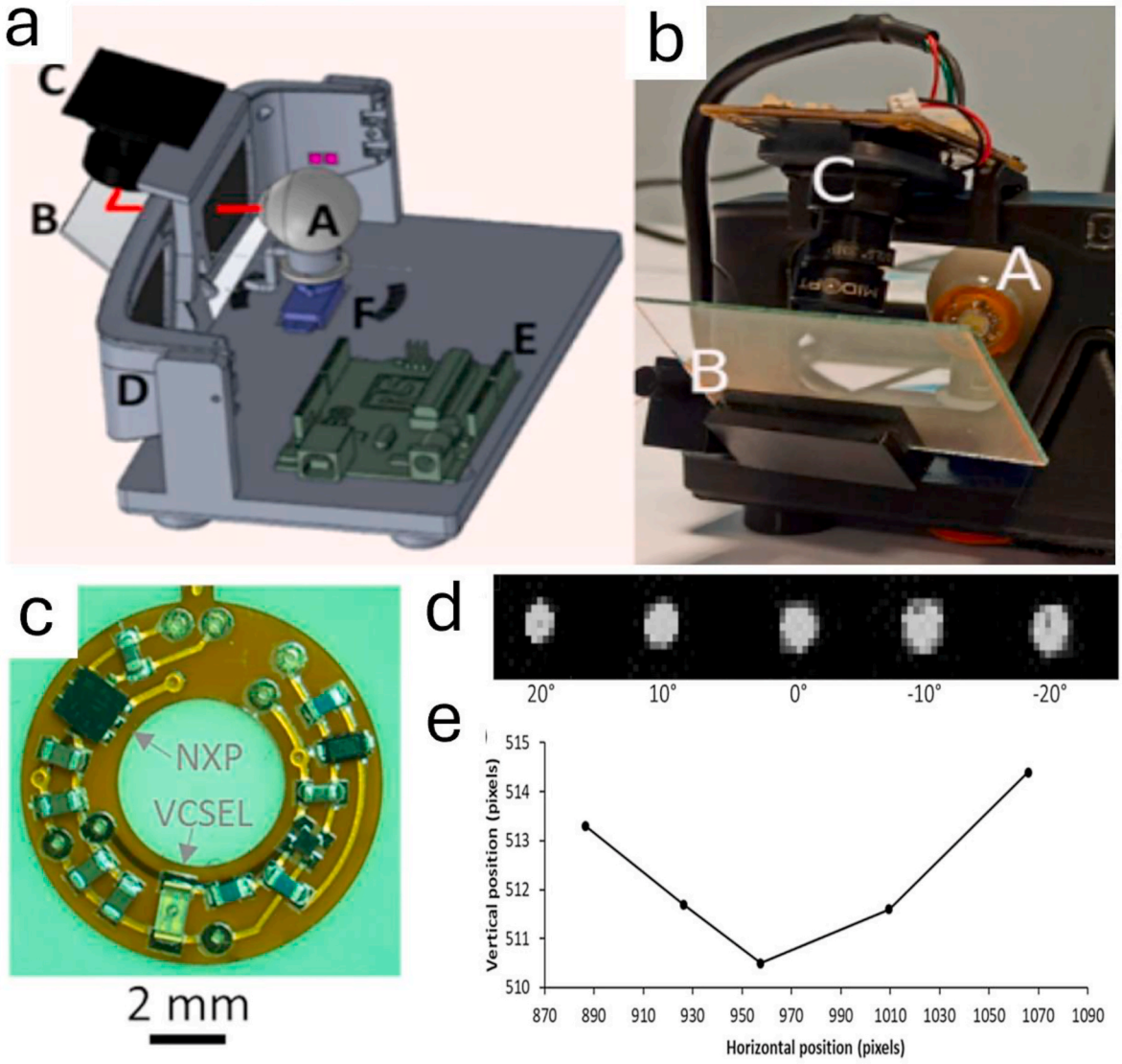

Fig. 6. (a) Diagram of the entire system showing the prosthetic eye (A), the servo-motor (F) and associated micro-controller (E) to control the direction of the eye, the eyewear (D) that contains the main antenna, the beam splitter (B) that channels the VCSEL beam (represented as a red solid line) towards the IR camera (C) (located above the eyewear). (b) A prototype image. (c) Eye tracking lens electronic circuit and componentry, (d) the vertical cavity surface emitting laser spot captured by the IR camera at five different orientations: −20°, −10°, 0°, 10°, and 20°, and (e) the graph depicts the coordinates of the vertical cavity surface emitting laser spot corresponding to these five orientations (Reproduced by permission of ref (Khaldi et al., 2020).). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

severity of DR. Additionally, the concentration of nerve growth factor in the tears of proliferative DR patients was higher compared to NPDR and non-diabetic patients, indicating possible marker for disease severity. Although there is a high noise level in the relationship between DR and proteins, combining a series of biomarkers may improve the accuracy of diagnosing and monitoring DR. The discovery of these biomarkers creates new opportunities for tailored screening and diagnostic instruments. However, further research is required to develop specialized analytical tools for SmCLs before these biomarkers can be applied successfully in POC settings.

4.2.1.3. Cystic fibrosis and similar conditions. A genetically inherited disease called cystic fibrosis affects the exocrine glands resulting in an abnormal buildup of mucus in the lungs, pancreas, intestines, and sweat glands (Davies et al., 2007). It might cause symptoms of dry eyes. Mrugacz et al. (2006) found a correlation between cystic fibrosis disease and ocular surface inflammation, which was associated with the expression of interleukin-8 (IL-8) and interferon-gamma (IFN-γ). Subsequent research revealed that macrophage inflammatory protein (MIP)-1β and MIP-1α play significant roles in the inflammatory responses in patients with cystic fibrosis (Mrugacz, 2010; Mrugacz et al., 2007).

4.2.1.4. Cancers. Recent studies suggest that tear fluid may contain biomarkers indicative of cancer. Evans et al. (2001) observed an association of lacryglobin in the patients' tears with breast cancer. The researchers also detected lacryglobin in patients' tear fluid with colon, prostate, breast, lung, and ovarian cancers in their investigation.

5. Smart contact-lenses based biosensors

SmCLs are a new platform for non-invasive ocular and systemic health monitoring through the analysis of tear fluid. The lenses use multiple sensors, which are classified primarily into two classes: physical sensors that detect physical biomarkers such as IOP and chemical biosensors that detect chemical biomarkers such as glucose, lactate, and

potassium in tear fluid. Physical sensors, including capacitive, microfluidic, and strain sensors, monitor mechanical or pressure-type dynamics, while chemical biosensors employ biological recognition elements (e.g., enzymes or antibodies) to selectively recognize chemical analytes. Physical sensors are described first, followed by chemical biosensors where their use in health monitoring is highlighted (Elsherif et al., 2022; Kim et al., 2020a).

5.1. Physical sensors

The IOP has been the primary focus of CL sensors in assessing physical biomarkers. The techniques utilized for measuring IOP are capacitive, microfluidic channel, and strain sensors. These sensors are important in monitoring IOP changes, which plays an important role in glaucoma.

5.1.1. Capacitive SmCL sensors

Capacitive sensing finds broad application in pressure detection with utilization in various fields, such as touchscreens, fingerprint recognition systems, and medical stethoscopes (Yuan et al., 2021). A capacitive sensor is a type of CL sensor employed in contact lenses to detect IOP. For sensor development to precisely measure IOP at the corneal curvature, a dielectric layer is positioned between two electrodes, forming a sandwich-like structure. The elevated IOP leads to an expansion in the cornea's radius of curvature, subsequently augmenting the capacitance. This increase in capacitance occurs due to reduced dielectric thickness (Chen et al., 2013; Kim et al., 2017). Capacitive CL sensors are described with more details in section S4 of Supplementary.

5.1.2. Sensors with microfluidic channels

Using microfluidic channels, IOP is regarded as microfluidic volume variations. A liquid occupies a chamber, and the fluid exits into the microfluidic channel when the IOP compresses the chamber. The fluid amount pushed into the channel reflects the IOP (Yan, 2011). Microfluidic SmCL was introduced by An et al. (2019) for continuous IOP monitoring, allowing visual monitoring of the dyed liquid's flow. The dyed liquid moves toward the sensing channel when the IOP rises. The colored liquid returns to the detecting chamber when the IOP levels normalize (Fig. 7a). The researchers determined the sensitivity of the microfluidic IOP sensor by measuring the liquid flow displacement while delivering IOP in the range of 0–40 mmHg. An SmCL was used to track the porcine eye's IOP level in real time (Fig. 7b and c). When the IOP was increased in the porcine eye, the pressure sensor (blue line) demonstrated the same value as the microfluidic CL (red line). Furthermore, the sensor's sensitivity was determined to be 0.283 $mmHg^{-1}$ (An et al., 2019). Wu et al. also developed a CL sensor that uses microfluidic channels to measure IOP. The soft, biocompatible PDMS material was integrated into the inner side of the lens to contact the cornea. The device's annular sensing chamber was filled with the dyed liquid. A smartphone camera was used to monitor changes in the liquid's displacement (Fig. 7d).

5.1.3. Strain SmCL sensors

Developing a strain sensor on CLs is another method of measuring IOP. These sensors detect IOP by converting variations in the corneal curvature into an electrical signal using strain gauges. The silicone-based CL sensor consists of four strain gauges: two resistive strain gauges for measuring corneal curvature and another pair for heat correction. The sensitivity to corneal curvature is effectively doubled by

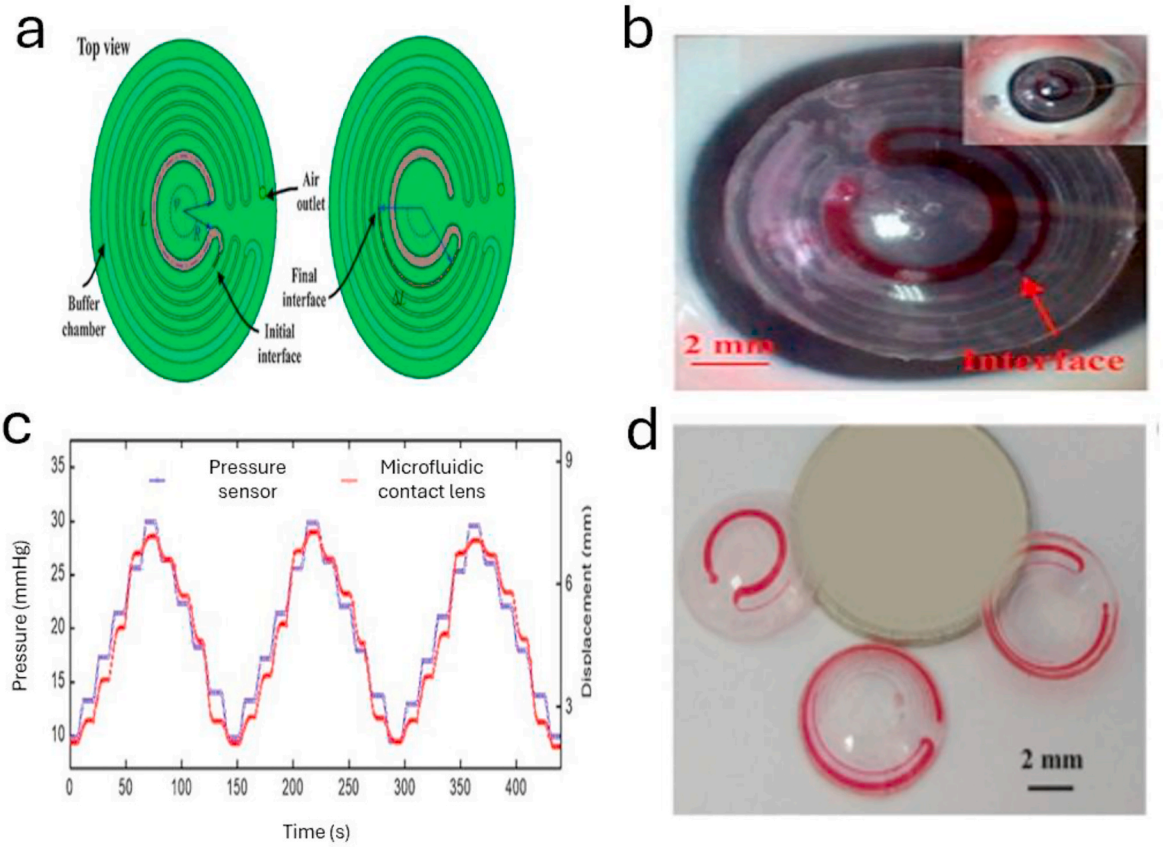

Fig. 7. Physical diagnostic SmCLs for microfluidic channel IOP monitoring. (a) Microfluidic CL schematics at different IOPs. (b) A picture of the microfluidic CL placed on an *ex vivo* porcine eye. (Reproduced by permission of ref (An et al., 2019)) (c) Displacement and IOP variation throughout three cycles. (d) CLs made of microfluidic materials. (Reproduced by permission of ref (An et al., 2019)).

employing two compensation-resistive strain gauges (Farandos et al., 2015b). The electrical resistance of the strain sensor varies in response to changes in its length and cross-sectional area. When the IOP increases, the strain sensor's resistance rises due to elongation, leading to length expansion, while concurrently, the cross-sectional area diminishes. The strain gauge is integrated into a Wheatstone configuration. Additionally, two resistors are included for temperature compensation, ensuring the sensor's performance remains independent of temperature fluctuations. Further research works have been reviewed in section S5 of Supplementary.

5.2. Chemical sensors

SCLs to date have been employing sensors to detect biomarkers such as glucose and lactate, and also devices to analyze ion concentration (Farandos et al., 2015a). Chemical biosensors are generally divided into electrochemical, fluorescent, or photonic sensors depending on the specific method employed to detect these biomarkers (Tseng et al., 2018).

5.2.1. Electrochemical SmCL sensors

Electrochemical sensors consist of a biological recognition element and an electrochemical transducer to generate an output signal. The recognition element such as an enzyme, protein, or antibody is designed to specifically interact with the target analyte. The transducer then changes this signal's biological domain into an electrical domain (Thévenot et al., 2001). These systems can achieve excellent selectivity by using enzymes that can catalyze processes relevant to electrochemical sensing. Typically employing a standard 3-electrode setups, these sensors able to quantify glucose concentrations in tear fluid. As seen in reactions (1) and (2), GOx facilitates the release and generation of electrical charge. The magnitude of the generated charge correlates directly with the glucose oxidized concentration (Elsherif et al., 2022; Yao et al., 2011).

Recognition of glucose enzymatically by GOx

$$\mathrm{D-glucose + O_2 \rightarrow\ H_2O_2 + D-gluconolactone} \quad (1)$$

Electrochemical oxidation of H_2O_2

$$\mathrm{H_2O_2\ \rightarrow\ 2H^+ + O_2 + 2}e^- \quad (2)$$

The produced electrons are used by the sensor's three electrodes to determine the glucose concentration of the fluid. Furthermore, chip-based electrochemical sensors have been incorporated into CLs to determine glucose concentration in artificial tear fluid (Kim et al., 2020a; Yao et al., 2011).

The electrochemical sensor in SmCLs utilizes a three-electrode configuration: working electrode, reference electrode, and counter electrode to detect electrical signals resulting from biochemical reactions in tear fluid (Sumitha and Xavier, 2023). These sensors employ a biorecognition element, such as GOx, that selectively binds to analytes, e.g., glucose, to catalyze reaction processes that produce measurable currents or potentials. More details about the electrochemical sensors have been provided in section S6 of Supplementary.

5.2.2. Fluorescence sensing

In fluorescence resonance energy transfer (FRET) -based sensors, analyte binding changes the distance between the fluorophores, decreasing FRET and thus increasing fluorescence for analyte concentration measurement. This reduced FRET results in a higher intensity of emitted fluorescence, which can be correlated to the analyte concentration (Springsteen and Wang, 2001). For continuous glucose monitoring in tear fluid, CLs were equipped with fluorescent glucose sensors. This subject has further been described in section S7 of Supplementary.

5.2.3. Photonic-based sensing structures

Photonic-based sensors offer an innovative platform for convenient, non-invasive, and continuous health monitoring. For example, a photonic sensor that detects specific biological markers in the eye tear fluid by measuring light phenomena, e.g., shifts in wavelength or intensity changes. These sensors can then be miniaturized into transparent, ultra-sensitive devices that seamlessly integrate with the CL matrix, for comfortable wear.

5.2.3.1. Holographic sensors: one-dimensional photonic crystal.

As shown by Equation (3), the interaction between the sensors and the analytes can alter the sensors' diffraction efficiency and spectral response, or visually, the brightness and color (Kabilan et al., 2005; Yetisen et al., 2014b).

$$m\lambda = 2nd\ sin\ \Theta \quad (3)$$

where m is the diffraction order, λ is the incident light's wavelength, n is the refractive index of the system, d is the photonic crustal plane's spacing, and θ is the diffraction angle. Consequently, any shift in the wavelength of diffracted light caused by spacing or refractive index changes will result in a color change.

Holographic sensors detect analytes by optical properties change via adjusting the grating surfaces. The holographic techniques were applied to create photonic structures that functioned as sensors for measuring glucose concentration in tear fluid (Yang et al., 2008). This strategy entails building a layered periodic structure, functionalizing with substances like boronic acid derivatives to covalently capture glucose. In contrast to fluorescent sensors, holographic sensors are dye-free, resistant to photobleaching, and have extended lifespans in CL sensors. Holographic sensors can also function at near-infrared wavelengths, making them compatible with consumer devices like smartphone cameras (Yetisen et al., 2014; Yetisen et al., 2014a).

5.2.3.2. Colloidal crystal arrays: multi-dimensional photonic crystal.

Three-dimensional photonic crystal array sensors are made of immobilized nanoparticles inside polymer matrices. Visible light is diffracted by a colloidal system that is incorporated in a polymer matrix to form photonic crystal array-based sensors. Similar to holographic sensors, this technology offers a novel method of developing optical sensors without requiring an organic dye for quantitative glucose measurements (Alexeev et al., 2004).

Alexeev et al. (Alexeev et al., 2004; Ben-Moshe et al., 2006) pioneered the development of photonic crystals for glucose-sensing applications. Their sensor was functionalized with boronic acid derivatives, utilizing polystyrene colloids embedded in a polyacrylamide-(bis-AA)-poly (ethylene glycol) matrix. Using this configuration allows the detection of glucose at physiological pH. Subsequent studies improved the sensors' sensitivity and response to detect glucose concentrations in tear fluid (0.15 mM) and blood (5 mM); at physiological pH and temperature, the optimal response times for blood and tear fluid measurements 90 s and 300 s, respectively.

6. Conclusion

SmCLs represents a transformative advance in personalized healthcare, offering a unique platform for non-invasive diagnostics and continuous monitoring through the analysis of tear fluid, as well as targeted drug delivery. SmCLs utilize tear fluid, which contains various biomarkers that continuously monitor important factors like glucose levels and IOP. This innovation addresses the drawbacks of traditional methods, providing quick results to improve patient care and outcomes. Advances in fabrication techniques, including 3D printing, microfluidics, and integrated microelectronics have further accelerated their development, enabling miniaturization of sensors, improved material biocompatibility, and enhanced comfort for long-term wear. Moreover,

the translation of SmCLs into clinical practice will depend on robust validation studies that establish diagnostic accuracy, therapeutic efficacy, and economic feasibility.

Future work should focus on large-scale clinical trials to validate the correlation between tear biomarkers and diseases, thereby defining actionable thresholds for diagnosis and treatment. Parallel efforts are needed to develop standardized tear collection and analysis protocols, as well as to optimize biocompatible materials that maintain oxygen permeability, wettability, and resistance to biofouling. Integrating multimodal sensing (e.g., chemical, physical, and optical biomarkers) with wireless data transmission and IoT platforms could expand their diagnostic reach and enable remote patient monitoring. Additionally, advancing power delivery solutions, such as biofuel cells and wireless charging, will be essential for long-term, continuous operation. Finally, interdisciplinary collaboration across materials science, nanotechnology, ophthalmology, and data science will be critical to transition SmCLs from experimental prototypes to clinically reliable, patient-centered tools. With these efforts, SmCLs have the potential to evolve into a cornerstone of preventive and personalized medicine, improving health outcomes across ocular and systemic diseases.

CRediT authorship contribution statement

Zahra Adibag: Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **Mahsa Ghanbarzadeh:** Writing – review & editing, Writing – original draft, Visualization. **Mohammad Amin Salati:** Writing – review & editing, Writing – original draft, Visualization. **Monireh Esmaeili Rad:** Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **Rais Ansari:** Writing – review & editing, Validation, Resources, Formal analysis. **Christopher N. Ta:** Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **Daddi Fadel:** Writing – review & editing, Writing – original draft. **Mohammad Mofidfar:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Conceptualization. **Farhang Abbasi:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Christopher N. Ta reports financial support and administrative support were provided by National Institutes of Health. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.biosx.2025.100734.

Data availability

No data was used for the research described in the article.

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