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Smart Contact Lenses for Biosensing Applications

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Smart contact lenses have emerged as novel wearable devices. Due to their multifunctional biosensing capabilities and highly integrated performance, they provide a great platform for the diagnosis of eye diseases and the delivery of drugs. Herein, a brief history of the development of contact lenses is given. Then, the state-of-the-art design and fabrication of smart contact lenses for biomedical applications, including contact lens materials, fabrication technologies, and integration, are presented. Furthermore, biosensors implemented in contact lenses to measure lactic acid, glucose, intraocular pressure, and other key metabolites in tears are highlighted. Applications of smart contact lenses in drug delivery are also described. These unique features make smart contact lenses promising diagnostic and treatment devices. Challenges and future opportunities for further applications of smart contact lenses in biomedicine are also discussed.

1. Introduction

Flexible and wearable medical devices with highly integrated circuits (ICs) have begun replacing traditional devices to achieve noninvasive and simple physiological measurements.[1] Recent technological advances in flexible and stretchable materials, microelectronics, and computer science have enabled combinations of soft electronics with wearable devices amenable for the development of personal healthcare monitoring systems. The human eye, as the only sensory organ in the human visual system, carries abundant vital, physical, chemical, and biological information relevant to human health. Thus, it becomes an important study object, which propels the fast development of soft electronic systems for eye study.

Smart contact lenses, as flexible and wearable medical devices, have shown significant potential for supporting the diagnosis and clinical treatment of eye diseases.[2–5] They have sensing components to monitor eye characteristics, such as intraocular pressure (IOP) and ocular fluid composition. In addition, they can provide valuable biological information for the diagnosis and treatment of diseases, such as glaucoma, keratitis, and diabetes.[6–9] Wichterle designed the first hydrogel contact lens, which dramatically shifted the field away from producing lenses made from hard materials. Wichterle's soft hydrogel processing method that involved the process of lathing hydrogels and direct spin casting enabled high volume production of hydrogel-based contact lenses.[10] Further advances in hydrogel biocompatibility, bioactivity, and biomimicry have

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DOI: 10.1002/aisy.202000263

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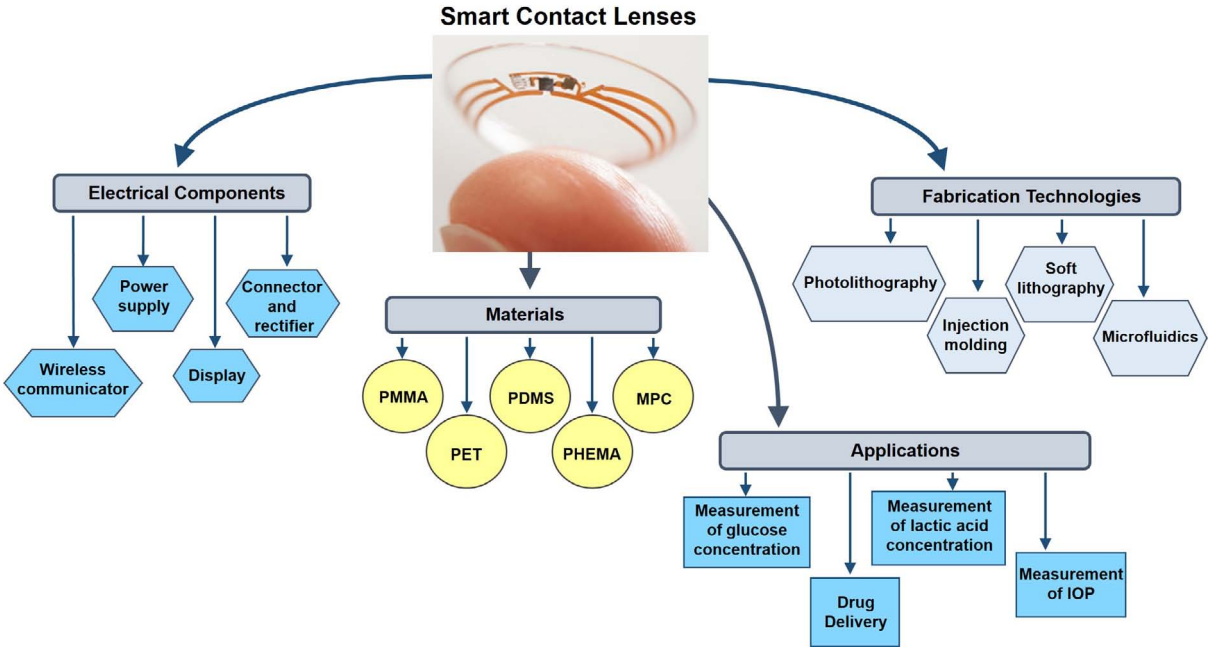
caused progress in the development of soft contact lenses. In addition, great advances have been made by microelectromechanical systems (MEMS). These advances have been achieved in device miniaturization for microsensors, microcircuits, and other devices in the microscale, which makes it possible to fabricate contact lenses with integrated biosensing functions. Moreover, flexible electronics are being rapidly integrated with microscale technology that can assist the development of various medical wearable devices. Consequently, contact lenses can be used as an effective wearable device for advancing medical and health-monitoring applications.[11–16]

Smart contact lenses are the collection of many technologies including biomaterials, microfluidics, biosensors, power supply, data transmission, and display circuits, all of which will be described in the following sections. This Review focuses on the current state-of-the-art smart contact lenses by summarizing examples of significant work and creative fabrication techniques (**Scheme 1**). Finally, we discuss several interesting future directions geared toward the fabrication and implementation of highly functional smart contact lenses in health-monitoring and drug-delivery applications.

2. Materials for Contact Lenses

Various materials can be used to make modern contact lenses, including poly (methyl methacrylate) (PMMA), poly (ethylene terephthalate) (PET), poly (2-hydroxyethyl methacrylate) (PHEMA), polydimethylsiloxane (PDMS), silicone, and 2-methacryloyloxyethyl phosphorylcholine (MPC). Smart contact lenses produced with PHEMA hydrogels or silicone are popular for biomedical applications. For instance, Ulu et al. fabricated an antibacterial contact lens composed of PHEMA hydrogel loaded with boric acid, an antibacterial agent, for the treatment of eye infections.[17] Ashtiani et al. made a PHEMA-based hydrogel as a



Scheme 1. An illustration showing a summary of materials, electrical components, and technologies for fabrication of smart contact lenses in different applications. Digital image of a contact lens sensor prototype. Reproduced with permission.[83] Copyright 2014, Google X.

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therapeutic contact lens for the delivery of small-molecule drugs.[18] In their study, chitosan was used to modify the hydrogel. Their therapeutic contact lens also showed antibacterial activity and sustained release of ascorbic acid. Contact lenses made of these mentioned materials have distinct characteristics and functions that are described later.

2.1. Polymethyl Methacrylate

Contact lenses were originally made of glass, which had significant disadvantages in terms of nonpermeability and processing. The emergence of PMMA in contact lens fabrication resolved processing problems; however, it did not offer an ideal solution.[19] PMMA is a polymer synthesized from methyl methacrylate monomers. PMMA is an ideal material for hard contact lenses due to several advantages, including excellent optical clarity, ease of fabrication, light weight, and low cost. In addition, PMMA is a glassy thermoplastic material with outstanding durability and facility of sterilization. However, PMMA lenses created a barrier to oxygen transport. Therefore, the development of contact lens materials with higher oxygen permeability compared with rigid gas permeable (RGP) materials was needed.[20] Currently, smart contact lenses use PMMA as substrates and covers, due to its durability and ease of manufacturing.[19,21,22]

2.2. Polyethylene Terephthalate

PET is a homopolymer, which is a type of plastic commonly used for plastic bottles. As PET has good chemical and heat resistance, and a low glass transition temperature (85 °C), it is easy to thermoform into various films with complex structures.[12,23] Due to their transparency, PET films are used as substrates or covers in smart contact lenses.[24] However, PET films lack gas permeability and are much stiffer than typical hydrogel materials. As a result, discomfort from long-term wear and corneal swelling can occur.[25] To improve the biocompatibility, gas permeability, and hydrophilicity of PET, PET-PDMS can be used to fabricate smart contact lenses.[21,26]

2.3. Poly (2-hydroxyethyl methacrylate)

PHEMA is synthesized by solution polymerization of 2-hydroxyethyl methacrylate with sodium pyrosulfite, which is an ammonium persulfate catalyst. PHEMA was introduced as a synthetic and biocompatible hydrogel for contact lens applications.[27] PHEMA is a high-performance material in biomedical applications, such as soft contact lenses and artificial corneas, because of its excellent biocompatibility, transparency, oxygen permeability, and sufficient mechanical strength.[17] PHEMA can swell in aqueous solutions to form a hydrogel, which was utilized in the first generation of soft contact lenses.[28] PHEMA contact lens material contains 38% water, and they maintain good wettability and comfortability. Many types of PHEMA-based hydrogels can be copolymerized with other monomers to form different contact lens materials with unique characteristics. For instance, PHEMA can be copolymerized with methacrylate and glyceryl methacrylate to obtain hydrophilic hydrogels with high oxygen permeability.

2.4. Polydimethylsiloxane

PDMS is a type of polymer organosilicon compound, which is elastic, transparent, biocompatible, and air permeable.[29] Biocompatibility is an important feature of PDMS, which has enabled its use in scenarios that require intimate contact with biological tissues.[30] PDMS is the most widely used silicon-based polymer.[31] Current smart contact lenses are commonly produced using PDMS as the substrate or the cover material.[26,32] For example, Hossein et al. designed a smart contact lens using PDMS for continuous monitoring of IOP. PDMS as contact lens material not only conformally puts the sensor over the curved cornea, but also maintains the user's normal vision.[33]

2.5. Silicone

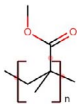
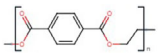
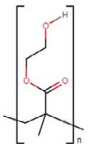
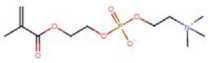
Silicone hydrogels are organic macromolecules that contain structural elements of silicone rubber. In 1999, silicone hydrogel soft lenses were developed, and a lot of work was then done on their surface hydrophilization.[34] As oxygen transport in conventional hydrogels is limited to water channels, oxygen permeability can only be improved by increasing the water content.[35] However, silicone hydrogels have both water and siloxane channels, which greatly enhance the oxygen permeability of contact lenses.[32] Based on the important characteristics of oxygen permeability, transparency, biocompatibility, and oxidative and thermal stability, silicone hydrogels have been widely used in ophthalmic and other biomedical applications.[36]

2.6. 2-Methacryloyloxyethyl Phosphorylcholine

MPC is an organic substance with a phosphorylcholine group that is biologically inert. As a result, MPC is resistant to protein adsorption, cell adhesion, and blood coagulation, making MPC highly popular in a variety of biomedical applications.[37] MPC polymer has been used in many biomedical devices as well as in clinical treatments, such as soft contact lenses,[28,38] implantable blood pumps,[39] artificial hip joints,[40] and diagnostic systems.[41] Shimizu et al. synthesized a silicone hydrogel using MPC and bis(trimethylsilyloxy)methylsilylpropyl glycerol methacrylate. The silicone hydrogel demonstrated good elasticity, high optical transparency, high oxygen permeability, and low protein adsorption capacity compared with traditional soft contact lens materials.[42] Mitsubayashi et al. fabricated a contact lens biosensor for monitoring eye fluid glucose in which biocompatible MPC polymer and PDMS were used as the contact lens material.[43]

Table 1 shows the common contact lens materials together with their molecular formulae and chemical structures. In addition to the materials mentioned earlier, there are also silicone rubber contact lenses and RGP contact lenses, which are rarely used. Most of the contact lens materials in the market today are hydrogels.[32] With an increase in the number of global contact lens users, research on contact lens materials is being developed rapidly, particularly toward improving their comfort, breathability, biocompatibility, and processability. In general, contact lens materials should be transparent, mechanically soft for wearing

Table 1. Molecular formula, chemical structures, and properties of commonly used contact lens materials.

Material	Molecular formula	Chemical structure	Advantages/Disadvantages	Reference(s)
PMMA	$(C_5H_8O_2)_n$		Outstanding optical properties, low oxygen permeability, high rigidity and toughness	[104]
PET	$(C_{10}H_8O_4)_n$		Low glass transition temperature, low rigidity, low surface energy, hydrophobic, excellent chemical resistance, and thermal resistance	[105]
PHEMA	$(C_6H_{10}O_3)_n$		Tunable mechanical properties, relatively high water content, and good chemical and thermal stability	[106]
PDMS	$(C_2H_6OSi)_n$		Flexibility and high oxygen permeability	[107]
MPC	$C_{11}H_{22}NO_6P$		Low protein adsorption, good surface wettability, high oxygen permeability, and mechanical weakness	[42,108]

comfort, hydrophilic for processability, and be permeable to oxygen and some metabolites for ocular biocompatibility.[19]

3. Electrical Components

Optimal design criteria for smart contact lenses should enable facile measurement and display of eye characteristics in real time without disturbing the patient's daily activity. Therefore, this type of device should be flexible, miniature, and able to integrate with many functional modules, including wireless communicators, sensors, powers, displays, and other microcomponents. These electrical components are described below.

3.1. Wireless Communicator

A wireless system in wearable electronics is the best way for transmitting signals instead of traditional wired data transmission approaches. Chiou et al. developed a wireless smart contact lens system composed of a wireless communicator to overcome the inconvenience of cable transmission (**Figure 1**a).[44] A wireless communicator uses radiofrequency identification (RFID) technology to transmit the information collected from contact lenses to a receiver, which is responsible for converting the data format and uploading the data to a medical instrument for calculation and analysis. RFID is an automatic identification technology that uses radiofrequency to identify any specific target and reads important information from the chip without touching the receiver.[45] RFID consists of two parts: RFID reader and RFID tag. When the tag enters an effective area of the reader, the reader transmits radio waves of a specific frequency. Then, if the tag is within the range of the waves, it sends data back to the reader. After receiving and interpreting the data, the reader sends it to a computer program for data processing and display. Hsu et al. proposed an RFID-based on-lens sensor system for long-term IOP monitoring. As shown in Figure 1b, the RFID reader and the Tx antenna details were embedded in the glass for data collection from smart contact lenses. Also, the Rx antenna was responsible for receiving the instruction signals from the Tx antenna, whereas the sensor chip was responsible for corresponding with the RFID reader.[44] In other studies, the antenna, embedded between two layers, generated electromagnetic waves through which the RFID reader could identify the specific target. As shown in Figure 1c,d,[11,46] the most smart contact lenses use a built-in antenna for data transmission, which does not affect the user's field of view. A microloop antenna is the most ideal choice for smart contact lenses. It enables wireless communication in specific electromagnetic waves and has the capability to convert power signals into electrical energy, which allows charging smart contact lenses while working as a communicator.[2,13]

3.2. Power Supply

Smart contact lenses for monitoring biomarkers in real time need a long-term and stable power supply. However, the energy-storage capacity of contact lenses is limited by their small size. Therefore, it is required to power biosensors wirelessly through external sources (e.g., inductive power, radio frequency [RF] power, or optical power). RFID is an identification technology that uses radio waves for identifying people or objects.[47] The introduction of passive RFIDs made power harvesting from radio waves. Power harvesting is a technique for repairing energy from external environment. This technique allows replacing small batteries in low-power electrical devices. The key parts of an RF power-harvesting system are antenna and rectifier circuit.[48] As shown in Figure 1e,f,[4,12] RF power was utilized in both examples to provide energy for biosensors and displays. ICs were slightly different for each case, but both included three key parts: RF power harvesting, a power management circuit, and a storage capacitor. The role of a rectifier in RF power harvesting is to convert RF power to direct current (DC), which in turn

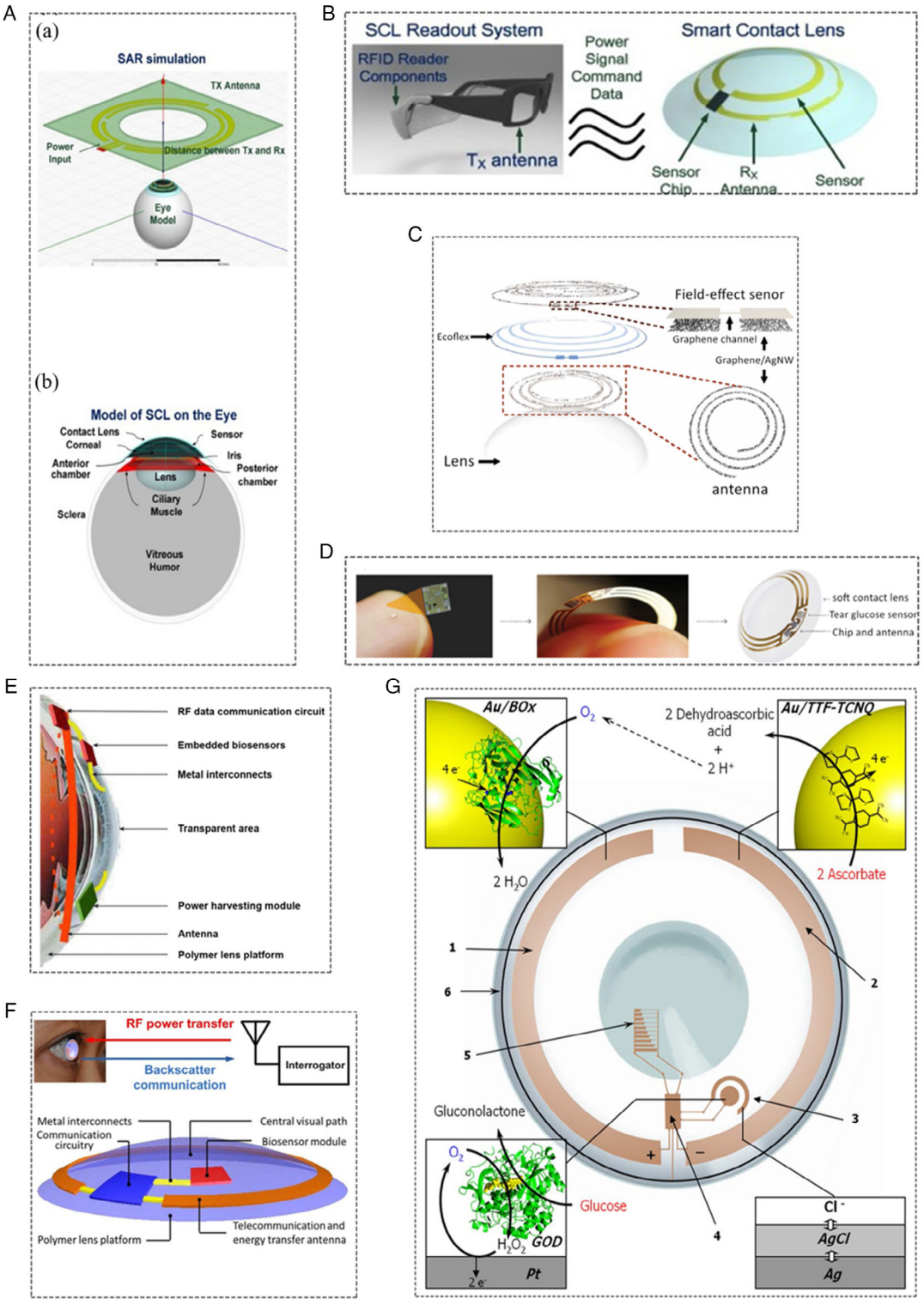


Figure 1. Various electrical components of contact lenses for different applications. A) A contact lens sensor with a wireless powered circuit.[44] B) Proposed smart contact lens system architecture. Reproduced with permission.[44] Copyright 2017, MDPI. C) Contact lens sensor composed of a field-effect sensor and antenna for wireless detection of glucose. Reproduced with permission.[19] Copyright 2017, Springer. D) The wireless chip and the sensor, which are mounted onto an electronic ring and then embedded into the contact lens. Reproduced with permission.[83] Copyright 2014, Google X. E) Integrated RF-powered contact lens. Reproduced with permission.[12] Copyright 2010, IEEE. F) Conceptual diagram of an active contact lens system with RF power transfer. Reproduced with permission.[4] Copyright 2012, IEEE. Solid-State Circuits. G) Self-powered contact lens, composed of (a) a biocathode, (b) an anode, (c) a glucose biosensor, (d) an interface chip, (e) a simple display, and (f) an antenna (as a communicator for data transmission), based on chemical reactions with ascorbic acid in human lacrimal fluids. Reproduced with permission.[3] Copyright 2013, ACS.

charges the storage capacitor. The goal of the power management circuit is to maximize the efficiency and performance of the equipment that requires power through the optimization of input and output signals. Through the cooperation of these three parts, the IC module can effectively provide a stable power supply for other electronic components. Chemical substances generated by the body itself, such as glucose and ascorbic acid, can react with a conductive anode or cathode in contact lenses to produce an electric current. Using this method, scientists successfully developed a biochemical battery that can power smart contact lenses.[3] Furthermore, the chemical energy of ascorbic acid in the human lacrimal fluid can be converted into electrical energy. This system can continuously power smart contact lenses and does not affect the concentration of tear glucose. Figure 1g shows the chemical reaction and the components of such contact lenses.[3]

3.3. Display

To display relevant information on smart lenses, it is necessary to use flexible and biologically stable electrode materials. In this regard, Lee et al. showed a simple microscale light-emitting diode (LED) device (**Figure 2**A) fabricated on a contact lens with graphene, which is a type of 2D carbon nanomaterial with excellent optical, electrical, and mechanical properties. Moreover, graphene has excellent electromagnetic wave absorption and air permeability, which is promising as electromagnetic interference shielding. The micro-LED device made of graphene was successfully tested at ≈9 V, yielding good electrical continuity and robustness.[49] In their design, graphene was used to create a highly conductive contact lens to avoid electromagnetic wave damage to the human eye. To confirm the electromagnetic wave shielding effects, they tested their lens in an egg model to demonstrate wave absorbance and reduced thermal radiation.[50]

Park et al. designed another type of wireless display, which consisted of three electronic components (rectifier, antenna, and LED pixel), as shown in Figure 2B.[13] These parts were fabricated on an 800 nm-thick Cu sacrificial layer deposited on a Si wafer. As a result, the contact lens wirelessly received inductively coupled alternating current (AC) from a transmission coil (50 MHz) within a 5 mm distance. To turn on the LED pixel, the transmitted AC signal was rectified to DC by a half-wave rectification circuit. Using a host–guest liquid crystal configuration, a spherically curved liquid crystal display was fabricated. In the latter approach, two substrates (top and bottom) encapsulated a liquid crystal layer with integrated powering and driving components. These substrates were made of PET with chosen thicknesses of 50 μm and 75 μm to avoid spherical deformation for convex and concave layers (Figure 2C(a)). Also, the researchers made another design to realize the integration of display components in the contact lens, which required the substrate to have more available space to mount electronics for power supply. The asymmetric display design was therefore introduced, as shown in Figure 2C(b). Using this device, more space near the eye was created from device miniaturization[14] The experimental results of the liquid crystal display layer are shown in Figure 2C(c).

3.4. Connector and Rectifier

Microwires are required to connect electrical elements within smart contact lenses. These wires are typically made of conductive silver or carbon nanotube inks, which are suitable for printing 2D or 3D flexible electronics.[51] They are frequently used due to their low cost compared with gold and platinum. In particular, silver ink has excellent electrical and thermal properties that make it extremely versatile for a broad range of applications.[52] During the past few years, many conductive silver inks have been developed to be used as silver art inks with glowing LEDs, 3D-printed and small antennas, and conductors for flexible paper display (Figure 2D).[52] Similarly, carbon nanotubes with great mechanical and electrical properties have widely been used in printing techniques for many electronic components, including emitters, radiofrequency inductors, and transducers.[53]

A wireless display circuit in smart contact lenses typically consists of an antenna, a rectifier, and LED pixels. The rectifier converts AC signals from the antenna into DC to power the LED pixels connected in parallel to the rectifier. Figure 2E(a) shows a rectifier consisting of Si nanomembrane diodes connected in series with capacitors, which is embedded in the strengthened area of the contact lens and is located outside the pupil to avoid disturbing the wearer's vision. Figure 2E(b),(c) shows the characteristics of the Si diode and the SiO_2 capacitor, respectively.[13] Smart contact lenses exploiting wireless communicators, powers, displays, and other components enable comfortable and noninvasive physiological detections, which are superior to conventional approaches that rely on rigid circuit boards, cables, needle electrodes, and terminal connections.

4. Technologies for Fabrication and Analyzing Smart Contact Lenses

4.1. Microfluidics

Microfluidics technology is the science and technology of systems with integrated channels on the microscale (from tens to hundreds of micrometers), through which small quantities of fluids (usually from 10^{-9} to 10^{-18} L) can flow in designed configurations that are controlled and manipulated systematically.[54] At present, microfluidics has been widely applied in organ-on-a-chip systems, manipulation of multiphase flows, chemical synthesis, and bioanalysis,[55] which render microfluidics particularly desirable for contact lens applications.

The principles governing microfluidics in contact lenses rely on microscopic forces, such as fluid surface tension, capillary forces, energy dissipation, and fluid resistance.[56] During ocular fluid collection, when the eyelids blink, the person's tears will cover the surface of the contact lens, which then go into microchannels due to the capillary force. Capillary phenomena occur when liquid flows through a narrow passage. [56] Also, Reynolds number (*Re*) is an important parameter in microchannels that measures the amount of resistance to the fluid flow. $Re = \rho v d/\mu$ is proportional to the flow velocity (v) of the fluid, the density (ρ) of the fluid, and the characteristic length (d) and inversely proportional to the viscosity coefficient of the fluid (μ). Generally, the *Re* of microfluidic channels in smart contact lenses is very

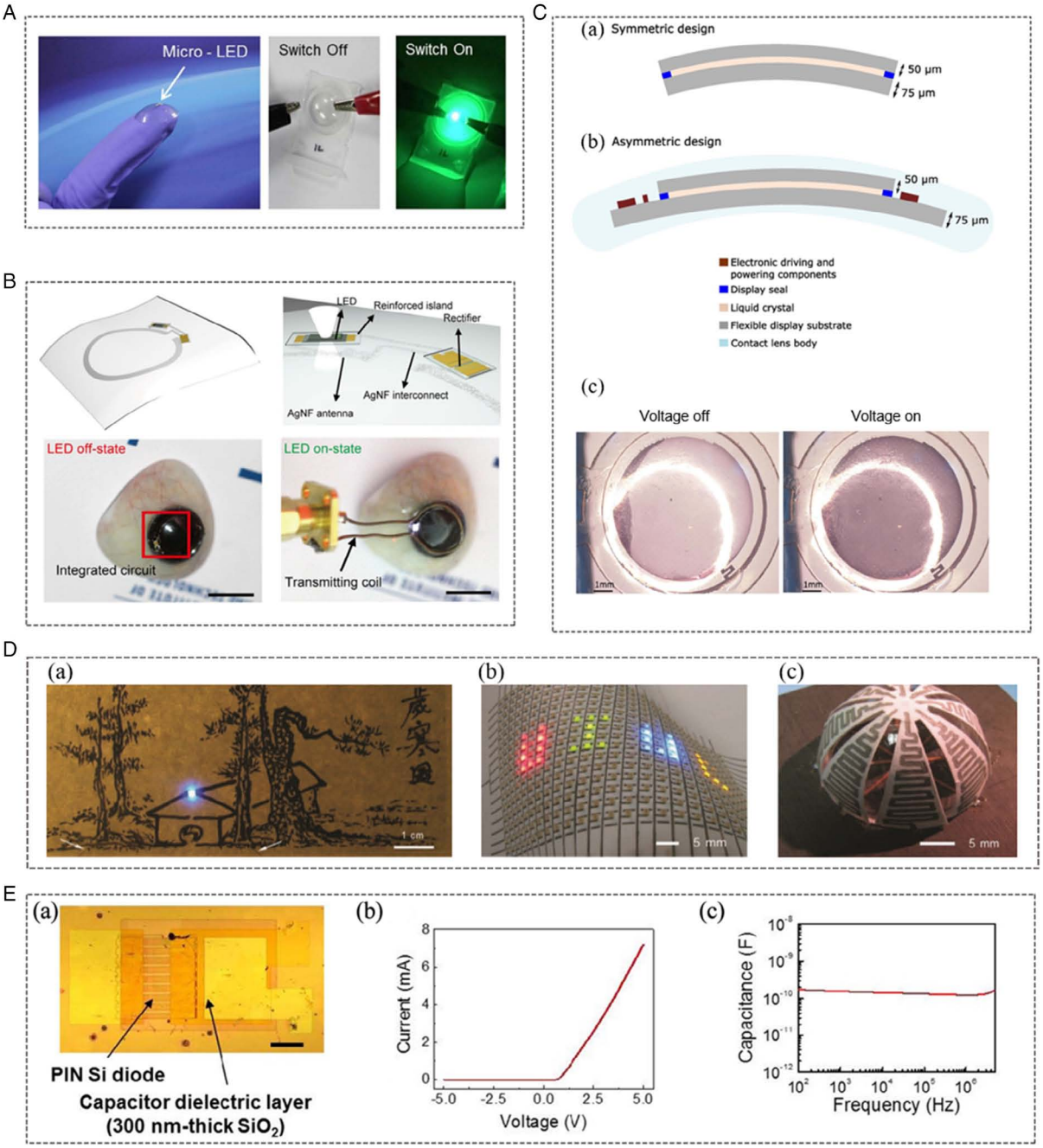


Figure 2. Smart contact lenses with different display designs, connectors, and rectifiers. A) On/off images of LED graphene contact lens operating at 9 V. Reproduced with permission.[49] Copyright 2017, ACS. B) Schematic of the wireless display circuit and photos (right, on-state; left, off-state) of operating wireless display with contact lens shape on the artificial eye. Reproduced with permission.[13] Copyright 2018, AAAS. C) (a) Symmetric display design, (b) a contact lens with an asymmetric design, and (c) the asymmetric display at the voltages off and on (left and right, respectively); Reproduced with permission.[14] Copyright 2017, Elsevier. D) Images of silver ink applications: (a) a conductive electronic art drawn by silver ink, (b) a flexible paper display with LED, and (c) a 3D antenna with electronic silver ink. Reproduced with permission.[52] Copyright 2015, Royal Society of Chemistry. E) (a) Microscopic image of a rectifier that consists of Si nanomembrane diodes connected in series with capacitors and characteristic of (b) the Si diode and (c) the SiO_2 capacitor. Reproduced with permission.[13] Copyright 2018, AAAS.

small between dozens and hundreds of micrometers, resulting in laminar flow in smart contact lenses.[57] The laminar flow of the ocular fluid in microchannels through microsensors allows specification of pH, concentration of various ions, and other biomarkers.[56]

Based on the mentioned principles, the characteristics of microfluidic systems should be modified in the design of smart contact lenses. For example, the size/shape and flow velocity in microchannels can affect the ocular fluid collection. The flow velocity of the ocular fluid plays a significant role in optimizing

smart contact lens characteristics as it affects the fluid absorption efficiency on microsensors and may change the detection accuracy of microsensors. To analyze the microfluidic flow velocity in smart contact lenses, Wu et al. measured the flow velocity through the direct integration of a flow velocity sensor into microchannels using the MEMS technology. They deposited a boron-doped polysilicon film on a microchannel wall, which was used as a heating element and a velocity sensor.[58] This approach can be used for smart contact lenses to manipulate the fluid in the microchannels in a precise manner.

Swelling is another consideration in designing smart contact lenses. The deviation of droplet trajectories to flow in contact lens microchannels largely depends on the degree of microchannel swelling.[59] The swelling capacity of microchannels changes with factors, such as temperature, pH, ionic strength, and surface property of the lens material.[60] As the weight variation in microchannels is too small to be measured by the gravimetric method, traditional methods may not be accurate to obtain the swelling capacity of microchannels in smart contact lenses. To overcome this problem, Dangla et al. used a charge coupled device (CCD) camera mounted on a microscope to record microfluidic images.[59] They determined the apparent displacement of microchannels by comparing the images before and after with a digital image correlation (DIC) algorithm and then, measured the microchannels' swelling capacity. This method can be suitable to measure the swelling of smart contact lenses.

4.2. Photolithography

In smart contact lenses, many microelectronic components and microchannels are fabricated indirectly or directly with photolithography technology. Photolithography is a process that uses light to transfer shapes from a photomask to the surface of a silicon wafer. As shown in **Figure 3**a,[61] the operation flow is described as follows: a silicon wafer is coated with a uniform thin film of photoresists by spin coating. To increase the adhesion of the photoresists, hexamethyldisilane is often placed on the wafer. After prebaking the coated wafer, to drive off the excess solvent in the photoresists, it is placed underneath a photomask that resembles the microchannel geometry in an optical projection system. The coated wafer, by illuminating ultraviolet (UV) light, leads to a chemical change in the exposed portion of photoresists. Then, a developer is used to etch away exposed or unexposed portions of the photoresists depending on their chemical compositions.[61,62] To seal microchannels, photolithography is first used to pattern a microstructure on a silicon wafer as the master mold. PDMS is then poured into the master mold and cured by heating to produce PDMS microchannels. Finally, a flat slab of PDMS is used to bind the PDMS mold surface after oxidizing it in a plasma discharge, leading to a spontaneous and irreversible seal. Figure 3b shows a method called "oxidized PDMS surface contact seal" to seal microchannels.[63] There are two main aspects of using photolithography for smart contact lenses. One aspect is to replicate any desired microstructure inside contact lens material and the other aspect is to fabricate microelectronics, such as flexible wires, microelectrodes, and other microsensor parts in contact lenses.

4.3. Injection Molding

Injection molding is a manufacturing process for making components by injecting molten materials into a mold. Figure 3c shows the parts of the injection molding process.[64] Smart contact lenses can be massively produced by an injection molding process, which results in cost reduction. Siegel et al. proposed an injection molding approach for microdevice production.[65,66] To fabricate contact lenses using injection molding, a mold should be designed for injection of contact lens material. After injecting, the contact lens material is crosslinked and fixed by changing the external conditions, such as temperature and UV light. Due to the throughput and reproducibility of this approach, it can greatly reduce the production cost.

4.4. Soft Lithography

Soft lithography can generate microstructures on nonplanar surfaces, which enables the fabrication of 3D microstructures in a layer-by-layer way. In addition, a wide range of materials can be used to make microstructures in soft lithography. In this regard, Agaoglu et al. reported the fabrication of sensors as thin as 150 μm for IOP monitoring in a wearable contact lens sensor using soft lithography.[67] Soft lithography has been used for microcontact printing (μCP), replica molding (REM), and microtransfer molding (μTM) methods to make master molds in contact lens fabrication.[68]

μCP is a method to make a pattern using self-assembled monolayers (SAMs) on a PDMS surface. Figure 3d shows three different methods for conducting μCP and their principles to make patterns.[68] In the μCP process, the PDMS stamp is wet with ink and placed in contact with a gold surface on the silicon substrate such that the ink is transferred from the stamp to the gold surface to form a SAM pattern. Microwires in smart contact lenses have to be firmly attached to the material surface to mitigate large mechanical deformation of the lens. μCP is highly suitable for this task. For example, Garcia-Cruz et al. used a silicon mold to produce micropatterned PDMS stamps to print microwires on polyimide and other material surfaces.[69] Wolfe et al. also used μCP to fabricate copper microwires for the electroless deposition.[51]

Another method is REM that can be used to make compact disks,[70] diffraction gratings,[71] holograms,[72] and microtools[73] in large quantities. Figure 3e shows a brief overview of the process based on the PDMS mold, which is prepared by casting against a rigid master. The fabrication procedure is affected by wetting, kinetic factors, and van der Waals interaction.[68] REM is often used to fabricate microchannels in smart contact lenses.[26,74] For example, Yan et al. fabricated a replica mold with microchannels using silicon as the substrate.[74] In another study, Surdo et al. fabricated microlenses with control of their geometry and size, independent of their material or substrate, by a combination of REM and laser-induced transfer methods.[75]

The μTM is a method that can produce microstructures. Figure 3f shows the schematic of the μTM process. Briefly, a liquid prepolymer is first placed into a PDMS mold. The mold is then placed on a substrate to let the prepolymer contact the substrate surface, followed by curing the prepolymer by heating or

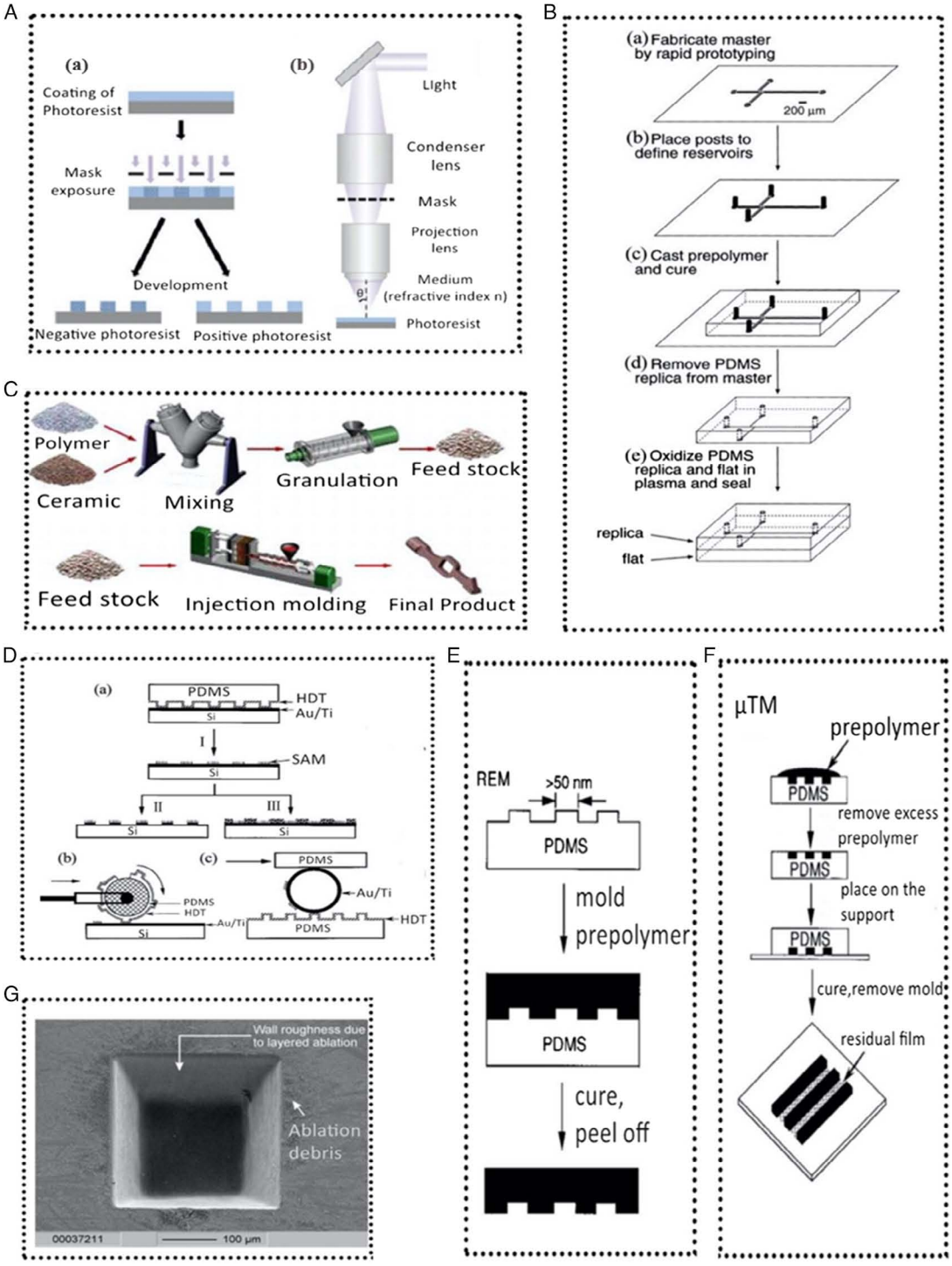


Figure 3. Various microtechnologies to fabricate contact lenses. A) Photolithography technology: (a) a mask photolithographic process and (b) a projection system. Reproduced with permission.[61] Copyright 2019, Wiley-VCH. B) A scheme for manufacturing closed microchannels in oxidized PDMS. Reproduced with permission.[63] Copyright 1998, ACS. C) Schematic diagram of injection molding. Reproduced with permission.[64] Copyright 2017, Taylor & Francis Group. D) Schematic diagram of μCP: (a) printing patterns on the plane, (b) printing a rolling stamp on a large area plane, (c) printing on a nonplanar surface with a planar impression. Reproduced with permission.[68] Copyright 1998, AIP Publishing. E) Schematic diagram of the procedures for REM. Reproduced with permission.[68] Copyright 1998, AIP Publishing. F) Schematic diagram of the μTM. Reproduced with permission.[68] Copyright 1998, AIP Publishing. G) Laser-ablated microwell structure. Reproduced with permission.[77] Copyright 2007, Springer.

with UV light. The mold is then peeled off carefully to leave the patterned microstructure on the substrate surface.[68] This method is widely applied to make flexible substrates in microfluidics and MEMS systems.[76]

4.5. Laser Ablation

Laser ablation is a technique commonly used in making microfluidic devices. This method applies a high-intensity laser beam to certain positions on materials such that the beam energy can eliminate the material at the contact point. A microstructure can be obtained by moving the laser source or shinning the laser projection on the substrate through a mask according to the substrate material type, laser intensity, and wavelength. Figure 3g shows the fabrication of a microwell structure using laser ablation.[77] The heat energy generated by the laser sometimes changes the chemical properties of the material surface, which is difficult to control and affects the performance of the devices. One way to overcome this problem is to use femtoseconds[78] or CO_2 laser.[79]

5. Smart Contact Lens Sensors and Their Applications

Human tears contain many chemicals including proteins, lipids, electrolytes, urea, ascorbic acid, L-lactic acid, cholesterol, and other key metabolites.[80] Also, the chemical composition of tears is very similar to blood. Measuring concentrations of these substances in real-time provides valuable physiological information on improving the treatment and prevention of some diseases.

5.1. Measurement of Glucose Concentration

Glucose concentration is an important parameter in the diagnosis of diabetes mellitus. However, a common way for a single-time-point blood glucose measurement is through the use of a painful finger puncturing to sample the blood.[81] Numerous studies and data have shown that the concentration of glucose in tears is positively correlated with blood glucose concentration.[81] Smart contact lenses with an embedded glucose sensor can monitor the concentration of glucose in tears.[13] One principle of biosensing tear glucose concentration is based on the combination of glucose oxidase (GOD) and catalase (CAT) by immobilizing GOD in graphene channels using pyrene joints via $\pi-\pi$ stacking. When glucose passes through the graphene channel of the sensor, it detects the concentration of glucose in tears. Then, it outputs the detected information to the display device (such as an LED display) through rectification and amplification. After detecting glucose concentration in tears and when it was above the threshold, the pixel is turned off. **Figure 4**a shows the operating mechanism of the sensor to detect glucose concentration in tears. [13] It is also important for clinicians to achieve continuous measurements in tear glucose monitoring.[82] Researchers used white rabbits as test subjects to study the effects of glucose consumption on dynamic changes in glucose levels, and they measured both blood and tear glucose concentrations. The experimental results showed that the glucose level in tears begins to increase 10 min after the glucose level increases in the blood, and the biosensor had a rapid response to tear glucose and appropriate calibration range (0.03–5.0 mM).[43] To monitor glucose concentration in eye fluid, Google designed a smart contact lens (Figure 4b),[83] which was then correlated with blood glucose concentration in diabetic patients. In addition, Google has heavily invested in the research and development of smart contact lenses for the detection and treatment of other eye diseases.[46] In another work, Yao et al. fabricated contact lenses with glucose sensors to detect glucose concentration (Figure 4c).[82] Advantages of this device include periodic monitoring, high accuracy, and comfort during long-term wear. A different type of glucose-sensing contact lens with electrical elements was designed by Park et al. for health monitoring of diabetic patients. Figure 4d (a) and (b) shows the image of the contact lens embedded with LED pixels and a schematic of the contact lens's sections, respectively.[13]

5.2. Measurement of IOP

Studies have shown that large IOP fluctuations are one of the causes of glaucoma.[84] However, frequent IOP measurement by Goldmann applanation tonometer, a conventional clinical measurement tool, is complicated.[85] Therefore, contact lens sensors have been represented as a promising method to monitor IOP by measuring corneal curvature. Leonardi et al. designed a wireless smart contact lens to sense IOP, which consisted of an antenna, passive gages, a microprocessor, and other electrical elements (**Figure 5**a).[9] This device enabled long-term minimally invasive IOP monitoring with diagnostic and therapeutic relevance for glaucoma treatment.[9] There are four basic types of contact lens sensors for IOP monitoring: capacitance sensor, piezoresistive sensor, strain gauge sensor, and microinductor sensor.[46] Figure 5b shows the conceptual deformations of capacitance-based IOP sensors on the contact lens under different IOP conditions.[86] In the initial state, the corneal curvature and the IOP are r and p, respectively. The corneal curvature (r) changes together with the IOP (p). As a result, the capacitance of the IOP sensor on the contact lens also changes, which is measured as the change in the gap between the top and bottom plates of the sensors. Another study reported continuous sensing of IOP with a resonance circuit lens comprising a thin-film capacitor with a sensing coil to monitor corneal curvature deformation (Figure 5c).[2] As another example, Greene et al. equipped strain sensors in a hydrogel contact lens, which allowed continuous measurement of IOP.[87] This sensor can measure changes in IOP by sensing the deformation of the meridional angle of juncture between the cornea and sclera.[87] Figure 5d shows another IOP contact lens sensor.[11] In this sensor, the corneal radius of curvature and the corneal capacitance increase when high IOP occurs. As a result, the readout equipment for wireless IOP sensing can detect the change in resonance frequency.[11]

5.3. Measurement of Lactic Acid Concentration

Lactate is an important biomarker for clinical diagnosis and health monitoring. It can be used to identify hypoxia or elevated salt concentrations due to physiological or pathological

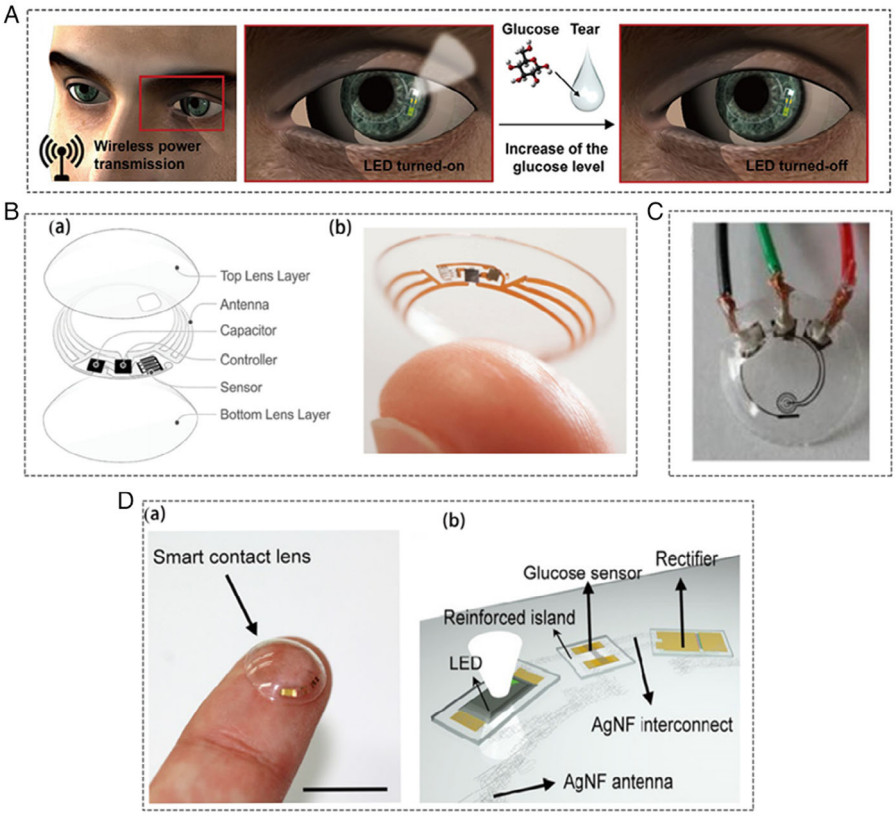


Figure 4. Operation and different designs of contact lenses to monitor glucose concentration. A) Operation process of the contact lens sensor for detecting glucose level in tear. Reproduced with permission.[13] Copyright 2018, AAAS. B) (a) Google's three-layer contact lens with an integrated sensor and (b) view of the contact lens sensor. Reproduced with permission.[83] Copyright 2014, Google X. C) A glucose contact lens sensor with a wired power supply. Reproduced with permission.[82] Copyright 2011, Elsevier. D) (a) Image of a smart contact lens with an LED pixel displaying the glucose level and (b) schematic of all integrated sections in the contact lens. Reproduced with permission.[13] Copyright 2018, AAAS.

conditions. In general, human blood lactic acid level > 2 mmol/L can be classified as lactic acidosis, and there are clinical manifestations that it may lead to lactic acid poisoning, such as toxins, shock, anemia, sepsis, and organ failure.[66] At present, tears have been used as a potential sampling medium with the ease of extraction to replace the pain and inconvenience of blood sampling. Real-time monitoring of lactate concentration in vivo using contact lens sensors has become a promising field.[66]

Thomas et al. designed and proposed an amperometric L-lactic acid sensor embedded in a contact lens. This sensor converted the electrochemistry into analytic current signals through redox reactions on the surface of electrodes. They used glutaraldehyde (GTA) to crosslink lactate oxidase (Lox) to the surface of the electrode and selectively recognize L-lactate while coating the substrate with medical-grade and biocompatible PU.[80] As shown in **Figure 6**a, an amperometric sensor with a reference electrode (RE), platinum working electrode (WE), and an auxiliary platinum counter electrode (CE) was designed to allow for a stable reference voltage between RE and WE. The sensor showed sufficient resolution in the physiological range of lactic acid concentration, a fast response time of 35 s, and an average sensitivity of $\approx 53\ \mu A\ mM^{-1}\ cm^{-2}$ in the linear range for L-lactate concentration measurement in tear fluid. Lin et al. designed a reliable tear lactate (TL) test strip composed of a three-electrode structure, as shown in Figure 6b. Similar to the blood glucose test strip, the TL sensor can also be used for the detection of lactate using contact lenses. The tear sampling element made of the Schirmer test paper was integrated into a TL sensor with a protein-engineered LOX, which became a feasible scheme to detect lactate concentration in tears. It was found that the sensor is insensitive to other interfering substances, such as uric acid and ascorbic acid, and its accuracy and robustness were proved.[66]

6. Drug Delivery Using Contact Lenses

At present, most ophthalmic drugs are perfused locally through eye drops. However, the efficacy of eye drops is compromised by a lack of patient compliance. In addition, the effectiveness of such treatments for chronic diseases, such as glaucoma and dry eye, is limited. An ideal drug-delivery system would comfortably deliver the required drugs to eye tissues without interfering with the normal physiological activities of patients. By embedding a drug-delivery system in contact lenses and releasing the drug into the tear film, the drug bioavailability can be increased by 50%.[15] Therapeutic contact lenses can become an important method in ophthalmic treatment in the future. Overall, contact lens-based drug delivery has various advantages,

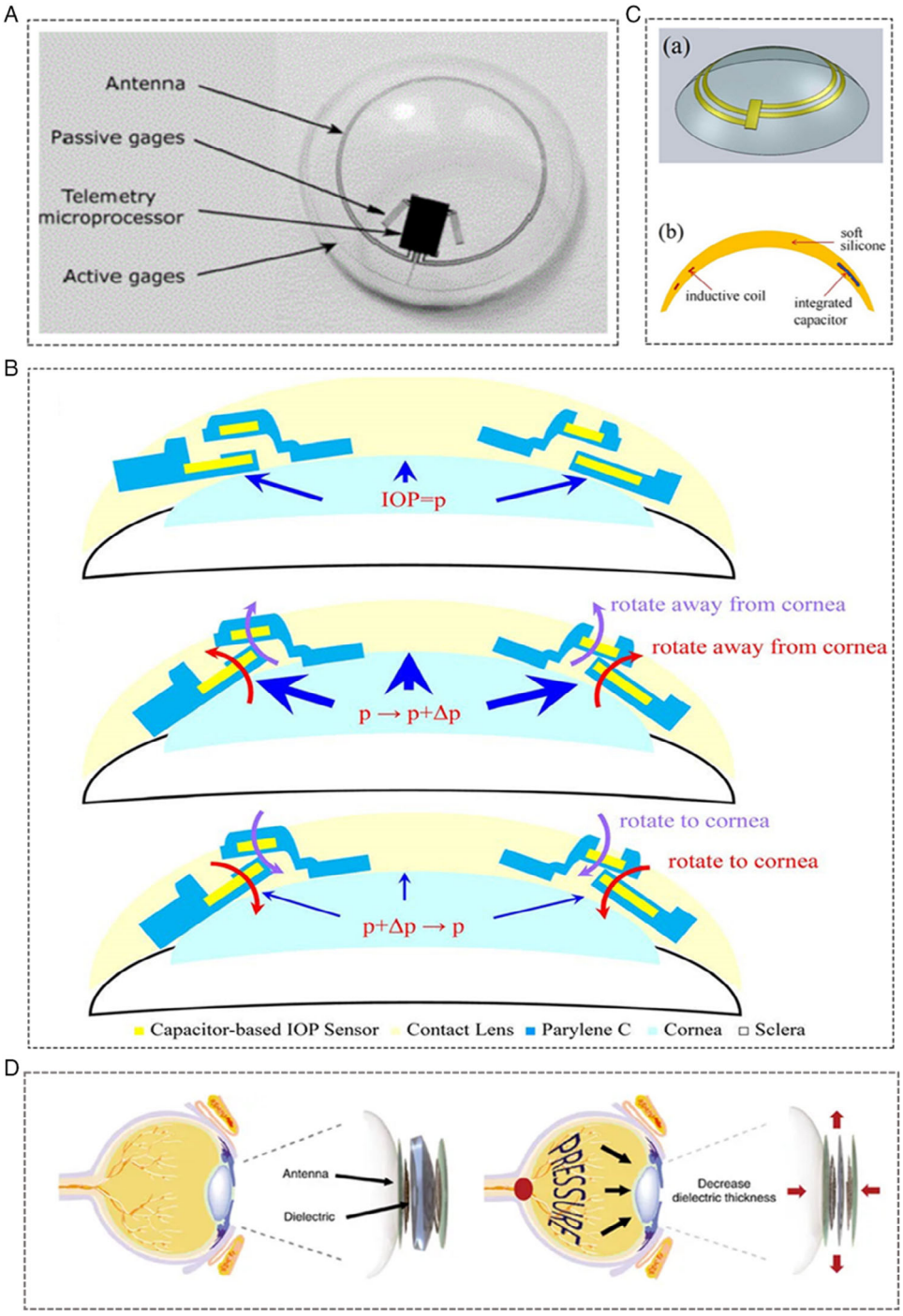


Figure 5. Different parts and mechanisms of IOP contact lens sensors. A) An IOP contact lens embedded with a sensor-passive gage (for thermal compensation), a sensor-active gage (to measure changes in the corneal curvature), telemetry microprocessor (for wireless power), and an antenna (for data transfer). Reproduced with permission.[9] Copyright 2009, John Wiley & Sons. B) Conceptual deformations of the capacitor-based IOP sensors on contact lens under various IOP conditions. Reproduced with permission.[96] Copyright 2017, IOP Publishing. C) An IOP contact lens sensor based on resonance circuit: (a) 3D and (b) cross-section views of the IOP contact lens sensor. Reproduced with permission.[2] Copyright 2014, Elsevier. D) Schematic illustration of the mechanism of IOP sensing in the contact lens sensor. Reproduced with permission.[11] Copyright 2017, Springer.

including higher efficacy, improved compliance, and fewer side effects from systemic absorption compared with eye drops. Also, contact lenses can provide high and sustained drug delivery on the ocular surface.[88] However, there are some challenges in

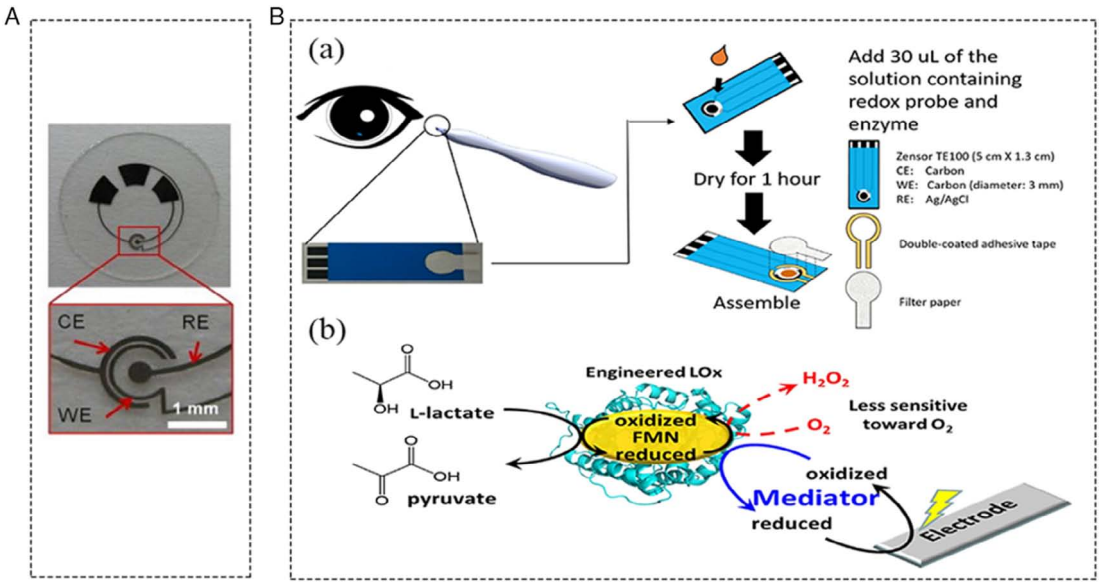


Figure 6. Contact lenses composed of different electrodes to measure L-lactate concentration in tear fluid. A) L-lactic acid sensor on contact lens. Reproduced with permission.[80] Copyright 2011, Elsevier. B) (a) Schematic diagram of lactic acid sensor fabrication and assembly and (b) enzymatic diagram of engineered lactate oxidase. Reproduced with permission.[66] Copyright 2018, Elsevier.

designing a practical and drug-eluting contact lens. Contact lenses should be able to load it with one or more drugs and release the drugs at therapeutic levels over the desired duration, in a way that unwanted systemic effects to the eye itself are not caused.

A variety of reasons, including recurrent erosions, corneal surgery, corneal dystrophies, and decreased corneal innervations, can cause corneal injuries along with delayed reepithelialization. Topical application of different biomolecules, such as the epidermal growth factor, has been introduced for promoting wound healing. In addition, contact lenses are often used as bandage lenses to shield the leading edge of the healing epithelium from damage because of blinking, allowing newly reproduced epithelial cells a greater opportunity to recover the corneal surface.[89] Therefore, contact lenses can play an important role as drug-delivery devices in accelerating wound healing in patients with corneal injuries. In this regard, Duru et al. compared two types of silicon hydrogel bandage contact lenses (a senofilcon A lens in one eye and a lotrafilcon B in another eye) for postoperative epithelial healing time and ocular discomfort score in patients. In this study, patients wear a senofilcon A lens in one eye and a lotrafilcon B in another eye. They showed that both contact lenses were not significantly different for duration of corneal reepithelialization.[90]

Therapeutic contact lenses are usually fabricated by immersion or molecular imprinting. Xie et al. reported a therapeutic contact lens with a molecular imprinted structure, which had significant effects on increasing drug loading, optimizing drug release behavior, and prolonging drug residence time.[16] The contact lens exploited a colorimetric mechanism to reflect the amount of drug release for the real-time monitoring of drug release. The method relied on the addition of customized functional groups in the hydrogel matrix, which produces specific interactions between functional groups and target drug molecules to increase drug loading in the contact lens. The functional groups were the molecularly imprinted site on the hydrogel matrix, which can effectively reflect the binding and dissociation behavior of target drug molecules. By combining the molecularly imprinted structure with contact lenses having inverse opal structures, the drug release profile can be assessed by the visible color change of lenses. This method is called a self-reported colorimetric assay for drug release.[16]

Fungal keratitis is a serious eye disease, which often leads to eye infections and blindness. Among treatments used for fungal keratitis, eye drops have demonstrated a limited efficacy due to their low bioavailability. Other methods include intraocular injections, but they may lead to serious side effects and safety concerns. The development of contact lenses with effective drug-delivery capabilities is expected to solve this dilemma. In this regard, Huang et al. designed a drug-delivery contact lens for the treatment of fungal keratitis based on hydrogels (**Figure 7**), which consisted of HTCC (*N*-(2-hydroxy) propyl-3-trimethylammonium chitosan chloride), graphene oxide (GO), silver nanoparticles, and Voriconazole (Vor). HTCC has good hydrophilicity and is an excellent hydrogel matrix. Silver nanoparticles and HTCC can enhance the antifungal and antimicrobial abilities of lenses. GO can be used as a drug carrier and provides anionic groups to form electrostatic crosslinks with cationic groups of HTCC, which can further interact with hydrogels to form strong bonding. Vor is a kind of synthetic antifungal drug that is superior to traditional antifungal drugs. Vor can effectively treat yeast and fungal infection, and it can be loaded onto the GO. GO enabled a sustained release of the drug in the contact lens. As another example, Ciolino et al. designed antifungal contact lenses with an embedded econazole-loaded PLGA film inside. This contact lens showed extended antifungal activity

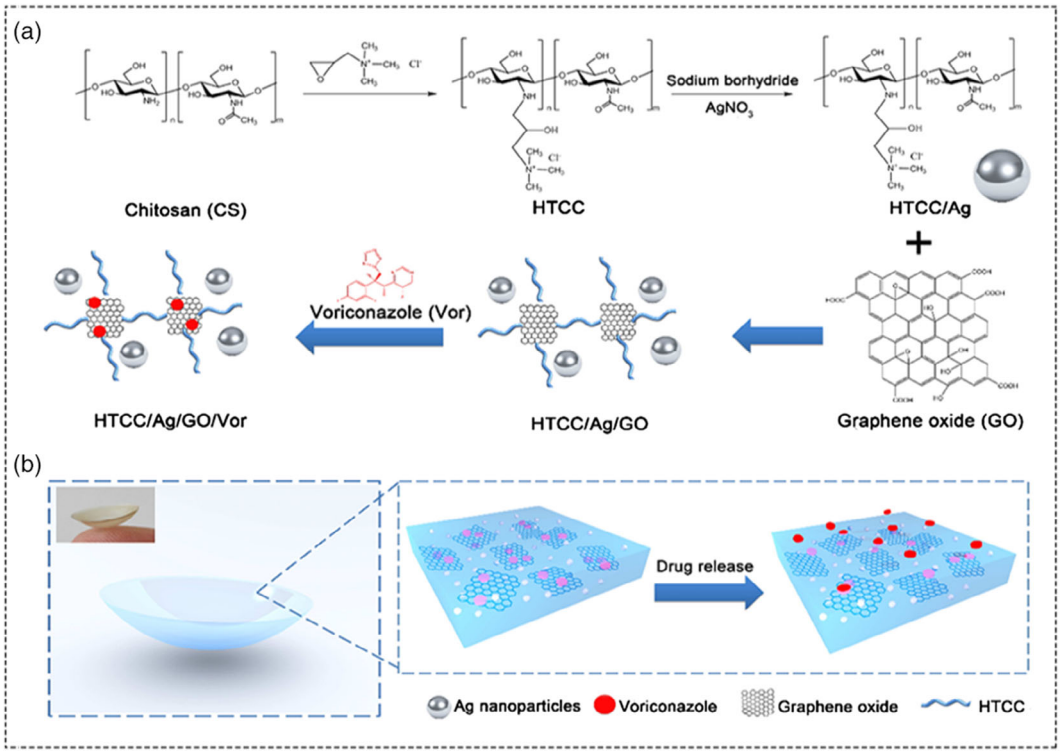


Figure 7. A drug-delivery contact lens for the treatment of fungal keratitis based on hydrogels. a) Synthesis of HTCC/Ag/GO/Vor and b) schematic diagram of a contact lens loaded with antifungal agent as a drug-delivery system. Reproduced with permission.[6] Copyright 2016, ACS.

against *Candida albicans* fungi.[91] The drug-delivering contact lens could easily adhere to the cornea, had excellent cell compatibility, and showed prominent antimicrobial activity.[6]

7. Market and Regulatory Process for Smart Contact Lenses

The growing demand for continuous monitoring of health conditions, implantable drug delivery systems, and in situ diagnosis of diseases has induced increasing commercial attention to smart contact lenses.[8] Although fierce competition in the development of smart contact lenses has challenged this field, several companies have achieved a position in the smart contact lens market. The key manufacturers and investors of these medical devices are mentioned in **Table 2**. In January 2020, MojoVision Inc. proposed the Mojo Lens with a built-in display that is able to provide useful and timely information to users. In addition, the Mojo Lens can provide real-time contrast, lighting enhancements, and zoom functionality. Therefore, it can be used for vision improvement.[92] However, Google and Alcon Vision LLC smart contact lens for monitoring diabetic symptoms failed

Table 2. Key producers of smart contact lenses with different biomedical applications.

Smart contact lens manufacturers	Function	Status (brand name)	Reference(s)
Sensimed AG	Ocular monitoring and glaucoma treatment	Developed (SENSIMED Triggerfish)	[109]
Google with Alcon Vision LLC	Glucose measuring	Discontinued	[110]
Mojo Vision Inc.	Data processing; Vision improvement	Developed (Mojo Lens)	[111]
Innovega Inc.	Virtual reality	Developed (eMacula)	[112]
Bausch & Lomb	Drug delivery	Developed (Soflens, Sauflon 55, Biotrue)	[113]
Johnson & Johnson	Delivery of ketotifen as antihistamine	Phase 3 clinical trials	[93]
Leo Lens	Drug delivery for treating glaucoma and allergies	Clinical studies	[114]
OcuMedic, Inc.	Drug delivery of the antiinflammatory bromfenac and antibiotic moxifloxacin	Preclinical phase	[115]
Cooper Vision	Drug delivery	Developed (Biomedics, Easy day, Proclear)	[46]
CIB Vision	Drug delivery	Developed (Focus Monthly, Precision UV)	[113]
Alden Optical	Drug delivery	Developed (Alden HP)	[113]

as there was weak correlation between glucose in the tear and blood. As another example, InWith Corporation and Bausch & Lomb have investigated to create an augmented reality contact lens. The lens is incorporated with a microchip, which is responsible for sending notifications and alerts to a smart phone. This lens can also analyze the chemistry of tears. A new therapeutic contact lens was developed by Queensland University as a bandage for ocular surface injuries. The bandage contains limbal mesenchymal stroma cells attached to the inner surface of the contact lens that can be useful in the treatment of chemical burns and heat injuries. Johnson & Johnson is also among the companies for developing contact lenses. This company has Phase 3 clinical data on an antihistamine-releasing contact lens. This contact lens can be used for reducing the symptoms of common allergic conjunctivitis.[93]

To achieve market approval, smart contact lenses must comply with regulatory requirements. These regulations assure that medical devices do not have negative health effects.[46] Based on the U.S. Food and Drug Administration (FDA) and Medicines & Healthcare products Regulatory Agency (MHRA) regulations, smart contact lenses must meet the requirements assigned for medical devices. Accordingly, the regulatory requirements categorize medical devices in three classes. Class I stands for the minimum risk and regulation associated with the product, and Class III is attributed to the highest risky products, which need the strictest regulations. The classification of a smart contact lens is based on its material and the performance of its sensor. An example of a company that received the FDA approval for its smart contact lens is Sensimed AG company (for SENSIMED Triggerfish).[94]

8. Challenges and Outlooks

At present, most contact lenses can only detect a single biomarker in the eye, such as glucose, lactic acid, K^+ , or Ca^{2+}. A potential advancement could be to develop contact lenses to detect multiple chemical components in real time, which will make contact lenses more powerful as biomedical tools. In addition, the implementation of electrical sensors would tremendously extend the performance of contact lenses to detect physical signals (i.e., temperature and pressure) and record or modulate electroretinography of the eye or electrical stimulation of visual neurons.[95]

Smart contact lenses are not only suited for continuous and minimally invasive disease monitoring, but also play an important role in the process of eye disease treatment. With developments in microscale technologies and biomaterials, contact lenses now can be designed with the ability to release drugs in a sustained manner.[15,16] These contact lenses are made of a mixture of drug and contact lens materials without affecting the refractive index and transparency of the lenses. Due to the tunable biological and physicochemical properties of hydrogels, it is expected that they can greatly improve the function of smart contact lenses in drug delivery. Also, the development of smart contact lenses with a drug-delivery system in which drugs may be reloaded is promising toward the development of reusable contact lenses amenable for extended usage.

Most existing sensory systems are not able to self-power. Flexible photovoltaic self-powered technology can replace traditional power supply mode in contact lenses as the natural sunlight is easy to obtain for energy conversion.[96] This can greatly reduce the connection line of internal devices and the complexity of electronic devices. These and other traits make photovoltaics a trend in flexible and stretchable electronics in the future.[97] Nanogenerators are tiny and can be used as a power supply module for contact lenses, which collect and convert mechanical energy from the constant blinking motion by the eyelids into electricity.[98] Using the triboelectric effect, a structurally simple, low-cost, and environmentally friendly nano-triboelectric generator can be achieved for contact lenses. The latter system has a broad development prospect to improve the service life of contact lenses and reduce their cost.[99]

Artificial intelligence can also be used to improve the therapeutic effect of smart contact lenses. In particular, machine learning algorithms can be used in smart contact lenses to recognize the human health status with long-term monitoring and provide personalized treatments for different types of diseases.[100] Collected data from individuals can be uploaded to a network and saved in cloud databases. These collective data will grow substantially and have to be analyzed using machine learning algorithms to predict the health state of people in diagnosis and clinical treatment.

To improve the performance and multifunctionality of smart contact lenses, it is necessary to add more chips and interconnects to the device. The task becomes more challenging as the circuit design and fabrications require miniaturization, flexibility, optical transparency, and resistance to repetitive wear. Major causes of the issues include opaque connection wires, rigidity of the chips, and size of sensing electrodes. Microinterconnects inside smart contact lenses are traditionally made of copper, silver, gold, and platinum that are opaque and can block people's vision. These materials can be switched to transparent alternatives, such as graphene, carbon nanowires, or indium tin oxide. The miniaturization of the chips embedded in the system for data storage, data transmission, and powering of the circuit has become increasingly important, pushing researchers and industrial vendors to develop the next generation of chips with multiplexed functions. Moreover, the sensitivity of the system is significantly reduced as the entire circuit scales down, especially with the size of the sensing electrodes. One possible solution for the aforementioned problems is using active sensors, such as field-effect transistors and complementary metal–oxide–semiconductor sensors, which show outstanding sensitivity despite having submicrometer sizes.[101]

An increasing density of active components in a device means higher power consumption, which becomes another major challenge. Many attempts have been made to increase the power supply capacity of circuits in smart contact lenses, including inductive, optical, RF power, and supercapacitors.[102] However, these methods cannot continuously provide power supply to meet the requirements for real-time health monitoring. A possible solution is to deploy biofuel cells in smart contact lenses, which can convert chemical energy into electricity from the chemicals found in tear fluids. The enzymes required to facilitate biochemical reactions can either be from the native biological fluids or be added from external solutions. The degradation

problem of the enzymes after a certain time can be solved by refilling fresh enzyme solutions.

Mechanical stability and biocompatibility of smart contact lenses represent another factor that affects its ability for chronic health monitoring, which can be addressed through advanced materials and technologies. For example, introducing oxygen channels in PDMS lenses can improve the long-term gas permeability of the device, thereby enhancing its biocompatibility.[103] The improved biocompatibility will minimize immune response and enhance healing functions without causing injurious, negative physiological, allergic, or toxic reactions and bring comfort to the wearers.

9. Conclusion

Smart contact lenses have shown significant capability in biomedicine with features of real-time and noninvasive diagnosis and drug delivery. In particular, we highlighted the applications of smart contact lenses in detecting glucose concentration in tear fluid, identifying glaucoma by measuring the IOP, assessing hypoxia or elevated salt concentration due to physiological or pathological conditions, and treating ophthalmic diseases by drug delivery. Multifunctional and integrated smart contact lenses can provide more effective physiological data collection of eye diseases than traditional ways, which will greatly facilitate the treatment of human diseases. Smart contact lenses hold great potential as routine wearable medical devices for accurate analysis of eye response to ophthalmic drugs, as well as for the evaluation of surgical procedures. We believe that smart contact lenses embody technical and material innovations that lead to the next generation of precision medicine-based devices.

Acknowledgements

This work was supported by a grant from CooperVision, Inc., to Department of Bioengineering at the University of California, Los Angeles, and Terasaki Institute for Biomedical Innovation (57179 BioEng). X. M., S. L., S. N., T. C., and D. W. acknowledge the School of Computer Science and Technology, School of Textile Science and Engineering at Tiangong University in China, and China Scholarship Council.

Conflict of Interest

The authors declare no conflict of interest.

Keywords

biosensors, diagnoses, drug deliveries, microfluidics, smart contact lenses

Received: December 3, 2020
Revised: February 25, 2021
Published online: May 5, 2021

[1] a) D. H. Kim, N. Lu, R. Ma, Y. S. Kim, R. H. Kim, S. Wang, J. Wu, S. M. Won, H. Tao, A. Islam, K. J. Yu, T. I. Kim, R. Chowdhury, M. Ying, L. Xu, M. Li, H. J. Chung, H. Keum, M. McCormick, P. Liu, Y. W. Zhang, F. G. Omenetto, Y. Huang, T. Coleman, J. A. Rogers, *Science* **2011**, *333*, 838. b) W. Gao, S. Emaminejad, H. Y. Y. Nyein, S. Challa, K. Chen, A. Peck, H. M. Fahad, H. Ota, H. Shiraki, D. Kiriya, D. H. Lien, G. A. Brooks, R. W. Davis, A. Javey, *Nature* **2016**, *529*, 509; c) K. I. Jang, S. Y. Han, S. Xu, K. E. Mathewson, Y. Zhang, J. W. Jeong, G. T. Kim, R. C. Webb, J. W. Lee, T. J. Dawidczyk, R. H. Kim, Y. M. Song, W. H. Yeo, S. Kim, H. Cheng, S. I. Rhee, J. Chung, B. Kim, H. U. Chung, D. Lee, Y. Yang, M. Cho, J. G. Gaspar, R. Carbonari, M. Fabiani, G. Gratton, Y. Huang, J. A. Rogers, *Nat Commun* **2014**, *5*, 4779; d) D. Kim, D. Kim, H. Lee, Y. R. Jeong, S. J. Lee, G. Yang, H. Kim, G. Lee, S. Jeon, G. Zi, *Advanced Materials* **2016**, *28*, 748; e) J. G. McCall, T. I. Kim, G. Shin, X. Huang, Y. H. Jung, R. Al-Hasani, F. G. Omenetto, M. R. Bruchas, J. A. Rogers, *Nat Protoc* **2013**, *8*, 2413.

[2] G. Z. Chen, I. S. Chan, L. K. Leung, D. C. Lam, *Med. Eng. Phys* **2014**, *36*, 1134.

[3] M. Falk, V. Andoralov, M. Silow, M. D. Toscano, S. Shleev, *Anal. Chem.* **2013**, *85*, 6342.

[4] Y.-T. Liao, H. Yao, A. Lingley, B. Parviz, B. P. Otis, *IEEE J. Solid-State Circuits* **2011**, *47*, 335.

[5] C. Jordan, Building An Electrochemical Contact Lens Biosensor, https://commons.pacificu.edu/work/4c43dcb4-a05a-42a9-ab10-458b6b338467 **2016** (accessed: March 2021).

[6] J.-F. Huang, J. Zhong, G.-P. Chen, Z.-T. Lin, Y. Deng, Y.-L. Liu, P.-Y. Cao, B. Wang, Y. Wei, T. Wu, *ACS Nano* **2016**, *10*, 6464.

[7] R. Badugu, J. R. Lakowicz, C. Geddes, *Anal. Chem.* **2004**, *76*, 610.

[8] S.-K. Kim, J. Koo, G.-H. Lee, C. Jeon, J. W. Mok, B. H. Mun, K. J. Lee, E. Kamrani, C.-K. Joo, S. Shin, *Adv. Sci.* **2020**, *6*, eaba3252.

[9] M. Leonardi, E. M. Pitchon, A. Bertsch, P. Renaud, A. Mermoud, *Acta Ophthalmol* **2009**, *87*, 433.

[10] P. C. Nicolson, J. Vogt, *Biomaterials* **2001**, *22*, 3273.

[11] J. Kim, M. Kim, M.-S. Lee, K. Kim, S. Ji, Y.-T. Kim, J. Park, K. Na, K.-H. Bae, H. K. Kim, *Nat. Commun.* **2017**, *8*, 1.

[12] J. Pandey, Y.-T. Liao, A. Lingley, R. Mirjalili, B. Parviz, B. P. Otis, *IEEE Trans Biomed Circuits Syst.* **2010**, *4*, 454.

[13] J. Park, J. Kim, S.-Y. Kim, W. H. Cheong, J. Jang, Y.-G. Park, K. Na, Y.-T. Kim, J. H. Heo, C. Y. Lee, *Sci. Adv.* **2018**, *4*, eaap9841.

[14] C. Vanhaverbeke, R. Verplancke, J. De Smet, D. Cuypers, H. De Smet, *Displays* **2017**, *49*, 16.

[15] F. A. Maulvi, T. G. Soni, D. O. Shah, *Drug Delivery* **2016**, *23*, 3017.

[16] J. Deng, S. Chen, J. Chen, H. Ding, D. Deng, Z. Xie, *ACS Appl. Mater. Interfaces* **2018**, *10*, 34611.

[17] A. Ulu, S. Balcioglu, E. Birhanli, A. Sarimeseli, R. Keskin, S. Koytepe, B. Ates, *J. Appl. Polym. Sci.* **2018**, *135*, 46575.

[18] M. Kazemi Ashtiani, M. Zandi, P. Shokrollahi, M. Ehsani, H. Baharvand, *Polym. Adv. Technol.* **2018**, *29*, 1227.

[19] T. S. Bhamra, B. J. Tighe, *Cont. Lens Anterior Eye* **2017**, *40*, 70.

[20] N. Efron, *Contact Lens Practice*, 3rd ed. (Ed: N. Efron) Elsevier, Edinburgh, UK **2018**, p. 115.

[21] H. Ho, E. Saeedi, S. S. Kim, T. Shen, B. A. Parviz, presented at *2008 IEEE 21st International Conference on Micro Electro Mechanical Systems*, **2008**.

[22] J. Bailey, S. Kaur, P. Morgan, H. Gleeson, J. Clamp, J. Jones, *J. Phys. D: Appl. Phys.* **2017**, *50*, 485401.

[23] A. Vásquez Quintero, R. Verplancke, H. De Smet, J. Vanfleteren, *Adv. Mater. Technol.* **2017**, *2*, 1700073.

[24] J. De Smet, A. Avci, R. Beernaert, D. Cuypers, H. De Smet, *J. Disp. Technol.* **2012**, *8*, 299.

[25] A. R. Lingley, M. Ali, Y. Liao, R. Mirjalili, M. Klonner, M. Sopanen, S. Suihkonen, T. Shen, B. Otis, H. Lipsanen, *J. Micromech. Microeng.* **2011**, *21*, 125014.

[26] H. An, L. Chen, X. Liu, B. Zhao, D. Ma, Z. Wu, *J. Micromech. Microeng.* **2018**, *28*, 105008.
[27] O. Wichterle, D. Lim, *Nature* **1960**, *185*, 117.
[28] T. Goda, K. Ishihara, *Expert Rev. Med. Dev* **2006**, *3*, 167.
[29] M. P. Wolf, G. B. Salieb-Beugelaar, P. Hunziker, *Prog. Polym. Sci.* **2018**, *83*, 97.
[30] A. Victor, J. Ribeiro, F. F. Araújo, *J. Mech. Eng. Biomech.* **2019**, *4*, 1.
[31] A. Mata, A. J. Fleischman, S. Roy, *Biomed. Microdevices* **2005**, *7*, 281.
[32] C.-H. Lin, Y.-H. Yeh, W.-C. Lin, M.-C. Yang, *Colloids Surf. B* **2014**, *123*, 986.
[33] M. H. M. Kouhani, J. Wu, A. Tavakoli, A. J. Weber, W. Li, *Lab Chip* **2020**, *20*, 332.
[34] L. Keay, D. F. Sweeney, I. Jalbert, C. Skotnitsky, B. A. Holden, *Optom. Vis. Sci.* **2000**, *77*, 582.
[35] J. Ruiz-Alcocer, D. Monsálvez-Romín, S. García-Lázaro, C. Albarrán-Diego, J. L. Hernández-Verdejo, D. Madrid-Costa, *Clin Exp Optom* **2018**, *101*, 188.
[36] F. Abbasi, H. Mirzadeh, A. A. Katbab, *J. Biomater. Sci. Polym. Ed.* **2001**, *2006*, 341.
[37] T. Goda, K. Ishihara, Y. Miyahara, *J. Appl. Polym. Sci.* **2015**, *132*, 41766.
[38] a) S. L. Willis, J. L. Court, R. P. Redman, J. H. Wang, S. W. Leppard, V. J. O'Byrne, S. A. Small, A. L. Lewis, S. A. Jones, P. W. Stratford, *Biomaterials* **2001**, *22*, 3261. b) G. Young, R. Bowers, B. Hall, M. Port, *CLAO J.* **1997**, *23*, 249. c) G. Young, R. J. W. Bowers, B. Hall, M. Port, J. Clao, *23*, 226; d) M. A. Lemp, B. Caffery, K. Lebow, R. Lembach, G. Young, *Eye Contact Lens* **1997**, *1999*, 40.
[39] S. I. Kihara, K. Yamazaki, K. N. Litwak, P. Litwak, B. P. Griffith, *Artif. Organs* **2003**, *27*, 188.
[40] a) T. Moro, Y. Takatori, K. Ishihara, T. Konno, Y. Takigawa, T. Matsushita, U. I. Chung, K. Nakamura, H. Kawaguchi, *Nat. Mater.* **2004**, *3*, 829; b) T. Moro, Y. Takatori, K. Ishihara, K. Nakamura, H. Kawaguchi, *Clin Orthop Relat. Res.* **2006**, *453*, 58; c) T. Moro, H. Kawaguchi, K. Ishihara, M. Kyomoto, T. Karita, H. Ito, K. Nakamura, Y. Takatori, *Biomaterials* **2009**, *30*, 2995.
[41] K. Nishida, M. Sakakida, K. Ichinose, T. Uemura, N. Nakabayashi, *Med. Prog. Technol.* **1995**, *21*, 91.
[42] T. Shimizu, T. Goda, N. Minoura, M. Takai, K. Ishihara, *Biomaterials* **2010**, *31*, 3274.
[43] X. C. Ming, K. Miyajima, D. Takahashi, T. Arakawa, K. Sano, S. I. Sawada, H. Kudo, Y. Iwasaki, K. Akiyoshi, M. Mochizuki, *Talanta* **2011**, *83*, 0.
[44] J.-C. Chiou, S.-H. Hsu, Y.-C. Huang, G.-T. Yeh, W.-T. Liou, C.-K. Kuei, *Sensors* **2017**, *17*, 108.
[45] V. Kumar, presented at *IFIP International Summer School on the Future of Identity in the Information Society*, Sweden, Springer **2007**.
[46] N. M. Farandos, A. K. Yetisen, M. J. Monteiro, C. R. Lowe, S. H. Yun, *Adv. Healthcare Mater.* **2015**, *4*, 792.
[47] U. Olgun, C.-C. Chen, J. L. Volakis, *IEEE Antennas Wirel. Propag. Lett.* **2011**, *10*, 262.
[48] L.-G. Tran, H.-K. Cha, W.-T. Park, *Micro Nanosyst.* **2017**, *5*, 1.
[49] S. Lee, I. Jo, S. Kang, B. Jang, J. Moon, J. B. Park, S. Lee, S. Rho, Y. Kim, B. H. Hong, *ACS Nano* **2017**, *11*, 5318.
[50] Y. L. Kong, I. A. Tamargo, H. Kim, B. N. Johnson, M. K. Gupta, T.-W. Koh, H.-A. Chin, D. A. Steingart, B. P. Rand, M. C. McAlpine, *Nano Lett.* **2014**, *14*, 7017.
[51] D. B. Wolfe, J. C. Love, K. E. Paul, M. L. Chabinyc, G. M. Whitesides, *Appl. Phys. Lett.* **2002**, *80*, 2222.
[52] P. Karthik, S. P. Singh, *RSC Adv.* **2015**, *5*, 77760.
[53] a) J. H. Kim, S. Lee, M. Wajahat, H. Jeong, W. S. Chang, H. J. Jeong, J.-R. Yang, J. T. Kim, S. K. Seol, *ACS Nano* **2016**, *10*, 8879; b) T. Cheng, Y. Zhang, W. Y. Lai, W. Huang, *Adv. Mater.* **2015**, *27*, 3349; c) H. L. Hsu, I. J. Teng, Y. C. Chen, W. L. Hsu, Y. T. Lee, S. J. Yen, H. C. Su, S. R. Yeh, H. Chen, T. R. Yew, *Adv. Mater.* **2010**, *22*, 2177; d) K.-Y. Chun, Y. Oh, J. Rho, J.-H. Ahn, Y.-J. Kim, H. R. Choi, S. Baik, *Nat. Nanotechnol.* **2010**, *5*, 853.
[54] P. N. Nge, C. I. Rogers, A. T. Woolley, *Chem. Rev.* **2013**, *113*, 2550.
[55] G. M. Whitesides, *Nature* **2006**, *442*, 368.
[56] E. K. Sackmann, A. L. Fulton, D. J. Beebe, *Nature* **2014**, *507*, 181.
[57] D. Psaltis, S. R. Quake, C. Yang, *Nature* **2006**, *442*, 381.
[58] S. Wu, Q. Lin, Y. Yuen, Y.-C. Tai, *Sens. Actuators, A* **2001**, *89*, 152.
[59] R. Dangla, F. Gallaire, C. N. Baroud, *Lab Chip* **2010**, *10*, 2972.
[60] a) H. Chen, Y. L. Hsieh, *J. Polym. Sci., Part A: Polym. Chem.* **2004**, *42*, 6331. b) M. Karg, I. Pastoriza-Santos, B. Rodriguez-Gonzalez, R. von Klitzing, S. Wellert, T. Hellweg, *Langmuir* **2008**, *24*, 6300. c) H.-j. Zhang, Y.-N. Zhang, B. Yang, L.-G. Wang, *Colloid Polym. Sci.* **2018**, *296*, 393.
[61] J. del Barrio, C. Sánchez-Somolinos, *Adv. Opt. Mater.* **2019**, *7*, 1900598.
[62] a) J. A. DeFranco, B. S. Schmidt, M. Lipson, G. G. Malliaras, *Org. Electron.* **2006**, *7*, 22; b) R. Balma, K. Petsch, T. Kaya, presented at *American Society for Engineering Education* **2011**.
[63] D. C. Duffy, J. C. McDonald, O. J. Schueller, G. M. Whitesides, *Anal. Chem.* **1998**, *70*, 4974.
[64] M. Mohan, M. Ansari, R. A. Shanks, *Polym.-Plast. Technol. Mater.* **2017**, *56*, 1.
[65] A. C. Siegel, S. K. Y. Tang, C. A. Nijhuis, M. Hashimoto, S. T. Phillips, M. D. Dickey, G. M. Whitesides, *Acc. Chem. Res.* **2010**, *43*, 4.
[66] C.-E. Lin, K. Hiraka, D. Matloff, J. Johns, A. Deng, K. Sode, J. La Belle, *Sens. Actuators, B* **2018**, *270*, 525.
[67] S. Agaoglu, P. Diep, M. Martini, K. Samudhyatha, M. Baday, I. E. Araci, *Lab Chip* **2018**, *18*, 3471.
[68] Y. Xia, G. M. Whitesides, *Annu. Rev. Mater. Sci.* **1998**, *28*, 153.
[69] A. Garcia-Cruz, M. Lee, N. Zine, M. Sigaud, J. Bausells, A. Errachid, *Sens. Actuators, B* **2015**, *221*, 940.
[70] B. D. Terris, H. J. Mamin, M. E. Best, J. A. Logan, D. Rugar, S. A. Rishton, *Appl. Phys. Lett.* **1996**, *69*, 4262.
[71] M. Hutley, *Diffraction Gratings, Techniques of Physics*, London **1982**.
[72] M. Nakano, N. Nishida, *Appl. Opt.* **1979**, *18*, 3073.
[73] D. Kiewit, *Rev. Sci. Instrum.* **1973**, *44*, 1741.
[74] J. Yan, presented at *2011 Annual Int. Conf. of the IEEE Engineering in Medicine and Biology Society* **2011**.
[75] S. Surdo, A. Diaspro, M. Duocastella, *Appl. Surf. Sci.* **2017**, *418*, 554.
[76] B. Gray, *ECS Trans.* **2010**, *28*, 535.
[77] H. Becker, C. Gärtner, *Anal. Bioanal. Chem.* **2008**, *390*, 89.
[78] a) K. Ke, E. F. Hasselbrink, A. J. Hunt, *Anal. Chem.* **2005**, *77*, 5083; b) K. Yamasaki, S. Juodkazis, S. Matsuo, H. Misawa, *Appl. Phys. A* **2003**, *77*, 371; c) D. Gomez, I. Goenaga, I. Lizuain, M. Ozaita, *Opt. Eng.* **2005**, *44*, 051105.
[79] J. Kim, X. Xu, *Journal of Laser Applications Lab on a Chip* **2003**, *2002*, 242.
[80] N. Thomas, I. Lähdesmäki, B. A. Parviz, *Sens. Actuators, B* **2012**, *162*, 128.
[81] N. Oliver, C. Toumazou, A. Cass, D. Johnston, *Diabetic Med.* **2009**, *26*, 197.
[82] H. Yao, A. J. Shum, M. Cowan, I. Lähdesmäki, B. A. Parviz, *Biosens. Bioelectron.* **2011**, *26*, 3290.
[83] B. Otis, B. Parviz, https://www.usatoday.com/story/tech/2014/01/16/google-smart-contact-lens/4540727/ **2014** (accessed: March 2021).
[84] a) K. T. Ma, C. Y. Kim, G. J. Seong, S. H. Lee, J. W. Park, S. J. Ha, B. J. Cho, J. A. Stewart, M. S. Kristoffersen, L. A. Nelson, *Int. Ophthalmol.* **2011**, *31*, 355; b) K. Nouri-Mahdavi, F. A. Medeiros, R. N. Weinreb, *Arch. Ophthalmol.* **2008**, *126*, 1168; c) J. Caprioli, A. L. Coleman, *Ophthalmol.* **2008**, *115*, 1123; d) K. Hoban, R. Peden, R. Megaw, P. Halpin, A. J. Tatham, *Ophthalmic Res.*

2017, *57*, 208; e) C. Gisler, A. Ridi, J. Hennebert, R. N. Weinreb, K. Mansouri, *Transl. Vis. Sci. Technol.* **2015**, *4*, 4.
[85] L. Agnifili, R. Mastropasqua, P. Frezzotti, V. Fasanella, I. Motolese, E. Pedrotti, A. D. Iorio, P. A. Mattei, E. Motolese, L. Mastropasqua, *Acta Ophthalmol.* **2015**, *93*, e14.
[86] J.-C. Chiou, Y.-C. Huang, G.-T. Yeh, *J. Micromech. Microeng.* **2015**, *26*, 015001.
[87] M. Greene, B. Gilman, *Invest. Ophthalmol. Visual Sci.* **1974**, *13*, 299.
[88] J. B. Ciolino, C. H. Dohlman, D. S. Kohane, Seminars in Ophthalmology **2009**, *24*.
[89] A. Guzman-Aranguez, B. Colligris, J. Pintor, *J. Ocul. Pharmacol. Ther.* **2013**, *29*, 189.
[90] Z. Duru, N. Duru, D. M. Ulusoy, *Cont Lens Anterior Eye* **2020**, *43*, 169.
[91] J. B. Ciolino, S. P. Hudson, A. N. Mobbs, T. R. Hoare, N. G. Iwata, G. R. Fink, D. S. Kohane, *Invest. Ophthalmol. Visual Sci.* **2011**, *52*, 6286.
[92] https://www.optometrytimes.com/view/smart-contact-lens-update. (accessed: March 2021).
[93] https://www.jjvision.com/press-release/johnson-johnson-visions-investigational-antihistamine-releasing-contact-lens. (accessed: March 2021).
[94] K. Mansouri, F. A. Medeiros, A. Tafreshi, R. N. Weinreb, *Arch. Ophthalmol.* **2012**, *130*, 1534.
[95] R. Yin, Z. Xu, M. Mei, Z. Chen, K. Wang, Y. Liu, T. Tang, M. K. Priydarshi, X. Meng, S. Zhao, *Nat. Commun.* **2018**, *9*, 1.
[96] A. E. Ostfeld, A. C. Arias, *Flexible Printed Electron.* **2017**, *2*, 013001.
[97] S. Park, S. W. Heo, W. Lee, D. Inoue, Z. Jiang, K. Yu, H. Jinno, D. Hashizume, M. Sekino, T. Yokota, *Nature* **2018**, *561*, 516.
[98] F. R. Fan, W. Tang, Z. L. Wang, *Adv. Mater.* **2016**, *28*, 4283.
[99] X. He, Y. Zi, H. Guo, H. Zheng, Y. Xi, C. Wu, J. Wang, W. Zhang, C. Lu, Z. L. Wang, *Adv. Funct. Mater.* **2017**, *27*, 1604378.
[100] a) Y. LeCun, Y. Bengio, G. Hinton, *Nature* **2015**, *521*, 436; b) A. Esteva, A. Robicquet, B. Ramsundar, V. Kuleshov, M. DePristo, K. Chou, C. Cui, G. Corrado, S. Thrun, J. Dean, *Nature Med.* **2019**, *25*, 24.
[101] G. Hong, C. M. Lieber, *Nat. Rev. Neurosci.* **2019**, *20*, 376.
[102] J. Park, D. B. Ahn, J. Kim, E. Cha, B.-S. Bae, S.-Y. Lee, J.-U. Park, *Sci. Adv.* **2019**, *5*, eaay0764.
[103] G. A. Salvatore, N. Münzenrieder, T. Kinkeldei, L. Petti, C. Zysset, I. Strebel, L. Büthe, G. Tröster, *Nat. commun.* **2014**, *5*, 1.
[104] A. W. Lloyd, R. G. Faragher, S. P. Denyer, *Mater. Trans.* **2001**, *2009*, 1730.
[105] a) J. Zhu, Y. Tian, C. Yang, L. Cui, X. Liu, *Microsyst. Technol.* **2017**, *23*, 1; b) Y. Cai, H. Ke, D. Ju, Q. Wei, J. Lin, Z. Yong, S. Lei, H. Yuan, F. Huang, W. Gao, *Appl. Energy* **2011**, *88*, 2106.
[106] E. García-Millán, S. Koprivnik, F. J. Otero-Espinar, *Int. J. Pharm.* **2015**, *487*, 260.
[107] R. K. Pal, S. Pradhan, L. Narayanan, V. K. Yadavalli, *Sens. Actuators, B* **2018**, *259*, 498.
[108] T. Goda, R. Matsuno, T. Konno, M. Takai, K. Ishihara, *J. Biomed. Mater. Res. Part B* **2009**, *89*, 184.
[109] https://www.sensimed.ch/sensimed-triggerfish/ (accessed: March 2021).
[110] https://www.fortunebusinessinsights.com/smart-contact-lenses-market-102717 (accessed: March 2021).
[111] https://www.mojo.vision/mojo-lens (accessed: March 2021).
[112] https://www.emacula.io/ (accessed: March 2021).
[113] X. Fan, C. Torres-Luna, M. Azadi, R. Domszy, N. Hu, A. Yang, A. E. David, *Acta Biomater.* **2020**, *115*, 60.
[114] http://leolens.com/medicated-lenses/ (accessed: March 2021).
[115] http://ocumedic.us/ (accessed: March 2021).

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