HHS Public Access

Author manuscript

Adv Mater. Author manuscript; available in PMC 2023 June 01.

Published in final edited form as:

Adv Mater. 2022 June ; 34(24): e2108389. doi:10.1002/adma.202108389.

Lab-on-a-Contact Lens: Recent Advances and Future Opportunities in Diagnostics and Therapeutics

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Conflict of Interest

The authors declare no conflict of interest.

The ORCID identification number(s) for the author(s) of this article can be found under https://doi.org/10.1002/adma.202108389.

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Abstract

The eye is one of the most complex organs in the human body, containing rich and critical physiological information (e.g., intraocular pressure, corneal temperature, and pH) as well as a library of metabolite biomarkers (e.g., glucose, proteins, and specific ions). Smart contact lenses (SCLs) can serve as a wearable intelligent ocular prosthetic device capable of noninvasive and continuous monitoring of various essential physical/biochemical parameters and drug loading/delivery for the treatment of ocular diseases. Advances in SCL technologies and the growing public interest in personalized health are accelerating SCL research more than ever before. Here, the current status and potential of SCL development through a comprehensive review from fabrication to applications to commercialization are discussed. First, the material, fabrication, and platform designs of the SCLs for the diagnostic and therapeutic applications are discussed.

Then, the latest advances in diagnostic and therapeutic SCLs for clinical translation are reviewed. Later, the established techniques for wearable power transfer and wireless data transmission applied to current SCL devices are summarized. An outlook, future opportunities, and challenges for developing next-generation SCL devices are also provided. With the rise in interest of SCL development, this comprehensive and essential review can serve as a new paradigm for the SCL devices.

Keywords

bioelectronics; biosensors; contact lens; diagnostics; integrated systems; personalized healthcare; therapeutics; wearable electronics

1. Introduction

The world has seen a significant growing interest in improving the quality of human life, especially against the backdrop of the severe global-spanning impact caused by the coronavirus disease 2019 (COVID-19) pandemic, together with other diseases or chronic health risks.[1–4] With the growing interest in health monitoring, wearable bioelectronic devices have been innovated to enable noninvasive, real-time, and continuous monitoring of physiological signals and biomarkers with little to no interference with users' daily routines.[5] Besides, by collecting and analyzing raw signals and then integrating them into understandable and actionable health knowledge, the wearable bioelectronic platform can significantly enhance the healthcare and information delivery efficiency in a timely, precise, and personalized manner.[6]

Tears, along with sweat and saliva, have tremendous potential for noninvasive monitoring biological signals.[7] As a source for monitoring biosignals, tears have the advantages of easy access, low complexity of sampling, and minimal invasiveness.[8] Furthermore, the tear fluid provides an on-demand supply for continuous and real-time health monitoring since it contains a wide variety of physiological indices such as proteins, glucose, and pH.[9,10] With the development of wearable bioelectronics, numerous efforts have been made to develop smart contact lenses (SCLs) that sense through the tear fluid.

The advent of SCLs enables noninvasive real-time detection of the key signals from the eyes and tear fluids.[11] After the first mention of "SCL" as a contact lens (CL) for measuring intraocular pressure (IOP) on the corneal surface in 2007, SCL research reports have been steadily increasing.[12] In particular, after Google's announcement of the SCL project in 2014, interest in SCLs began to drastically increase, and related research papers have also increased since 2017. These SCL studies range from biosignal detection (IOP, glucose, cortisol)[13–15] to therapeutic tools (aniridia, chronic ocular inflammation).[16,17] In addition, multidisciplinary research is continuing to develop advanced SCLs in various attributes such as sensitivity improvement,[18] wireless signal transmission,[13] and personalized design using 3D printing technology.[19]

As one of the most recent examples, in early 2020, an American startup company named Mojo Vision drew attention as it introduced the first SCL concept that could demonstrate

data and health statistics based on augmented reality (AR) technology. Although the state-of-the-art technology has been included in the products, the ease-of-use lowers the barrier to entry for SCL users. When the user wears the lenses, pop-up icons with features such as calendar, music, and weather forecast, enabled the wearer to choose the next action actively and accurately. As Mojo Vision's product is defined as "a vision of the future," SCLs hold considerable promise for the next generation of smart bioelectronics and make a breathtaking breakthrough in the high-tech world.[20,21]

In addition to the information transmission and sensing aspects, the SCLs have the promising potential to be used as a drug delivery platform for therapeutic applications. Ocular drug delivery remains challenging due to various anatomical and physiological drug penetration barriers, including the precorneal and corneal barrier, the conjunctival barrier, the blood-aqueous barrier, and the blood-retinal barrier.[22,23] Currently, ocular drug delivery methods to treat eye diseases mainly rely on eye drops and ointments for noninvasive drug administration.[24,25] However, limitations such as poor patient compliance, low bioavailability, and high systemic drug uptake, still make current treatment strategies not optimally efficient enough for managing ocular disease.[26]

To solve these shortcomings, the SCL-based drug delivery wearable platform has been devised and developed.[27–29] SCL-based drug delivery systems are designed to achieve efficient drug encapsulation, accurate drug dose delivery, sustained drug release, adequate drug bioavailability, and better patient compliance.[25,29] As a very recent example, the first clinical trial investigating LLT-BMT1, a drug-eluting SCL product from MediPrint Ophthalmics, has been shown to be safe and well-tolerable for the treatment of glaucoma. These uplifting trial results will undoubtedly boost the advances in CL products for patients suffering from conceivably-disabling ocular diseases such as glaucoma and diabetic retinopathy.

Despite these promising prospects and expectations of SCL, there remain problems to be solved such as transparency (opaque electronic material), reliability (scalability, repeatability), and biocompatibility (rigidity, size, irritation) for commercialization of SCL devices. In particular, the underlying side effects that may occur due to the use of CLs, such as dry eye syndrome (DES), aggravate the developmental difficulties of SCLs.[30] To overcome these limitations, the development/design of new biocompatible materials and multifunctional/ultrasensitive biosensors, as well as recent developments in wearable information and communication technology (ICT) will further accelerate the development of SCLs by enhancing the usability and minimizing side effects.[11,31,32] Through significant multidisciplinary research efforts, innovations of SCLs with the ability to 1) continuously monitor real-time physiological signals in a wireless manner, 2) provide reliable diagnosis, and 3) offer beneficial feedback to users for follow-up treatment, which will ultimately enable personalized medicine.

In this comprehensive review, we provide recent progress and future opportunities for the use of SCLs for diagnostic and therapeutic applications (Figure 1). First, we review the SCL materials and manufacturing methods, followed by an extensive discussion in SCLs as an effective diagnostic tool to sense biosignals from the eye or tear fluids. Then,

SCLs for therapeutic applications, including typical characteristics and responsive strategies were summarized. Besides, we offer an outline of current marketable therapeutic SCLs and examples under the clinical trials. Subsequently, we provide a summary of wearable powering systems and wireless transmission technologies, and representative examples for the next generation of SCL wearable platforms are highlighted. Finally, we conclude this review by focusing on current challenges and future perspectives for developing next-generation SCL devices.

2. Material Designs and Considerations

Physical properties are critical when choosing CL materials. First, the ideal candidates should be gas-permeable and have an antiabrasiveness feature for user comfort. Second, excellent optical transparency, proper structural hardness, and stability are required to maintain the lens curvature.[33] The wettability, low nonspecific absorption, and compatibility with circuit/electronic components have to be considered if an electrochemical sensing unit is integrated into SCL devices.[33] Furthermore, integrative sensor modalities and desired biocompatibility should be regarded for SCL applications.[34,35] Finally, it is essential to consider the length of wear, durability, raw materials, and manufacturing cost, as these factors can affect the commercialization of SCL devices.[19,36] In this section, we summarized classic CL materials and their improved utilization for SCL device fabrication. Moreover, we highlighted the advances in materials and designs of the SCLs used for diagnostic and therapeutic applications.[10,37,38]

2.1. CL Materials

2.1.1. Polymethyl Methacrylate (PMMA)—Developed in the 1940s, PMMA was the first CL material.[10] As a biocompatible plastic, PMMA is well known for its transparency, rigidity, and durability.[39] Dipole–dipole interactions and physical entanglement between polymer chains serve as the intermolecular forces to lead to excellent rigidity.[33] Albeit strong durability and optical transparency, its poor oxygen permeability, inflexibility, and weak hydrophilicity hampered PMMA's role as a CL.[36] It has been studied that wearing CLs with low oxygen permeability may trigger several ocular diseases, such as hypoxia and corneal neovascularization.[34] Furthermore, the rigidity of PMMA and its limited hydrophilicity could cause weak flexibility and uncomfortable compliance with the eyes.[11] As a result, although PMMA CLs have been reported to manage keratoconus after an intrastromal corneal ring segment (INTACS) procedure,[40] PMMA CLs are not suitable for long-term use.[36] A study shows that an estimated 45 million Americans use CLs, with only about 1% of lenses from PMMA.[41] Therefore, aside from the integration of biosensors and AR with PMMA CLs, the field has been unattractive to researchers thus far.[11]

2.1.2. Silicone—Silicone represents a series of popular and modern CL materials.[34] Silicone hydrogels are naturally oxygen-permeable and durable due to intrinsic robust silicon-oxygen bonding.[33]

These features make silicone CLs durable for long-term wear and commercially attractive, as seen by the largest CL market share (Table 1).[33,42] However, silicone materials are inherently hydrophobic,[43] resulting in CL-induced ocular dryness, reducing their

biocompatibility.[44] In addition, silicone CLs may irritate eyes due to the higher modulus compared to conventional hydrogel lenses.[34] Therefore, copolymerization of the silicone monomer with a hydrophilic comonomer, such as polyhydroxyethylmethacrylate (PHEMA) and methacrylic acid (MAA), was adopted to address the hydrophobicity.[34,45] For example, Mendelez-Ortiz et al. reported MAA-grafted silicone CLs, with a superb anti-fouling effect that showed a negligible protein absorption when exposed to albumin and fibrinogen. Cooper Vision, a CL manufacturer, recently introduced Smart Silicone, a chemically modified CL with silicone channels combined with hydrophilic materials (note that the specific hydrophilic material is not mentioned due to the commercial privacy) that increase oxygen permeability to almost 100% while using less silicone.[46] Furthermore, nonsteroidal anti-inflammatory drugs can be loaded into these SCLs to achieve controlled release.[47] Therefore, silicone is a promising material for the construction of SCLs.

2.1.3. Polyvinyl Alcohol (PVA)—PVA is a relatively new synthetic polymer characterized by the single hydroxy (–OH) group present within its repeating monomer unit.[48] This unique composition allows PVA hydrogels to be both hydrophilic and biocompatible.[49] A study found that PVA hydrogels exhibited higher tensile strength and lower protein absorption than other CL materials, such as silicone.[50] In addition, the low cost, increased bioavailability, and hydrophilic properties make PVA a promising material for CLs.[48,51] However, similar to PMMA, PVA suffers from low gas permeability, which would cause user discomfort and eye irritation after long-term use.[33,52] Therefore, there is room for improving PVA properties for SCLs.[33]

2.1.4. Polyhydroxyethylmethacrylate (PHEMA)—PHEMA is an optically transparent polymer material commonly used for soft CL fabrication, making up almost 22% of the CL market (Table 1).[33,53,54] Due to the high oxygen permeability and great hydrophilicity, the hydroxyethyl methacrylate (HEMA) monomer has frequently been copolymerized with other polymers to improve the wettability and structural stability after soaking-drying cycles within the polymer network.[34] For example, typical monomers such as MAA and N-vinylpyrrolidone (NVP) have been coupled with HEMA to generate PHEMA-MAA and PHEMA-NVP hydrogels, respectively.[55] Fares et al. grafted polylactide (PLA) onto a PHEMA-NVP copolymer and found increased control over drug release.[56] Besides, PHEMA-based copolymer systems also possess great mechanical flexibility that is desired for SCLs. To improve the structural integrity of PHEMA CLs, crosslinkers, such as ethylene glycol dimethacrylate (EGDMA), have been introduced. EDGMA significantly improves gelling ability by forming covalent bonds between adjoining polymer chains. However, it is of great importance to keep well-balanced stability and oxygen permeability, as the porosity inside the CL reduces with a higher crosslinking degree. Therefore, it is crucial to optimize the crosslinker-to-HEMA ratio for CL manufacturing. Although commercial microfabrication technologies, such as soft lithography and photolithography, are not currently compatible with PHEMA, its high transmittance and attractive mechanical properties make it an ideal material to construct SCLs for intelligent diagnostic and therapeutic applications.

2.2. Functional Integrations

Compared with traditional CLs, SCL devices have been integrated to endow enhanced properties and other functionalities to meet various market needs. In the past decade, material and structure innovations have constantly evolved to empower SCL devices to realize various application scenarios in sensing, diagnostics, and therapeutics.[10,31,62,63] Herein, we summarize the recent modifications and improvements to enable SCLs with newly integrated functionalities and enhanced properties.

2.2.1. Surface Modifications—Applying surface coatings onto CLs has been used to improve the adhesion, hydrophilicity, and other functionalities such as antifouling, electromagnetic interference shielding, and electrical sensing.[64–66] Generally, after a period of use, the CL surface is prone to accumulating ocular metabolite deposits and contaminations from the surroundings, which can cause ocular diseases and wearer discomfort.[67] Therefore, a safe, stable, and antifouling lens surface is one of the initial focuses in material selections, modifications, and fabrication. With proper surface modifications, the undesired adhesion can be eliminated to avoid unexpected ocular contaminations.[67,68] For example, polyethylene glycol (PEG) has been widely used to improve the surface hydrophilicity property of silicone CLs.[69] Besides PEG, zwitterionic coatings have been reported to effectively prevent ocular dehydration (Figure 2a) since some zwitterionic polymers are able to trap water molecules to keep CL highly hydrated and prevent biofilm formation.[57] Two approaches to zwitterionic coatings can be separated into graft-from (GF) and graft-to (GT).[57,70,71] Zwitterionic monomers are polymerized from surface grafted initiators/catalysts for the GF process. In contrast, a zwitterionic polymer is chemically grafted onto the SCL surface for the GT process, typically modified with functional groups, such as poly (2-methacryloyloxyethyl phosphorylcholine) (PMPC).[70] Furthermore, particular functionalities such as antibiotic and sensing capabilities can also be incorporated into the SCL systems via surface modifications.[10,72] For example, coating a thin conductive layer (e.g., copper, silver, or liquid metals) on a parylene film allowed the construction of a stretchable circuit on an SCL to achieve multimodal sensing functionalities.[35,38,61,73] Bioinspired strategies can also be applied to surface coatings.[74–76] Mucin coatings have been utilized to reduce friction and prevent bacterial, protein, and cell adhesion[58] and could significantly improve the lubricated performance of hydrogel SCLs due to an autolubrication ability upon contact with the eye. The use of mucin coatings can effectively prevent adhesion wear on corneal tissue and increase the CL's liquid breakup times while maintaining its optical transparency (Figure 2b).[58] Besides, mucin coatings exhibit excellent stability to confront complicated mechanical, thermal, and chemical conditions.[77] These characteristics make mucin-based surface coatings promising to overcome biofouling,[77] and it has also been shown that purified gastric mucins could efficiently prevent damage to the cornea.[78]

To achieve the various functionalities of an SCL device, surface coatings are applied to conventional CL materials.[58,66,79] For example, to improve the interfacial interactions of silicone CLs with the ocular surface, a layer of hydrophilic glycosaminoglycan hyaluronic acid (HA) was covalently attached to the lens surface through UV-induced thiol–ene "click" chemistry (Figure 2c).[59] This HA-grafted PHEMA hydrogel was optically transparent and

showed improved surface wettability and anti-biofouling properties.[51] Another example of the covalently bonded HA to the PHEMA surface achieved noncytotoxic coating fabrication with enhanced surface hydration and protein-resistance properties.[80] In addition, the inherent carboxylic acid moiety of HA during its grating with PHEMA provided a strategy for immobilizing antibodies or proteins on an SCL surface to achieve biosensing functions.[81,82]

2.2.2. Copolymerization—Synthesis of CL materials relies on polymerization or copolymerization. Compared to polymer-based CLs, copolymer-based CLs have multiple advantages: enhanced physical features, alleviated rigidity, and improved oxygen permeability.[71] For example, silicone polymers have high oxygen permeability, and therefore, silicone polymers have been grafted to modify low oxygen-permeable CLs to improve oxygen transfer.[83] In addition, copolymerization of silicone into hydrophilic materials such as PHEMA or poly(ethylene glycol) methacrylate (PEGMA) to enhance hydrophilicity has been explored.[60] Various silicone CLs have been prepared through a UV-initiated polymerization process, such as the copolymerized procedure of PDMA–PEGMA with NVP and PEGMA (Figure 2d).[60] This design showed that a higher content of hydrophilic polymers could enhance CL wettability and result in softer CLs without affecting optical transparency.[60] Another example is the copolymerization of HEMA monomers with a biocompatible compound 2-methacryloyloxyethyl phosphorylcholine (MPC), which has been found to maintain the high water content but also increase the surface roughness.[67] Zwitterionic polymers, reported to improve the hydrophilicity and antiadhesion properties, could also be copolymerized to an SCL system.[57,70,71] A copolymer-based CL was synthesized through a radical copolymerization of HEMA, NVP, and sulfobetaine methacrylate monomer (SBMA).[71] Interestingly, the microstructured pore sizes were positively correlated to the SBMA content, the equilibrium water content, and the visible light transmittance. Besides, the introduction of this compound improved anti-biofouling ability, indicating the practicality of the method.[71]

2.2.3. Encapsulation—Encapsulation of specific components is another method to endow SCLs with enhanced properties and more functionalities.[32,33] For example, a metal-organic framework (MOF) silver cluster with antimicrobial properties could be incorporated into HEMA-based polymers to allow SCLs to be antibiotic.[84] Similarly, mixing silver nanoparticles (AgNPs) into silicone CLs demonstrated significant inhibition of bacterial growth and biofilm formation. Besides, the mechanical properties of the gel materials, such as tensile strength, were also improved.[85] Integration of sensor units into SCLs has been reported to manufacture flexible and transparent multifunctional sensor systems,[65] such as transition metal dichalcogenide (TMDC) semiconductors or flexible electrodes integrated into an SCL device.[35,64,86,87] For example, molybdenum disulfide (MoS_2) transistors were used as the core sensing unit, and the optimal charge transfer properties, large surface-to-volume ratio, tunable bandgap, and good biocompatibility indicated the potential applications and further exploration on this system (Figure 2e).[35] Functional nanoparticles with unique properties, such as no/low cytotoxicity, excellent physical/chemical features, and drug-delivery ability, have also been employed to improve/integrate some SCL properties.[51,62,88–90] For example, it has been reported that the nanoparticles

were incorporated into CL polymers and gelling systems to enhance mechanical strength and elasticity of CLs.[34] For example, organic dye-encapsulated silica nanoparticles were applied with PHEMA or PDMS to obtain precise biosensing capability, with the detection sensitivity of 0.5–5 × 10^{-3} M of blood glucose.[10] Carbon nanoparticles have also been introduced in an ophthalmic lens.[33,50,91] The wettability and tensile strength of the CL material were improved by chemically functionalized carbon nanoparticles, while retaining no cytotoxicity and exhibiting excellent impact resistance.[92] Other examples, such as titanium dioxide (TiO_2) nanoparticles, were also explored to increase the refractive index and maintain the high transparency of the SCL device.[93]

2.2.4. Integration Manufacturing—Not only does research focus on the improvement of traditional material properties, but investigators have also been focusing on designing SCLs for diagnostic and therapeutic applications by incorporating functionalities to traditional CL materials.[13,31,38,62,94,95] A novel power-free soft PDMS CL has been fabricated to measure IOP and achieve extended drug delivery with the ability to monitor glaucoma-related biomarkers.[37] The material designs used anodic aluminum oxide (AAO) thin film as the IOP sensor with a biomarker-specific antigen modified on the AAO surface.[37] Another example to monitor IOP was developed to achieve glaucoma diagnostics by using a mobile phone.[96] Altogether, a strain sensor, a wireless antenna, capacitors, resistors, stretchable metal interconnects, and an integrated circuit for wireless communications were combined to achieve the proposed aim.[96] Recently, a disposable SCL was integrated with a functional corneal sensor, which was tailored for ophthalmic electroretinogram (ERG) testing in human eyes (Figure 2f).[61] They used a biocompatible polymer doped with rosulate linked to an elastomeric connection wire composed of PDMS and silver flake-filled polystyrene polymer.[61]

2.3. Guidance of Material Selections for SCL Applications

The material choice and properties are also important to take into consideration when engineering the lens for various functional diagnostic and therapeutic applications which will be discussed in later sections. Therefore, we briefly highlight the importance of choosing the right CL material when engineering them for various applications. For example, when designing a SLC for sensing pH and ions, it is important that the chosen material is not pH sensitive or can interact with ions that may destabilize the polymer material and lose integrity. In addition, when engineering a SLC for various light or thermo-responsive drug delivery, a material that responds to light and heat with optimal diffusion properties needs to be chosen. Silva et al. described how silicone-hydrogel CLs may be preferable to HEMA-based lenses for drug delivery owing to their higher permeability to oxygen, however the use of silicone lenses for the release of ophthalmic drugs have been unsuitable in the past.[97] Engineering them for this application involves the application of layer-by-layer coatings and imprinting technologies to make the material suitable for the release of antibacterial drugs. Furthermore, when using hydrogel materials for sensing applications, the material properties need to be engineered to be conductive and possess fracture energy while still being wearable. Zha et al. highlighted that regulating polymer networks to fabricate highly conductive, sensitive, robust, and transparent materials is of vital importance for CLs for sensing.[98] The traditional PVA material needed optimization

for this application and they demonstrated a cosolvent strategy to fabricate organohydrogels. These were unlike traditional PVA hydrogels with microscopic networks, but this possessed a high cross-linking density with excellent tensile strength and when soaked in a NaCl/glycerol/water solution, the hydrogel displayed linear, stable, and repeatable sensing properties.

2.4. SCL Fabrication

2.4.1. Traditional Methods—The manufacturing of CLs plays a critical role in the mechanical properties of the resulting lenses. As shown in Figure 3a–c, Three conventional techniques to CL fabrication, including lathe-cutting, spin-casting, and cast-molding, are prevalent in the CL market today.[99] Lathe-cutting is a method of cutting lenses from non-hydrated disks of CL material using precise, computer-controlled cutting tools.[100] These non-hydrated disks have high surface-to-volume ratios, and CLs can be created from the inside of these disks to negate surface degradation easily.[101] Although this method is relatively time-consuming, automation is possible.[11] Spin-casting is another manufacturing method in which a liquid polymer is exuded into a spinning mold, and centripetal force is then applied to shape the curvature of the lens.[99] Besides, spin-casting allows for resultant CLs to be relatively thin, and the process can be much faster than lathe-cutting. It takes few minutes to polymerize the final lens via spin-casting. However, spin-casting requires anaerobic conditions and nitrogen-cleansed machinery to reduce irreversible surface degradation effects.[101] Cast-molding entails two molds being pressed together to harden and shape the material into SCLs. It is an inexpensive method and additionally avoids the need to polish finished lenses. Because of these advantages, it is a popular method for the manufacturing of disposable CLs.

A study involving a novel CL used the cast-molding technique to implant drug-loaded, semi-circular rings within the periphery of the CLs.[102] However, due to its rapid polymerization time, resultant lenses have inefficient cross-linking and are susceptible to oxygen-related surface degradation effects.[103] In most cases, injection molding was used to fabricate CLs based on novel solutions incorporating biosensing units. Here, the material is injected between molds that are UV-transparent, and the UV-triggered polymerization proceeds rapidly. However, this may lead to a low volume-to-surface ratio and possible oxygen degradation.

As mentioned previously, the manufacturing of CLs plays a critical role in the mechanical properties of the resulting lenses, with a study showing that when using the same CL material of PHEMA, cast molded PHEMA CLs had the highest modulus but much lower elongation. The spun cast PHEMA CLs had the lowest modulus but the most elevated break extension and the lowest penetration force. Ball milling (a method to indicate how easily a crack could take place) and tear tests demonstrated no significant differences between the PHEMA lenses manufactured by these three methods.[101]

2.5. Additive Manufacturing (3D Printing)

Addictive manufacturing, well-known as 3D printing, has been an emerging technology for the fabrication of CLs. It is time-saving and cost-effective and allows for precise

control over dimensions without surface geometry restrictions. This technique can architect structures at a microscale resolution, giving rise to functional SCLs with inbuilt sensing capabilities. As shown in Figure 3d–f, there are various types of 3D printing technologies used for the fabrication of SCLs, including stereolithographic apparatus (SLA), digital light printing (DLP), fused deposit modeling (FDM), direct ink writing (DIW), extrusion-based, and selective laser sintering (SLS).[19] While FDM and SLS are limited because of low transparency and the necessity for postprocessing treatments, light-curing-based 3D printing, such as SLA and DLP, are preferred due to high resolution of printing and minimal thickness of the printable layers.[19,41] A recent study used DLP 3D printing to manufacture SCLs using a transparent resin and achieved acceptable transmittance levels with good mechanical properties (Figure 2g). This versatility also facilitated manufacturing the lenses with various geometries, microchannels, and textured nanopatterns on the surface of the lens. Extrusion-based 3D printing was also highlighted in a recent work discussing drug-eluting SCLs as an optimally alternative to eye drops.[104] It was investigated that the 3D printing technique increased the swelling ratio, which resulted in superior control drug release compared to the lenses prepared using solvent casting.

Overall, when selecting proper fabrication techniques, it is critical to analyze various factors, such as the usage conditions, resultant desired function and cost control based on material designs, including modification, and copolymerization.

2.6. SCLs on the Market

Glass lenses were used for vision correction in the 1800s. In 1936, commercially available PMMA replaced glasses for soft CLs due to their better transparency and durability.[105] The commercial introduction of poly (2-hydroxyethyl methacrylate) (PHEMA), invented by Wichterle in 1960, facilitated the development of soft CLs,[106,107] and in 1971, Bausch & Lomb's SofLens was the first soft CL to be FDA approved.[108] This marked a milestone in the CL industry, followed by the introduction of hydrogels into SCL devices. Later, an increasing amount of CL manufacturers joined the competition for the emerging and promising CL market.[109] To date, functional SCLs and their therapeutic aims have been evolving, and major manufacturers, such as Johnson & Johnson continue to make great efforts to provide a safe and cost-effective solution to patients suffering from various ocular illnesses.

According to a recent report, the CL market revenue is predicted to grow at a compound annual growth rate (CAGR) of 5% from 2019 to 2025.[110] Although the global CL market experienced a decline of around $1409.62 million resulting from the COVID-19 outbreak, which is responsible for more than a 10% decrease in the market revenue,[110] the demand for CLs continues to grow due to the prevalence of visual dysfunctions and eye disorders across the world. The increasing demand from users for CL to restore vision dysfunctions such as myopia, hyperopia, astigmatism, corneal protection, and corneal pain relief is expected to account for the market growth in the following period.[110] In Table 2, we provided several examples of the FDA-approved CL products on the market.

In fact, beyond vision correction, emerging smart CL (SCL) wearable platforms have been flourishing recently with newly launched and patented SCL products with some examples

in Table 3. High-tech pharmaceutical companies and startups, including Google, Samsung, InWith Corp, Mojo Vision, Novartis, and Johnson & Johnson, have made progress in the SCL field. For example, incorporated with AR technology, Mojo Vision launched the AR CLs,[111] with which the wearer can gain information about the local temperature, weather forecast, and driving guidance. Another example is presented by Innovega Inc., a company that works to produce SCLs, and the eMacula CL is the example with several advantages such as light-weight, unobtrusive, and no interference with life and wearing experiences. Notably, eMacula has been under the FDA market clearance review process.[112]

It is also worthy of paying attention to patented SCLs. Based on the database from Google Patents, there has been a rise in the number of patents in the last decades when entering the term “smart contact lens.” Many SCL systems have embedded electronic components into the substrate to achieve various functions. The SCL system, filed by Aleksandr Shtukater, was granted in 2020 and presented the integration of electronic, electro-optical, or optical components on the CL substrate.[113] The design aims to track conditions affecting reflexes, including pupillary reflex or accommodation reflex, to determine pupil dilation due to mental task engagement. Another patent granted in 2021 demonstrated the design, manufacturing, and operation of an SCL AR system. Compared to traditional head-mounted VR devices that the movements may affect the quality of images, this disclosure can eliminate the movement effects and enhance the viewing angle.[114]

3. SCLs for Diagnostic Applications

Wearable biosensors have received increasing attention due to their ability to provide real-time and reliable physiological information via a noninvasive measurement of biochemical markers in biofluids, including sweat, tears, and saliva.[7] Tears can provide an excellent source of biomarkers for diagnostic purposes. Unlike complex physiological fluids such as urine and blood, tears are considered to be “cleaner.”[8] Therefore, the SCL wearable platform has been employed as a diagnostic tool to monitor ocular health. Unlike blood or urine, the concentration of biomarkers in tears is often fluctuating, in that the secretion of tears is highly dependent on the environment. The presence of lacrimation agents or irritating volatile organic solvent can result in higher tear flow[135–137] whereas drier atmospheric conditions or underlying health problems can decrease tear flow.[138–141] Furthermore, tear film composition varies during sleep due to the cornea cellular regeneration process.[142] All these factors can result in changes in the overall biochemical composition and the detectable biomarkers within tears. Hence, establishing a validation that calibrates for the dynamic environment in the eye is critical for SCL designs. In this section, we will summarize the recent advances in SCLs for different diagnostic applications.

3.1. SCLs for IOP Monitoring

IOP refers to the fluid pressure of the eye.[143] It is determined by measuring the force that the aqueous humor applies on the internal surface area of the anterior eye. The IOP is regulated delicately by an equilibrium between the production and drainage of aqueous humor to maintain the spherical structure of the eye.[144] Abrupt increases or decreases of

the IOP are clinically relevant due to the increased risks of developing pathologies, including glaucoma, uveitis, and retinal detachment.[145]

Glaucoma is identified as progressive neurodegeneration of the optic nerves.[146] It can cause vision loss, pain or discomfort, and nausea.[147,148] The major reason for glaucoma development results from obstructed drainage of the trabecular meshwork at the ocular area.[149] Consequently, the continuous build-up of IOP causes damage to the optic nerve and induces glaucoma. Hence, IOP is a significant clinical parameter for the diagnosis and therapy of glaucoma.[150] In the current clinical practice, the IOP is assessed by applanation tonometry. Applanation tonometry relies on measuring the force required to flatten a part of the cornea for a short period, estimating the pressure inside the anterior eye. However, it implicates using a slit lamp armed with forehead and chin supports and a tiny, flat-tipped cone that gently comes into contact with the cornea of the patient. Furthermore, since the equipment set-up and operation require the patient to visit the clinic and a trained operator to perform measurements, only a single measurement of IOP is performed per patient's visit. Therefore, measuring IOP in the clinic is not convincing enough for pathologies such as glaucoma. Instead, a small, operator free, and continuous IOP monitoring system is expected for advanced diagnostics of glaucoma.[151]

The IOP fluctuation range is 10–21 mmHg, with an average indicator of 15.8 mmHg for healthy people.[152] However, the IOP can exceed the normal range in glaucoma patients, leading to the corneal curvature change.[153,154] This distinctive variation creates a reliable physical marker to monitor glaucoma development. Therefore, there is an ongoing drive to develop SCL biosensors for real-time, continuous, and accurate IOP detection.[155,156]

A microfluidic strain sensor has been designed based on a camera-detectable transduction technique, for which the subtle strain changes could be converted into a fluidic volume expansion/contraction (Figure 4a).[157] This microfluidic strain sensor could achieve a 0.06% and 0.004% detection limit for uniaxial and biaxial strain, respectively, and the strain sensor was then integrated onto silicone CLs. IOP-induced strain fluctuations in porcine eyes were detected continuously for more than 19 h and a robust shelf life of 7 months was determined, indicating the sensor's long-term use potential for ophthalmic monitoring applications.

Encouraged by the advantages of volumetric amplification, passive microfluidic sensors with high sensitivity can be further optimized. The approach is promising in fostering microfluidic strain sensors in various clinical setting applications.[157] Similarly, a microfluidic SCL sensor was also engineered for power-free, continuous, noninvasive IOP monitoring based on pressure-induced volume changes.[158] Although this microfluidic system offers high sensitivity, it relies on external image processing and requires a high resolution from the readout camera. In order to address these issues, a closed-loop SCL sensor was designed to serve as a strain sensor for monitoring corneal deformation and an inductive antenna for wireless data readout.[159] The SCL device provided clinical translational opportunities for continuous IOP measurement systems with high reliability, sensitivity, and low cost.

In addition, a biocompatible PHEMA hydrogel-based SCL biosensor has been fabricated with the self-reporting ability. The CL colors would vary with the moisture and IOP changes. The moisture and IOP are the key parameters for diagnosing DES and glaucoma. Moreover, this colorimetric-based SCL sensor could be connected to portable smartphones to provide innovative ophthalmic healthcare information.[160,161] Similarly, a photonic crystal (PC)-based IOP sensor was embedded into a CL to detect the IOP variation through an integrated microhydraulic amplification system (Figure 4b).[162] The IOP changes could trigger continuous visual color changes because of the PC structures. As a result, no external battery or power source was required. The color variation could be recognized by analyzing the RGB values with a smartphone camera to achieve the quantitative IOP measurement in a non-invasive and cost-effective manner.[162]

Inspired by these works, the colorimetric sensing system could be integrated into a wearable or implantable medical device to develop next-generation diagnostic tools for healthcare applications. For example, the graphene woven fabric (GWF) is reported to be sensitive to strain change.[163,164] Therefore, the use of transparent GWF as a sensing component, without built-in complicated and costly circuits in an SCL, was developed to provide real-time IOP information,[165] indicating the promising applications to achieve future low-cost disposable wearable SCL biosensors.

Graphene nanowall (GNW) was used as another new strain gauge material to monitor IOP continuously.[166] GNWs remarkably reduced the power consumption, fabrication cost, and complexity of amplification and readout circuit with a high gauge factor, which provided another alternative to the IOP monitoring system. Graphene was also developed based on their self-assembly behavior, for which a self-assembly graphene (SAG) biosensor with excellent piezoresistive properties was integrated onto a flexible substrate.[167] A Wheatstone bridge strain gauge circuit was adopted with simulation and analysis of the correlations between corneal deformations and IOP. An SCL sensor of high sensitivity was fabricated via microelectromechanical systems (MEMS) technology (Figure 4c). Although the testing showed the SCL sensors retain data-reliable under various set conditions such as different amplitudes and the frequencies of IOP fluctuation, the wireless data transmission still needs further optimization with algorithm and processing chip. Therefore, it could avoid any adverse effects on users' daily routines.[167]

A metal electrode could serve as a strain gauge to measure the subtle deformation caused by IOP fluctuations.[168] With the transparent polyethylene terephthalate (PET) substrate, two counterpart active strain gauges were embedded into a CL. The Wheatstone circuit was engineered to increase precision and avoid temperature drift. The resultant excellent IOP responses showed promise for continuous IOP monitoring and future POC management for glaucoma patients. Even though current SCL systems can provide continuous measurements of IOP, some critical issues remain to be solved. For example, the semiconductors-based sensors are not sensitive enough to the minute IOP fluctuations, with a CL deformation of only 0.03% in tensile strain per mm Hg.[96] Besides signal quality, possible eye damage caused by rigid and opaque electric materials and bulky equipment limited the clinical use of SCLs.[96,169–172] To improve the SCL for real-time IOP monitoring, Kim and co-workers designed and tested a soft and transparent SCL to real-time quantitatively monitor IOP with

a smartphone.[96] The SCL included a strain sensor, a wireless antenna, stretchable metal interconnects, and an integrated circuit for wireless transmission (Figure 4d).[96] This SCL does not bring any adverse effect on the users' vision field due to the components that are placed outside the wearers' pupil. Rabbit models were applied for the in vivo validation of IOP monitoring, and the calibrated IOP value could be real-time and wirelessly recorded with a smartphone.

The manometry was used as a gold standard to compare with the SCL for IOP measurements, showing similar fluctuation profiles of IOP. An infrared camera was used during the lens operation to investigate the safety concerns of the SCL, such as the Joule heat generated by the electronic units. The results showed that the operating SCL temperature was kept at around 36.4 °C, because of the magnetic coupling at the relatively low-frequency band (13.56 MHz). Although a slightly higher temperature of the transmitting coil was approximately 40.2 °C, the coil did not touch the rabbit's eyes (with a gap of around 5 mm) due to the wireless design. In vivo biocompatibility was also carried out by a slit lamp examination, suggesting that the SCL could be worn for over 48 h without harming the eyes. Volunteers were also recruited for the clinical trial of the SCL wear. For example, a 28 year old female human wore this as-prepared SCL to allow real-time wireless IOP monitoring with a smartphone. After 12 h, no overt reaction of the cornea to the SCL and no conjunctivitis injection was detected, showing medical safety at the human level. Overall, the integration of manufacturing technologies combining advanced materials fabrication made this SCL possible. In the future, the soft SCL offers a noninvasive, battery-free, mobile healthcare device for the monitoring of IOP in patients.[96]

3.2. SCLs for Glucose Monitoring

The most commonly used route for glucose detection is the finger-prick method, which is used by diabetic patients to monitor their blood glucose levels on a daily basis. However, this sampling method brings pain and inconvenience,[173] which is expected to be addressed by other noninvasive approaches. For instance, monitoring the glucose level in urine, saliva, intestinal, or tear fluid is feasible to manage diabetes progression.[174] As forementioned, tears are less complicated in composition and offer abundant detectable biomarkers, such as amino acids, enzymes, and small molecules, for different diagnostic purposes.[32,175–177] Notably, a strong correlation was found between blood and tear glucose levels after carbohydrate intake.[178] In addition, based on a tear sample and blood sample collected from 30 testing subjects, there is a significant association between plasma and tear glucose concentration.[179] Sensor devices continue to show evidence of the significant association between blood and tear glucose levels.[180–182] However, the correlation between blood and tear glucose concentration was questioned during the attempt to distinguish between diabetic and nondiabetic individuals using tear glucose levels. Later, this inquisition was further fueled by the hiatus of the Verily-Alcon SCL program claiming a lack of correlation between tear and blood glucose.[183] Here, it is essential to clarify, despite their inability to make a clear distinction between diabetic and nondiabetic individuals using tear glucose level, it does not equate to a lack of correlation between tear and blood glucose. Verily-Alcon's SCL program clearly stated that the reason for failing was the small quantities of glucose and other contaminants. If future SCLs can resolve the fourth-mentioned issue,

they can still be adopted for diabetes diagnosis. Hence, in this section, we highlight the most recent advancement made of SCLs in glucose detection. The recent technological advances in wearable bioelectronics have enabled the continuous monitoring of tear glucose levels.[184] However, the opaque, brittle electric units may interfere with the wearer's vision and trigger eye damage. To address these concerns, Park and co-workers fully integrated glucose sensors, wireless power transfer circuits, and a signal-visualizable light-emitting diode (LED) display into a transparent and flexible CL (Figure 5a).[38] The system could operate properly under mechanical deformations by molding the integrated components to the SCL for the fabrication process. Besides, the molding method can be combined with conventional photolithography and vacuum metallization, indicating mass production ability. The in vivo test proved to be safe and a fast signal-to-result transformation for glucose level monitoring via glucose oxidase (GOD) surfaced modification.

Glucose monitoring this SCL showed substantial promise for future non-invasive healthcare diagnostics via the tear fluid.[38] Graphene is attractive because of its structural uniqueness and excellent electrical performance, and the glucose sensor has been fabricated based on the graphene field-effect transistor (G-FET).[185] However, concerns about the mechanism and the fabrication techniques of G-FET devices still exist. Most G-FET devices are based on the enzymatic reaction, which may cause problems with their accuracy and stability. They are usually constructed on rigid substrates such as glass, which limits their wearability. [185] With the improvements in materials and fabrication techniques, Zhi et al. developed a wearable pyrene-1-boronic acid (PBA)-based G-FET glucose sensor with a wide detection range, a high sensitivity, and a low detection limit, opening up opportunities for G-FET sensors for other body fluid diagnostic developments and applications.[185]

Another example is a biocompatible nanoparticle embedded CL (NECL), developed by incorporating GOD and cerium oxide (III).[186] Through reflectance spectrum analysis and the established correlation of the reflection spectrum with the known glucose level, the NECL offered a noninvasive glucose monitoring technique to develop future SCL biosensor devices for glucose level monitoring.[186] A photonic microstructure-based SCL sensor was developed with a direct-stamping approach on the glucose-responsive hydrogel surface to overcome the time-consuming calibration and instability issues present in the electrochemical sensors.[187] This hydrogel sensor could be attached to the CL surface and showed efficient feedback to the glucose changes in the form of diffraction wavelength changes, which offered a facile fabrication strategy and allowed smartphone readouts.

Surface-enhanced Raman scattering (SERS) has also contributed to the SCL advances. [188–190] For example, Lee et al. constructed a multilayered structure that could detect glucose levels through SERS. On this SCL, a layer of protective film was embedded with AgNWs. 4-mercaptophenyl boronic acid (MBA) was covalently coated to the AgNW network. The AgNWs were further covered with a silk fibroin (SF). The SF acts as a sieve layer, allowing glucose to diffuse to the 4-MBA modified AgNWs. The interaction of glucose and 4-MBA molecules was detected using Raman spectra due to the SERS enabled by the AgNWs. The developed SERS-CL exhibits excellent glucose sensing performance in the concentration range of 500×10^{-9} to 1×10^{-3} M, and the limit of detection of 211×10^{-9} M. Volunteers' glucose data were collected before and after a meal, proving the

potential use of the SERS for developing noninvasive tear glucose monitoring integrated systems, and also for the broader applications for other biofluidic metabolites and chemical biomarker monitoring.[188]

One of the classic approaches in glucose sensors is through an electrochemical platform. A real-time tear glucose sensor was developed in a combination with electrically controlled drug delivery units (Figure 5b).[94] Three electrodes were integrated with low chemical resistance during the electrochemical glucose reaction. In this design, the working electrode (WE) and the counter electrode (CE) were fabricated with platinum (Pt) to achieve sufficient efficiency of the electrochemical glucose reaction. To increase the adhesion between polyethylene terephthalate (PET) substrate and Pt, a chromium (Cr) layer was predeposited on the PET substrate. For the reference electrode (RE), a silver/silver chloride (Ag/AgCl) mixture coating was applied to obtain the accurate amperometric electrochemical glucose sensor. A mixed solution of chitosan and PVA hydrogel co-immobilized with glucose oxidase and bovine serum albumin (BSA) was coated on the WE to accomplish the sensitive and stable tear glucose monitoring. With the correlation confirmed between blood and tear glucose levels, the SCL displayed a strong diagnostic potential for medical applications in measuring tear glucose levels.[94]

Besides the ability to detect a single biomarker, a multifunctional wearable SCL was designed to measure tear glucose level and IOP simultaneously.[172] The graphene/AgNW-based SCL ensured the users' comfort and clear vision with excellent transparency and stretchability. The real-time in vivo glucose detection and in vitro IOP monitoring performance were confirmed with a rabbit and a bovine eyeball. Holding the potential to incorporate multiple sensing units, the SCL wearable platform could enable noninvasive, wireless, and real-time continuous biomarker detection and monitoring for a vast range of ocular diseases.[172] Recently, Guo et al. reported a multifunctional SCL platform, which integrated three sensor systems to perform multiple functions with flexible electrical interconnections. Specifically, the integrated sensors could achieve glucose detection as well as temperature sensing, which could offer essential ocular diseases-related healthcare information (Figure 5c).[35] The integrated ultrathin MoS_2 transistor and the gold wire-based sensor system with direct eye contact provided high detection sensitivity through a facile fabrication process. Besides strong mechanical robustness and excellent stretchability, the thin serpentine mesh structure ensured wear comfort and visual transparency.

From fabrication to utilization, the integrated SCL system has inspired researchers to develop SCL platform systems with more advanced functional components and implant them for in vivo applications. Google and Novartis International, in 2014, have jointly announced the futuristic project to design, develop and commercialize SCL platforms for diabetes, where the wearables are expected to free diabetes patients from painful finger pricks to track glucose levels.[183]

3.3. SCLs for Ocular Electrolyte Analysis

The electrolyte concentrations and pH values of ocular microenvironments have been correlated to several ocular diseases. For example, in a patient with DES, the pH value of tear could increase to 7.9 compared to the pH value of healthy ocular fluid around 7.4. In

addition, the sodium ion (Na^+) concentrations can also be increased for patients with DES.[191,192] Therefore, it is essential to develop biosensing systems that monitor the electrolyte concentrations and pH values of the ocular microenvironment to provide timely and accurate guidance for patients with ophthalmic diseases. Accordingly, a variety of SCL biosensors have been engineered to detect changes in pH and ion concentration. To achieve biosensing capabilities, bioactive molecules have been incorporated into SCLs. For example, Riaz and co-workers used naturally-derived anthocyanins that can undergo chemical conformational changes with various H^+ concentrations/pH values to fabricate a biocompatible SCL pH sensor. The SCL sensor showed a systematic color shift as a function of pH value change.[193]

Microchannels have not been widely adopted in commercially available hydrogel SCLs because they are difficult to fabricate using conventional manufacturing techniques.[53] Nevertheless, microchannels may serve as a significant component of SCLs. For example, microchannels in PHEMA hydrogels have been developed incorporating colorimetric-based pH and Na^+ sensors to monitor tear osmolarity for the diagnosis of DES.[53] This work has shown great promise in promoting the micromachining of commercial PHEMA hydrogel SCLs for further biosensing and drug delivery applications. Similarly, Moreddu and co-workers reported a wearable SCL biosensor engraved with microchannels for in situ tear pH, nitrite ions, and glucose sensing.[194] The pH sensor demonstrated a sensitivity of 12.23 nm per pH with a LOD of 0.25 pH variation.

Another example was the integration of paper microfluidics within the laser-inscribed commercial CLs, achieving the detection of various biomarkers, including H^+, glucose, and nitrites. The current tear sampling procedure, which uses Schirmer's paper strip inserted into the lower eyelid for 5 min, has been reported to have contamination risks of eyes and induced tear overflow.[76] To extend the in situ tear fluid analysis, Moreddu et al. explored the multiplexed integration of the paper microfluidics in wearable devices to monitor clinically meaningful biomarkers.[195] Incorporating paper-based microfluidic components into the SCL device, this design can prevent leakage and facilitate capillary flow (Figure 6a). The biosensor was eventually chemically bonded to a PHEMA SCL device with an inlet designed for tear fluid flowing from the concave surface into the microchannel. Besides, a readout platform via a mobile phone has been established for data processing.

It is widely agreed that measuring total tear osmolarity is the most suited for DED diagnostics. However, not all ionic concentrations can be measured during the test.[196] A hydrogen ion (H^+)- and chloride ion (Cl^-)- selective SCL biosensor was engineered based on silicone hydrogel to address the concern.[196] Similarly, Yetisen et al. reported a scleral SCL sensor for quantitative analysis of the tear ion compositions (Figure 6b).[197] Instead of complete surface modification of the SCLs, this work designed a microreaction chamber in the lens with ion-responsive dye for ion-sensing such as H^+ (pH), Na^+, K^+, Ca^{2+}, Mg^{2+}, and Zn^{2+}. Our group has also demonstrated the application of PHEMA hydrogel-based CL for monitoring pH via ion-sensitive dyes. Microchambers were integrated into the PHEMA structure and were modified with pH-sensitive dyes, that changes color with different pH levels ranging from 5 to 7.5 (Figure 6C). Finally, various ion probes such as benzenedicarboxylic acid, crown ether derivatives, etc., were incorporated to serve the

corresponding ion-detecting roles. The representative ion-sensitive probes, along with their sensitivity and detection range are provided in Table 4.

Overall, ion and pH sensing remain limited to incorporating color changing or fluorescence changing probes into the SCL. However, the ion-selective field-effect transistor (FET) sensors have been reported to record electrophysiological signals[198] and have also been desired to be explored for ocular biomarker detections. Based on previously discussed FET sensors for IOP and glucose monitoring, it is likely to see FETs adapted into pH and ion sensing.

3.4. SCLs for Hormones, Enzymes, and Cytokine Monitoring

In addition to monitoring physical parameters, such as IOP and ocular electrolytes. Monitoring of other physiological biomarkers, including hormones, enzymes, and cytokines are gaining momentum under the SCL wearable platform.[8,10,13,76]

For example, cortisol, a steroid hormone also known as a stress hormone, is secreted by the adrenal glands and can be triggered by psychological or physical stress.[200] However, chronic stress can introduce abnormal secretion of cortisol, the accumulation of which increases the concentrations of fat and amino acids. This, in turn, can lead to several diseases, such as cardiovascular complications, diabetes and anxiety disorders.[13,201–203] Thus, monitoring cortisol levels is believed to be correlated with the quantitative analysis of individual stress levels. Although cortisol detection system in various samples (blood, sweat, and interstitial fluid) has been developed, biological instability caused by temperature, mechanical stress, and inconvenient external equipment hindered measurement accuracy and used mobility.[13] Therefore, it is essential to explore the noninvasiveness and wearability of the biosensors for the purpose of wirelessly monitoring the cortisol concentration in real time with high precision.

With the rapid advances in smart bioelectronics, the tear fluid containing cortisol has been explored as a promising sampling area.[10] Ku and co-workers first reported the methods to fabricate an SCL device for sensing the tear cortisol. The composition of the SCL device includes a cortisol sensor based on a graphene FET sensor, an antenna for real-time wireless data transmission, and the integrated circuit, all without any interference with the clearance of the users' view (Figure 7a).[13] Human pilot trials and in vivo rabbit models' validation were conducted, confirming the biocompatibility of the SCL device. Besides, remote wireless data transmission provided the convenience for the wearer to obtain cortisol levels in real time. Driven by this work, in the future, more SCL wearable platforms capable of monitoring multiplexed vital biomarkers in tear fluids are greatly anticipated.

The rise in chronic ocular surface inflammatory (OSI) diseases and the lack of adequate approaches to screening and responding to OSI treatment have spurred further improvement in diagnostic methods.[204,205] Jang et al. developed an SCL wireless system that could remotely monitor and digitize the chronic OSI levels based on quantitative analysis of matrix metalloproteinase-9 (MMP-9), known as a typical OSI biomarker.[206] Compared to several commercial medical devices, such as the LipiFlow thermal pulsation system, this newly reported SCL device is portable and visually precise, making it easy for daily use by

patients.[207–209] The graphene FET biosensor was fabricated from graphene functionalized with the F(ab')2 region of an anti-MMP-9 antibody levels to measure the MMP-9 levels in the tear fluid. The hybrid electrodes were constructed by graphene and AgNW networks to achieve excellent transparency and stretchability[206] (Figure 7b,c). The quantitative measurements of the MMP-9 concentration from tear fluids allowed timely and accurate identification of the underlying risks of eye inflammation. Besides, aging tests proved the long-term use of the SCL system for patients, demonstrating that the SCL platform could diagnose chronic OSI in clinical applications.[206]

It is worth noting that the SCL device has been developed as a theranostic platform to modulate and detect viral infections.[210] For example, Mak and co-workers engineered a theranostic SCL device via a layer-by-layer technique, which showed excellent optical transparency, satisfactory surface wettability, and good biocompatibility. Though a proof-of-concept, the developers demonstrated the capability to measure the cytokine and interleukin-1α (IL-1α) that are unregulated during herpes simplex virus type 1 (HSV-1). This work exemplified the potential of SCLs as a theranostic platform, which is a concept of great relevance, especially during the current COVID-19 pandemic.

On the implantable spectrum of SCL biosensors for protein biomarkers in tears, Shin et al. presented an implantable biosensor towards MMP-9, which is tied to neurodegeneration and eye disorders.[211] The intraocular lens (IOL) sensor described here was fabricated through cross-linking polyethylene (PEG) bases acrylamide to form a hydrogel, then MMP-9 degradable fluorogenic peptide conjugated was combined into the IOL gel matrix. In the absence of MMP-9, the quencher attached to the peptides suppressed the fluorescence signal. When MMP-9 was presented, it cleaved the hydrogel conjugate peptides, resulting in detectable fluorescence (Figure 7d). The sensor demonstrated a LOD of 4.02×10^{-9} M in the detection range of 0–20×10^{-9} M toward MMP-9. Compared to the previous CL sensor structure, the IOL hydrogel base CL sensors here are more invasive and require surgical intervention. However, the peptide conjugated sensing approach is interesting and can quickly be adapted to measure other protein targets.

In conclusion, the SCL biosensor has been promising to accelerate the next generation healthcare platform for IOP, glucose, ion, and other biomolecular sensing. However, despite extensive investigations of the SCL wearable platforms, challenges remain in material designs, fabrication techniques, and future commercialization. Furthermore, the selection of appropriate biomarkers to diagnose specific diseases and subsequent therapeutics is also critical to the whole process of diagnosing SCL wearers. Driven by intensive research worldwide, we envisage that the ocular biosensors will become a powerful diagnostic tool in the near future.

4. SCLs for Therapeutic Applications

CLs have been approved as medical devices by the US Food and Drug Administration (FDA)[10] and used to correct refractive errors in approximately 150 million wearers worldwide.[76,212] The therapeutic applications of SCLs have been explored to achieve topical sustained drug release and to heal corneal wounds.[74,213,214] Compared to

conventional approaches to treat ocular illnesses with eye drops or ointments, SCLs can achieve better patient compliance and controlled drug delivery at the target sites through direct and continuous contact with the treated areas.[215] Furthermore, the global SCL market is projected to reach over 19 billion US dollars by 2024,[76] indicating promising research potentials towards clinical translations. However, even with advances in various applications, concerns about the side effects of wearing SCLs,[216] such as allergies,[217] microbial keratitis,[218,219] CL acute red eye,[220] SCL-induced peripheral ulcer,[221] and other unfavorable side effects remain.[76,213] Therefore, it is indispensable to develop SCL devices with both the desired physical and biological properties to achieve therapeutic efficacy and bench-to-bedside translations. The following section discusses the fundamental properties of therapeutic SCLs, summarizes recent advances in the research field (Table 5), and focuses on potential clinical translations.

4.1. Fundamental Characteristics of SCLs for Therapeutics

Therapeutic SCLs should be comfortable for users, physiologically stable, durable, and transparent. To ensure ocular safety, the biological evaluations should be biocompatible, no/low immunogenicity, and no/low cytotoxicity to the wearers. Precisely, among the various factors that should be evaluated, one biocompatibility consideration is the biological response to the mechanical failure of the devices.[249] Accordingly, it is crucial to evaluate the fundamental characteristics of SCLs, such as mechanical and biological properties, to develop SCLs as therapeutic medical devices.

4.1.1. Physical Properties—The geometric design is critical for personalized SCL products because the surface morphology of the eye can vary from individual to individual. As for the mechanical properties, the wearers' comfort is influenced as it affects the tear exchange and oxygen permeability between the corneal epithelial cells and the surrounding air.[10,250] Besides, the clarity of vision, wearability, and durability are important considerations when designing SCLs. The geometric design of SCL should include several parameters that are consistent with current optically correcting CLs; base curve radius (BCR) refers to the curvature of the back surface of an SCL in the range of 8–10 mm. The proper BCR promotes fluid and gas exchange between the corneal tissue and the surrounding air, ensuring patient comfort with a proper fit between the cornea and the SCL. For reference, the size of the average eyeball measures approximately 24.2 mm in the transverse, 23.7 mm in the sagittal, and 23.4 mm in the axial directions.[251]

A center thickness (CT), usually around 0.1 mm, refers to the consistency between the inner and outer surfaces through the central axis of the SCL. Combined with material-dependent oxygen permeability levels, CT serves as a determinant of the oxygen transfer flux to corneal tissue. Factors related to the mechanical properties of a CL, including its ability to resist applied stress (compression, tensile, or shear) and coefficient of friction (CoF), serve essential roles in the SCL performance. Optical properties, such as optical transparency and refractive index, can significantly affect the visual performance of SCLs. Therefore, the physical properties should be considered as the top priority while developing therapeutic practices of the SCL.

4.1.2. Biological Evaluations—Biological assessments of any medical devices such as an SCL should be fully studied due to its direct or indirect contact with body issue. Several material factors may affect the biological system's response to the assistive SCL, including its water content, wettability, and oxygen permeability. Water content and wettability would influence the microbial adhesion onto the lens surface and the ability to keep good contact with physiological tear fluid, respectively.[213,252] Oxygen, as the critical health factor for the corneal to prevent microbial invasion,[253] should be easily transmissible and transferable between corneal epithelial cells to avoid hypoxia-related complications.[213]

Biocompatibility, defined as the ability of a medical device or biomaterial to perform with an appropriate host response for a specific application,[249,254] is one of the most critical factors in engineering SCLs. Inappropriate materials and application methods may cause toxicity to corneal epithelial cells and trigger severe immune responses.[213] Hence, both in vitro and in vivo tests should be performed at an early stage of development to evaluate the safety and corresponding therapeutic effects.

The International Organization for Standardization (ISO) has developed and published regulations for medical devices.[255] Without enforcement to comply with ISO standards, corporations adopt ISO requirements to meet product commercialization. ISO 10993–1 indicates that SCLs are classified as direct contact devices due to their physical contact with body tissue. In other words, marketability is only possible after complete supervision and audit of safety, function, and reliability.[256] Issued in September of 2020, entitled: Use of International Standard ISO 10993–1, "Biological evaluation of medical devices-Part 1: Evaluation and testing within a risk management process," this document specifically sets out the requirements for the biological evaluation of sterile and non-sterile medical devices that come into direct or indirect contact with the human body.[249] The considerations that should be examined include evaluation of cytotoxicity, sensitization, hemocompatibility, pyrogenicity, genotoxicity, and degradation.[249] Because mechanical failure could alter the biological responses to a medical device, biocompatibility testing should investigate changes during the use of material properties, such as geometric and/or physiochemical, on biological system response.[249] Consequently, it is essential to study the fundamental mechanical and biological properties of a SCL prior to developing therapeutic functions.

4.2. Applications of SCLs for Therapeutics

4.2.1. Treatment of Glaucoma—Glaucoma is the leading cause of blindness worldwide due to irreversible progressive optic neuropathy,[257,258] and may affect approximately 112 million people by 2040.[257] The main treatment for glaucoma is to reduce IOP.[258] The commercially available formulations for the treatment of glaucoma either have difficulty crossing the blood-retinal barrier or possess low bioavailability.[143] As a result, various therapeutic platforms such as microneedles, nanoparticles, and SCLs have been developed to achieve better drug effects in the treatment of glaucoma.[143]

Layered double hydroxide (LDH) nanoparticles have gained significant attention for their applications in drug-eluting biomaterials.[259] However, drug delivery systems based on LDH nanoparticles confront undesired aggregation[260,261] and uncontrolled drug release.[262] To overcome the drawbacks, Sun and co-workers have developed the

brimonidine@LDH thermogel (Figure 8a), an SCL drug delivery system based on poly (DL-lactic acid-co-coglycolic acid)-polyethylene glycol-poly (DL-lactic acid-co-coglycolic acid) (PLGA-PEG-PLGA) loaded with Bri.[226] The soft lenses are formed by applying Bri@LDH thermogel solution to the ocular surface. The proposed drug release mechanism is that when the tear film solution is hydrated, Bri is released from the LDH nanoparticles into the thermogel matrix and then diffuses from the matrix into the tear film solution. In vitro and in vivo experiments confirmed the efficacy of sustained brimonidine release to reduce the IOP for glaucoma treatment.[226]

In another study, nanopores were embedded into an SCL device and used as a drug reservoir.[231] The soft CL requires no electrical power and can be used to measure IOP and detect glaucoma biomarkers, while simultaneously extending in situ drug delivery and release. Besides, this device was the first to accomplish the three applications in a single all-in-one device.[231] Later, continuing their nanopore-embedded work, the same group reported an SCL device with incorporated microtubes (μ-tubes) to achieve successful drug release based on diffusion and IOP-triggered mechanisms (Figure 8b,c).[230] This device features self-adaptative timolol-controlled release using the IOP as the release trigger. This tactic helps reduce drug-related side effects and provides safer therapies.[230] In another example, timolol was chemically coupled to the starting material of SCL via a photocleavable caged crosslinker. This study showed that drug release could be successfully mediated by daylight (Figure 8d).[229] With several advantages such as optically triggered drug release, lower dose use compared to eye drops, and lower cost, this technology broadens the potential of developing integrated SCLs for therapeutic applications.[229]

4.2.2. Treatment of Corneal Melting—Corneal melting is caused by the uncontrollable and excessive degradation of corneal tissue and is related to several ocular diseases, such as ulcerative keratitis and Sjögren's syndrome.[263,264] Various factors, such as eye surgical procedures, chemical burns, and improper treatments of ocular diseases, would increase the risk of corneal melting, which can ultimately lead to loss of vision.[246] To date, there are various ways of treating patients with corneal melting, such as steroidal anti-inflammatory drugs, tissue adhesives, amniotic membrane transplantation, and corneal transplantation. However, there are no satisfactory techniques for curing corneal melting.[246,265] To tackle this area, Chelsisi and co-workers developed a hydrogel therapeutic SCL that inhibits the corneal melting process by inactivating zinc-dependent MMPs (Figure 8e). Dipicolylamine (DPA) was selected to form DPA-conjugated PHEMA (pDPA-HEMA) hydrogels for zinc ion removal.[246] Although few studies have developed therapeutic SCLs to treat corneal melting, this investigation provides an option and inspiration for researchers to work on these challenging research subjects.

4.2.3. Treatment of Ocular Inflammation—The inflammation of the eye can occur on the cornea or inside the eye and may cause vision loss or even blindness.[242] Ocular inflammation could be caused by several issues such as trauma, allergies, and infections. The most widely applied method to treat ocular inflammation is to take eye drops on a regular basis. However, the required frequent administration of eye drops leads to low patient compliance and difficulty teaching the treated eye site, which can result in undesired

side effects.[242] Hence, to overcome such issues, SCLs have appeared and attracted a lot of attention for delivering therapeutic effective drugs to the site of reaction, and various drug delivery/eluting SCL studies have been carried out to treat ocular inflammation. [79,234,242,266]

Bacterial and fungal keratitis inflammation can occur when SCLs are contaminated by pathogenic bacterial and fungal strains.[79] Therefore, antifouling and antimicrobial properties are highly desired for SCL application. A prototype antifungal SCL was engineered by embedding econazole in PLGA to achieve extended antifungal activity. [267] The coated SCL has been reported to exhibit significant antibacterial (>$\log_{10}$ 5.60), antifungal, and antibiofilm performance against (bacterial keratitis) BK-causing multidrug-resistant bacteria and fungal keratitis (FK)-related pathogenic fungal strains.[79] The SCLs also showed good antioxidant, biocompatibility, and wettability characteristics.

Another case of an antibacterial coating on the SCL surface was achieved via a layer-by-layer (LbL) electrostatic self-assembly method.[268] The positively charged sodium tripolyphosphate (CTVNP) was applied for LbL deposition with negatively charged heparin (HEP), generating a multilayered $(HEP/CTVNP)_n$ structure.[268] In vitro and in vivo antibacterial experiments have shown a therapeutic effect on keratitis treatment without influencing light transmittance and patient vision.[268] Based on the fact that the conventional therapeutic method by using eye drops for treating keratitis is limited due to low bioavailability for specific eye tissues. Huang et al. designed a hybrid hydrogel-based SCL composed of quaternized chitosan (HTCC), AgNPs, and graphene oxide (GO), which endowed anti-microorganism properties.[233] These chemical components also achieved great hydrophilicity for hydrogel formation, served as a drug carrier, and aided in sustained drug release to increase antibacterial and antifungal ability.[233]

Conjunctivitis occurs with the dilatation of the conjunctival vessels that can cause hyperemia, chemosis, lid edema, and the typical eye discharge.[269] It is commonly seen among red-eye patients in adults and children in the US.[102] This illness can be caused by allergens, irritants, bacteria, and viruses, such as the coronavirus that causes the common cold and COVID-19.[270] The typical therapeutic approach involves the use of eye drops, which are inefficient due to the low drug residence time of the tear fluid and poor ocular bioavailability.[271] Therefore, it is desired to develop a feasible approach to overcome the weak efficacy of eye drop therapeutics to combat conjunctivitis.[102] Drug-loaded SCLs have been considered a suitable alternative to eye drops and have received much attention for their excellent performance and biomedical applications.[234] Li and co-workers developed a PHEMA/β-CD-crHA hydrogel with the ability to reduce tear protein adsorption and bacterial adhesion. In the in vivo treatment of conjunctivitis using rabbits, the SCL showed excellent drug encapsulation, sustained drug release capability, and therapeutic effects on ocular inflammation.[234] Similarly, to suppress protein and bacteria adsorption, Ogawa and co-workers developed an SCL platform to prevent and treat ocular diseases with a drug loading capacity.[232] In order to introduce pranoprofen, a hydrophobic drug for allergic conjunctivitis, into the SCL system, a “hot-melt press method” was innovated, and the sustained drug release has been proved to be workable. This development is expected to

improve the quality of life of the SCL wearers and prevent and treat the progression of allergic conjunctivitis.[232]

Furthermore, wearable bioelectronic devices are incorporated with the SCLs to achieve real-time monitoring and therapy of ocular diseases.[94,243] Keum et al. reported a smart medical SCL device that measures and treats diabetic retinopathy in real time.[94] Using a graphene field-effect transistor that continuously measures the concentration of a biomarker (MMP-9) for OSI, these therapeutic SCLs are stretchable for human eyelid design. It is designed to be transparent and can connect to smartphones for wireless communications. The proof-of-concept has been demonstrated by in vivo experiments and a human pilot trial.[243] These works demonstrate how combining bioelectronic monitoring with therapeutic functions can inspire the next-generation multifunctional SCLs to improve personalized healthcare.

4.2.4. Treatment of Cataracts—Opacification of the lens, known as cataracts, is the leading cause of vision loss globally and has been considered an intractable social concern due to the rapid growth of the human population and the increasing public expectations toward better quality of life.[272] Various factors may induce cataract formation, such as aging, trauma, metabolic disorders, and drug-induced changes.[272] However, except for surgery, there is still no effective method to treat cataracts.[244,273] A drug delivery system for cataract treatment based on CLs is highly desired with improved ocular bioavailability.[274,275] However, the drug loading may alter properties of CLs such as swelling, optical transparency, and oxygen permeability.[276–279]

To address this issue, Zhu and co-workers, first reported Pluronic F68 stabilized pegylated solid lipid nanoparticle-laden SCLs to deliver hydrophobic Epalrestat to the anterior and posterior segment of the eye for the treatment of diabetes-related cataracts and diabetic retinopathy.[241] Intraocular lens (IOL) modification is considered a viable strategy to prevent posterior capsular opacification (PCO),[280,281] the most common complication of cataract surgery.[273] However, it is challenging to maintain the refractive properties of the IOL and avoid possible damage to intraocular tissue. Zhang et al. reported a drug-eluting IOL using PLGA with sustained bromfenac release to prevent posterior capsular opacification (PCO) development using ultrasonic spray technology.[244,273] In this study, bromfenac was used for PCO prophylaxis; bromfenac can inhibit TGF-β2-induced lens epithelial cell migration and EMT by regulating ERK/GSK-3β/Snail signaling, an important pathological mechanism involved in the development of PCO. The bromfenac-eluting IOLs were engineered and implemented for cataract surgery. This design is effective in PCO prevention and has been demonstrated to be biocompatible for in vivo experiments, showing great potential for future clinical applications.[244]

4.2.5. Treatment of DES—Keratoconjunctivitis sicca, also known as DES, is a common medical complaint because it causes discomfort to patients[282] due to low tear production and/or excessive tear evaporation.[283] In practice, eye dryness can be associated with Sjögren’s syndrome, allergies, infection, blepharitis, and preservative-containing eye drops.[284] Besides, DED is one significant cause of persistent corneal epithelial defects (PEDs), among the other three causes, including keratoplasty, chronic infection, and limbal stem cell

deficiency.[285] However, for conventional dry eye treatments with eye drops, these methods always experience a short residence time (≈ 5 min) and low bioavailability (≈50%). To address the above shortcomings limiting applications, higher doses of eye drops have been advocated, despite the increased risk of side effects.[239] Therefore, it is beneficial to explore effective therapeutic medical devices for ocular diseases.

In the past decades, wearable SCLs have been investigated for treating DES.[237] However, the uncontrollable initial burst release of drugs from the SCL remains to be addressed to achieve constant and sustained drug release. Elham and co-workers reported a therapeutic SCL system based on hyaluronic acid (HA)-loaded chitosan nanoparticles (CS NPs) in a ring-implanted CL to achieve sustained HA release for treating DES.[239] The stepwise design for the CL fabrication, from preparing HA-loaded CS NPs to embedding CS NPs into a PVA implant ring to incorporating the ring into the PVA-based hydrogel CLs, has proven effective for controlled HA release for up to 14 d.[239]

Regarding the mechanism of DED, it is reported that T cell-mediated inflammation at the ocular surface and periocular tissue could cause this disease.[286] Lifitegrast has shown the ability to lower T-cell activation, reduce cytokine release, and mitigate downstream inflammatory processes.[287] Mu et al. achieved controlled and sustained drug release upon exposure to indoor/outdoor daylights by binding lifitegrast throughout the hydrogel polymer of CL via a photolabile crosslinker. Apart from the therapeutic applications of the SCLs, they are highly effective in protecting the retina from harmful UV-A1 wavelengths.[238] Molecular imprinting technology has received great attention as a contribution to advances in drug delivery in therapeutic SCLs.[288–290] Works with sustained HA release ability (>24 h) have been reported based on the molecular imprinting technology. The SCL device can improve the ability of HA delivery to the eye surface to achieve the treatment of the dry eye symptoms.[240]

4.2.6. Treatment of Diabetic Retinopathy—Diabetic retinopathy (DR), a microvascular disease, is a common complication of diabetes mellitus (DM) and a leading cause of vision loss among the population.[291] The development of DR can be divided into two stages: non-proliferative diabetic retinopathy (NPDR) and a more advanced pathological stage, proliferative diabetic retinopathy (PDR), wherein the patient may experience severe vision impairment.[291] Throughout the course of DR, diabetic macular edema (DME), which is the swelling or thickening of the macula, may cause vision loss.[292] The use of SCLs is well established as a noninvasive means to work at the site of action of the eye.[293]

Among various methods of monitoring and treating diabetic retinopathy, soft bioelectronics has been widely explored due to the unique properties of polymers fabricated for wearable and implantable healthcare devices.[294,295] Keum and co-workers engineered a remotely controllable SCL to implement a wirelessly powered controlled drug delivery system that provides real-time noninvasive glucose monitoring for diabetic retinopathy.[94] A set of control and comparator groups was established to demonstrate the therapeutic effect of genistein-loaded SCLs on diabetic retinopathy. The results indicated the feasibility of the as-designed medical device for genistein delivery to the eye.

Based on the well-known properties of the vision system, the retinal oxygen consumption is highest in the dark. In order words, retinal metabolism increases at night.[296] However, diabetic patients tend to develop severe hypoxia in the retina at night, which promotes progressive retinopathy.[296] Accordingly, Cook et al. reported the first phototherapeutic SCL to suppress rod cell dark current, thereby lowering retinal metabolism and combatting diabetic retinopathy.[293] With the success for the SCL applications, multifunctional SCL devices are expected to be investigated for next-generation wearables that can achieve the real-time monitoring of biomarkers and on-demand drug release for diabetic retinopathy medication in patients.

4.3. Responsiveness Strategy in Ocular Therapeutics

Among the various designs and applications of functional biomaterials, stimuli-responsive polymers have been widely investigated as they are sensitive to certain triggers from the external environment, including temperature, pH, and light. Therefore, the design principles and synthetic routes in achieving stimuli-responsiveness should be well considered for future applications and potential clinical prospects. In this section, we summarize the stimuli-responsiveness strategies for developing therapeutic SCLs as well as the excellent clinical values of stimuli-responsive SCLs for therapeutic applications.

4.3.1. pH-Responsive Drug Releasable SCLs—During bacterial infections, the microenvironment of the eyes becomes more acidic.[297] Therefore, pH-responsive antibiotic (gentamicin sulfate, GS)-loaded SCLs can be an effective prophylactic/therapeutic strategy through reversible implantation of antibiotics based on Schiff base reaction to prevent severe bacterial infection.[68] The antibacterial property was imparted via self-assembly of the antibiotic-loaded ALG-GS/PEI (polyethyleneimine) multilayer films coated on the lens surface. Five cycles of GS loading and release testing demonstrated excellent ability to maintain drug loading capacity on the multilayer films.[68] The GS was bound to AI-ALG through dynamic chemical bonding that could load and release drugs in neutral and acidic environments. Both in vitro and in vivo antibacterial assessments showed the intelligent bacterial-cased pH-triggered drug loading and delivery processes.

Eudragit S100 is a pH-sensitive anionic copolymer consisting of MAA and MMA with a free carboxyl to the ester groups ratio of 1:2. This polymer has been used to construct pH-responsive therapeutic SCLs.[223,236,247] For example, a blended film of cellulose acetate and Eudragit S100 was adopted as the inner layer and silicone hydrogel was used as the outer layer to construct internal layer-embedded SCLs.[223] Similarly, an inner layer-embedded SCL consisting of a film blended with ethyl cellulose and Eudragit S100 as the inner layer and PHEMA hydrogel as the outer layer was engineered. The pH-responsive drug-eluting mechanism allows the inner layer-embedded SCL to be stable and storable in PBS (pH = 6.8) without drug loss. An in vivo study in rabbits showed sustained drug release in tear fluid for over 12 h, indicating the practicability of the drug delivery platform for ocular therapeutics.[247] Another approach loaded pH-sensitive cyclosporine-loaded Eudragit S100 nanoparticles into SCLs to obtain sustained cyclosporine release for the treatment of several ophthalmological diseases, including DED.[236]

4.3.2. Light-Responsive Drug Releasable SCLs—Combined with rapid advances in chemical and material sciences, biomaterials research and development have fueled growth in drug delivery, cell biology, microdevices, and tissue engineering.[298] In addition to the precise control of material synthesis and desired applications, an increasing amount of attention has been paid to control material properties over time and space changes by external triggers (e.g., light).[299] An attractive energy source, light has been used in modern medicine to treat skin-related illnesses.[300] Among various light-dependent innovations, photo-responsive biomaterials in biomedical engineering have been advanced for controlled therapeutic applications.[301,302] In the development of therapeutic SCLs, daylight serves an essential role in sustaining drug release for the treatment of ocular diseases (Figure 9a). Two different photo linkers, dimethoxy-substituted 2-nitrobenzene and 4-[4-(1-hydroxyethyl)-2-methoxy-5-nitrophenoxy] butyric acid, were adopted as the photo-linkers to link timolol and lifitegrast, respectively in these SCL systems. Both drugs can be released when exposed to daylight with a wavelength of 400–430 nm, which triggers a bond cleavage reaction, passively releasing timolol and lifitegrast into the surrounding body fluids.[229,238] Consequently, the future opportunities and challenges to develop photoresponsive therapeutic SCLs may arise from multifunctional integrated manufacturing, starting from the designs of materials and more drug screening with the photoliable properties for ocular disease treatment.

4.3.3. Thermoresponsive Gelling System for Localized Ocular Drug Release —Because of physical blinking and fluid on the surface of the eye, many drugs applied to the ocular surface cannot be well maintained, making them inefficient for treating eye diseases.[303] Therefore, other approaches, such as in situ gelation systems, have been reported for local ocular drug delivery.[304] However, gelling droplets can form clumps that would reduce vision clarity. To address the issue, Kim and co-workers adopted a hypotonic formulation to help to develop a highly consistent, transparent thin layer on the ocular surface and prevent the removal caused by blinking.[303] This strategy increased the absorption of hydrophilic and hydrophobic drugs and extended drug-ocular-epithelium contact time, thereby improving the therapeutic effect on the ocular surface. More importantly, this drug-loaded gelation system technology can provide more opportunities in medical conditions where other gelling/adhesives are required.[303]

4.3.4. Smart Wireless Responsiveness—Remote controllable SCLs have been engineered for the diagnosis of diseases such as diabetes and ocular inflammation.[94,243] An electrically controlled drug delivery system has successfully achieved and combined with real-time biometric analysis to provide precise diabetic prognosis and therapy (Figure 9b).[94] Therefore, the development of biodegradable and bioresorbable bioelectronics[305] for medical applications holds great promise to better human health.

4.4. Real-Time Self-Regulated Therapeutic SCLs

Besides integrating the diagnosis and therapeutics of ocular diseases into a bioelectronic device, as described via smart wireless responsiveness,[306–308] real-time monitoring of the drug release in the SCL remains challenging. In molecular imprinting technology, Deng and co-workers developed a convenient self-reporting therapeutic SCL that can convert drug

release information into readable color changes based on colorimetric analysis (Figure 9c).[228] Another example is a sustained delivery system based on embedded μ-tubes in SCLs as drug containers.[230] These SCL devices can have self-adaptive drugs that are released in response to fluctuations in the patient's IOP. Additionally, the device can also achieve stable drug storage and sustained release.

4.5. Therapeutic SCLs in Clinical Trials

A wide variety of therapeutic SCLs has achieved lab-to-bedside translation over the past decades. However, the underlying side effects of an SCL should be taken into account before its use, as some ocular reactions to external stimuli, such as dryness, discomfort, and nonreal infections may occur during/after the lens application.[212] Therefore, well-established clinical trials of an SCL for therapeutic applications are of considerable importance before commercialization can occur. Herein, we summarized the currently developing clinical trials for SCLs shown in Table 6 (Data accessed in August of 2021).

5. Ocular Signal Extractions

To realize the full potential of the SCL wearable platform, a suitable power supply and data transfer units are required to be integrated.[318] However, current wearable power sources face several challenges: relatively bulky size, low energy densities, undesirable biocompatibility, and incompatible mechanical properties.[319–321] Similarly, current data transfer techniques are bottlenecked in reducing power consumption, increasing the data transfer rate, and extending the working/communication distance.[319,322] In recent years, researchers from different fields have worked to solve these challenges to make the SCL wearable platforms more practical.[184,319,323] In this section, we provide discussions about the applicable powering techniques for SCLs, such as radio-frequency identification, wearable batteries, and solar cells. Moreover, we summarize the advanced wireless data transfer technologies, including optics, remote resonance detection, and custom-built application-specific integrated circuits (ASIC). Finally, we highlight the pros and cons of wearable applications.

5.1. Powering Methodology for SCL Wearable Platform

As summarized in the above section, the SCL wearable platform enables more versatile functions than solely vision correction, such as pressure sensing, temperature measurement, biomarker detection, or even treatments to alleviate or prevent ocular diseases. These features are accomplished by integrating functional units/active components onto the CL. The power supply is critical to achieving those functions without interrupting the users' daily route. One standard method is to introduce ultrathin conductive wires connected to an external power source.[38,61,324,325] For example, Renaud's group pioneered a noninvasive IOP sensor for diagnosing glaucoma. This pressure sensor was placed circumferentially to detect corneal curvature changes caused by IOP shifts. A custom-built microflex connection cable was employed to connect the sensors to the external power source (Figure 10a).[326] Recently, similar examples have been reported applying flexible connection wires such as conductive serpentine trace to connect the integrated functional units to the external power supply module within the SCL wearable platform.[73,327] For instance, Mitsubayashi's group

was the first to monitor tear glucose levels via an electrochemical sensor within the SCL wearable platform.[328] This SCL sensor was connected to a Potentiostat or analog/digital converters via a custom-built flexible electrode (Figure 10b).

The connection wires can provide an efficient and straightforward strategy to power the functional units within an SCL wearable platform. However, ocular discomfort/user-inconvenience is an uprising concern. The discomfort caused by the flexible power wires would adversely affect the users' compliance with long-term continuous monitoring. Therefore, wireless powering strategies are much more appropriate for further commercialization of the SCL wearable platform. RFID-based powering and data transmission techniques have been adapted to the SCL platform. The fundamental principle is illustrated in Figure 10c.[38] The RF power can be transmitted to the receiver unit with coil or antenna-based inductive coupling. A rectifier in the receiver unit is utilized to convert the RF waveforms to direct-current (DC) voltages, which are used as a power supply to sensors or integrated circuit (IC) chips.

Mokwa and Schnakenberg reported the first wireless powered micro-transponder system for continuous measurement of IOP shown in Figure 10d.[329] The external 13.56 MHz RF source was used to power the microtransponder based on complementary metal-oxide-semiconductor (CMOS) technology, with a typical power consumption of around 240 uW. The capacitive pressure sensor was integrated with the RF transmission electronics by MEMS. The RF frequency used for RFID-based inductive powering varies from MHz to GHz and from near field coupling to far-field radiation.[319]

However, the selective resonant frequency and antenna designs need to be considered to achieve higher power transmission efficiency and meet the dimensional constraints of the SCLs. In principle, the lower resonant frequencies generally have less power loss to the antennas, but the corresponding impedance matching components occupy a large portion of the circuit area. The higher frequencies allow for far-field energy harvesting, but the Joule-heating effects caused by the power transfer became more observable.

The NFC (13.56 MHz) technique has been modified for low energy consumption and efficient power delivery among the acceptable frequency range. Loop or spiral antennas are primarily used in CL receivers because of their simple design and integration.[171,319,325] It is critical to achieve parameter matching for the resonant circuits due to the space constraints within the SCLs.

In addition to inductive or field coupling-based wireless powering, many other powering methods are reported for SCL applications. For example, Lee's group developed an aqueous battery based on tear liquids and Prussian blue nanocomposites shown in Figure 10e.[320] It can achieve a discharging capacity of 155 μAh in tear fluid with 0.15 M Na^+ ions and 0.02 M K^+ ions, which is sufficient to operate a low-power microprocessor. It is also mechanically stable and bio-compatible, giving rise to a long lifetime and the possibility of integrating bioimplantable devices.

Flexible solar cells can also be an excellent candidate for energy harvesting from solar light in SCL applications. For example, Ghannam's group proposed a hybrid energy harvesting

system on the SCL platform assisted with RF electronics and solar cell units shown in Figure 10f.[63] Although not yet reported, ultrasonic power transferring is another possible candidate for wireless powering of the SCL. The power transmitting link could be composed of an ultrasonic oscillator in the frequency range of 200 kHz to 1.2 MHz and an ultrasmall piezoelectronic transducer embedded in the SCL (Figure 10g).[330–332]

5.2. Optical Signal Output

The multifunctional integrations within the SCL platform facilitate the detection of a variety of physiological signals and data generation. As part of these efforts, colorimetric techniques are widely used in several research groups as a power-free signal extraction strategy.[10,160,162,187]

A pattern or color output, which can be recognized by eyes and/or instruments, can reflect the changes in detected parameters. For example, IOP has been displayed as perceivable optical patterns, as shown in Figure 11a.[333] The high-aspect-ratio spiral parylene tube structure was fabricated based on a buried channel process. A circular air reservoir surrounded by 10 parylene spiral tubes resided in the center of the lens. When the central reservoir detected pressure, the inside air was then pushed into the tubes at different angles. This SCL platform can be optimized to have a resolution of up to 0.22° per mmHg.

Moreover, IOP fluctuations can be detected by the microfluidic pressure sensor integrated-SCL. In general, the microfluidic system-based CL usually contains liquid and air reservoirs. The liquid-air interface and pressure can be detected via the change in volume of the liquid reservoir. Yan demonstrated the concept based on a dyed glycerol and PDMS microchannels, as shown in Figure 11b.[334] Multiple circular sensing chambers surrounded by the zig-zag microchannels were constructed. Applying pressure to these sensing chambers would push the dyed glycerol into the microchannel. Therefore, one can visualize the IOP differences with the length of the dyed glycerol along the microchannels. The sensitivity can be adjusted by changing the width of the microchannels. Similar works have been reported and optimized by fluid dynamic simulations, simplifying pattern designs, or decreasing fabrication complexity.[158,157,335]

LEDs were also employed for the rendering of optical signal extraction. For example, as shown in Figure 11c,[38] a glucose sensor was prepared by immobilizing glucose oxidase with a pyrene linker on the graphene surface through the π–π stacking interaction. As a result, the increased glucose concentration decreased the resistance of the integrated glucose sensor, which reduces the biased voltage and the light intensity of the LED unit. In addition, a transparent circular AgNF film was patterned to assemble the RF antennas. This antenna could convert the external RF signals to the DC voltage. Therefore, the custom-built rectifier could power the integrated sensor and LED unit.

Structured color induced by the photonic crystal is another method category for IOP detection. Mechanical changes of the SCL substrate can be transferred to affect the periodic modulation of the photonic crystal, indicating a shift of the apparent color.[160] For example, colloidal silica particles were assembled into the CL template by photopolymerization. The color can change from red to green and blue, indicating a broad detection range

with outstanding sensitivity of 0.2 kPa nm^{-1} and a detection limit of 0.18 kPa (Figure 11d). Another example has been reported with an optimized structure (Figure 11e).[336] A ring-shaped microfluidic channel could concentrate the sensed pressure by the whole ring channel and direct it to the outlet. Here, the color changes could be measured and analyzed by a smartphone camera or spectrometer. In addition to being used for IOP monitoring, color changes can be used for temperature sensing. Precisely, a temperature sensor based on a temperature-sensitive cholesteric liquid crystal (CLCs) was integrated within the SCLs (Figure 11f).[337] In CLC, the distance between two equally oriented layers varied with temperature in a non-linear manner, generating a reflection peak shift. The temperature sensing resolution could reach up to 0.1 °C, suitable for body temperature monitoring.

This sensing strategy has also been explored to characterize ion species and concentrations in tear liquid. For instance, an ion sensor within SCLs for DEDs was designed based on ion-sensitive fluorophores integrated with silicone hydrogels.[200] The shift of the wavelength-ratiometer changed according to pH values and chloride concentrations, as shown in Figure 11g. The light scattering through SCLs could be used to detect glucose in diabetic patients. For example, Chen's group presented phenylboronic acid-based HEMA SCLs, exhibiting reversible swelling/shrinking effects in Figure 11h.[338] The smartphone camera can recognize the thickness difference without using specific photo-sensors.

5.3. Signal Extraction Based on Remote Resonance Detection

Mechanical changes caused by the IOP can be converted into electrical signals, which can be detected by the impedance spectrum response measurement based on the inductive coupling and the impedance reflection. An inductive coil and integrated capacitor were fabricated on soft silicone CLs (Figure 12a).[324] The resonance frequency of the sensor was set to depend on the lens curvature induced by the IOP changes, achieving excellent linearity of 8 kHz per mmHg. Later, a thin-film capacitor was fabricated on an SCL with an induction coil, as shown in Figure 12b.[339] The resonant capacitance was designed according to the lens curvature, which magnifies the linearity to 32 kHz per mmHg. However, further optimization of the conductive material and pattern design was required to achieve greater versatility and linearity. A wearable SCL was fabricated with highly transparent and stretchable sensors (Figure 12c).[171] A hybrid structure of 1D and 2D nanomaterials could provide conductivity, flexibility, and transparency and showed the ability to wirelessly and continuously monitor glucose and IOP levels. For example, stretchable serpentine wires for both the sensor and antennas have been developed, as shown in Figure 12d.[340] The pressure response can be 523 kHz per 1% axial strain and 35.1 kHz per mmHg. In another study, a liquid metal-based SCL sensor for continuous IOP monitoring was explored (Figure 12e).[72] The stretchable inductance coil was fabricated by sealing the liquid metal into ultrasoft channels and a linearity of 86.7 kHz per mmHg could be achieved.

5.4. Signal Output Based on Integrated ASIC Chip

Physiological signals, such as the IOP, temperature, pH, or ion concentrations, are analogous. If these signals could be digitalized, it would be much more efficient for collecting, storing, and processing information. The previously discussed signal extraction methods typically rely on an external system or instruments to complete the conversion;

these include optical spectrometers, camera systems, or electrical impedance measuring systems. The advanced integrated circuit industries have also driven SCLs' information conversion and processing. They have gradually reduced the need for bulky external modules, miniaturized the systems, and allowed higher functionalities for the SCLs. For example, RFID, invented over the past decades, is fully developed for the internet of things (IoT). It can convert the carrier frequency into DC voltage to provide energy to embedded IC chips and transmit digital information through impedance modulations (Figure 12f). Researchers have extended the design architecture of the existing RFID tag by adding various physiological signal sensing interfaces to the previous RF link for data uploading, integrating signal sensing, preamplification, conversion, and transmission on the SCL platforms.

Mokawa and Schnakenberg did initial work on integrating RF transmission modules within the IOP sensor.[329] The IC chip was built based on 1.2 um CMOS technology with a carrier frequency of 13.56 MHz and data transmission up to 26.5 kbit s^{-1}. Researchers have investigated appropriate technological pathways to improve SCLs by integrating the system with an artificial intraocular lens. Besides, investigators have been optimizing the RFID-like SCLs to improve biocompatibility, comfort, and functionalities.[15,322,341,342] Recently, an innovative soft SCL platform was developed with high transparency along with the integration of strain sensors, wireless antennas, stretchable interconnections, and the ASIC chips, as shown in Figure 12g.[96] The reinforced ring could transfer the overall strain variations through the rigid regime to the small elastic regime, which can then be detected by the Si strain sensor and acquired by the ASIC chip. The antenna was fabricated by an AgNF-AgNW mixture for better stretchability and transparency. The quality factor and spectral response were comparable to that of the conventional opaque copper antenna. Therefore, the soft CL may offer a noninvasive mobile healthcare solution for patient IOP monitoring. A similar design has been applied for glucose sensing after integrating the front-end circuits for impedance analysis or differential voltage amplifier.[184]

5.5. Integration Challenges for SCLs

In the future advances in SCL development, the requirements of material selections, fabrication techniques, and integrated manufacturing will undoubtedly increase. In other words, more efforts should be focused on material processing for developing soft and stretchable wearable SCL platforms. Park's group reported an excellent example to address the integration challenges in the SCL system. Two methods were used to mount the ASIC chip on the board, including wire-bonding and flip-chip. Free-standing wire bonding could achieve interconnections because the liquid metal pad could match the shape changes of the substrate. If the conventional gold pad was used for the ASIC chip, flip-chip bonding could be a better approach.[15,322,341,342] The soft substrate placed more stringent requirements regarding the stretchability of the conductive materials. For example, nanomaterial conductive networks or serpentine paths could be used to address this issue.[96,340] The heat tolerance of a soft substrate is another consideration during fabrication. Accordingly, the temperatures for film deposition or bonding of ASIC chips should be carefully adopted. Moreover, multiple electronic components require strictly electrically isolated conditions and resistance against electrochemical erosions, especially in tear fluid

containing electrolytes. A thick parylene coating is a typical solution for encapsulation because of its vacuum deposition, great electrical isolation, excellent film coverage, and most importantly, biocompatibility.[15,96,342] Finally, forming a tight interface with the eye prevents uneven tear-film production which may disrupt readings and promises higher signal acquisition.[344] Therefore, it is therefore necessary to produce soft CL electrodes that can flexibly mold to the eye curvature.[65]

5.6. Electroretinogram Recording Using SCLs

Electroretinogram (ERG) is an ophthalmic diagnostic test to evaluate the functional integrity of the retina.[65,345] It is a technology that analyzes the activity of various neurons and non-neuronal cells in the retina in response to light stimuli by measuring changes in the potential of the corneal surface. Yin et al. demonstrated soft graphene CL electrodes (GRACEs) for electroretinography (ERG). These soft electrodes allow the measurement of higher signal amplitudes compared to conventional methods. Also, this technology made multifocal ERG with topographical mapping possible.[65] Another example of soft sensor for ERG reading was developed by Kim et al. In this study, stretchable sensor was 3D printed onto a commercially available CL. The results showed high signal the noise ratio as well as good adaption to eye with minimal intervention of blinking and eye movements.[346] All three studies aimed for soft and flexible designs to increase the interface with the cornea and maintain high signal intensity without sacrificing comfort.

6. Outlooks, Opportunities, and Challenges

CLs have experienced rapid evolution for diagnostic and therapeutic applications.[11] In particular, the SCL platform achieves noninvasive, real-time continuous monitoring of physical parameters of the eye or tear fluid-related biomarkers. Thus, an intelligent ophthalmic management system is necessary.[31] To realize their great potentials, SCLs are designed or integrated with specific features, such as antibiotic ability on specifically designed CL surface coatings; stimuli-sensitivity for wearable diagnostics; drug loading/controlled releasing profile for wearable therapeutics, and proper energy storage/wireless information transmission for CL power supply and readouts, as summarized in the sections above.

Despite the tremendous advances and possibilities of SCL devices, several challenging and untapped opportunities remain that provide ample room for future development into multiple research areas. Here, we will discuss future research directions for an SCL on five significant aspects: a) novel SCL materials with extraordinary properties; b) SCL with brand-new functionalities; c) SCL platform via wireless power; d) intelligence and programmability of SCL wearable platform; and e) bench-to-bedside translations and commercialization of SCL wearable platforms for diagnostics and therapeutics.

6.1. Novel SCL Materials with Extraordinary Properties

Based on the discussion above, a CL with specific functions requires unique properties. Therefore, the development of function-oriented CL materials serves as a critical trend in the research field.

Surface coating or nanocomposited mixing[347,348] strategies have been widely employed as current CLs lack antibiotic properties. However, long-term stability and biocompatibility require further investigation. Joule heating is another concern due to the current flow generated by the integrated module.[31] Increased temperature can cause eye-related health/safety concerns such as ocular dryness and discomfort. In addition, a CL is a cause of DED, which results in visual disturbances, tear film instability, increased tear osmolarity, inflammation, and even impaired vision.[349] Therefore, it is crucial to keep the lens moist and maintain a stable tear fluidic exchange between the contact lens and the ocular surface. Based on these aspects, the search for new CL materials with antibiotics, supreme wettability, and appropriate temperature tolerance may represent the future direction of the field.

6.2. SCLs with New Functionalities

Besides the existing functions of SCLs, scientists have shown a growing interest in developing multifunctional SCLs. For instance, current single-modal SCL might not accomplish the future multiparameter detection to accurately predict or diagnose the diseases during their early progressive stage. Therefore, the next-generation SCL is expected to integrate multiple sensing modal components (e.g., vital physical signs and metabolites in tear fluid) to achieve precise medical care. Besides the role for biosensing, optical/electrical communications, visual stimulation, and recording are envisioned to be achievable by incorporating electrically conductive coatings or applying intrinsic conductive CL materials.

In addition to the functionalities, additive manufacturing (3D printing) can construct microscaled structures, enabling CL fabrication without surface geometry restrictions.[19,36] For example, 3D printing can create embedded microchannels or microchambers into the CL. These inbuilt channels or chambers can be employed to load drugs/mRNA/stem cells for promising personalized therapeutic applications.[29,54] More sophisticated SCL wearable platforms are expected in the future, such as a medical bandage SCL that can simultaneously include biosensing, drug delivery, and electrical stimulation.

Augmented reality (AR) is another vital feature that could be integrated into an SCL device. Over 253 million people worldwide suffer from permanent visual impairments that cannot be rectified via refractive correction or surgery. Canes, monocular, and service dogs are sometimes needed for patient mobility, which, while effective, do not provide rich information and are not hand free.[350,351] AR SCLs can be considered a promising candidate for hands-free, real-time, enhanced-image overlays that highlight objects and obstacles.

Furthermore, intelligent point-of-care (POC) systems that can monitor real-time illness/disease progress and provide intelligent corresponding therapies hold great promise for the emerging development of precision medicine. Therefore, a highly integrated closed-loop SCL platform will be steering the direction for next-generation SCL devices.

6.3. Wireless Powering Package of SCL Wearable Platform

Existing powered SCLs have been achieved by a wired system or wireless power transfer with temporal and spatial restrictions, limiting their real-time continuous long-term

operation and required energy storage devices.[321,322] The rigidity, heat, and bulk shape of conventional batteries for wired system make them unsuitable for the practical SCL wearable system. Besides, the safety of CL is undoubtedly a top priority when the device is applied to human eyes. Although the potential for mechanical failure or leakage of batteries composed of toxic, flammable, or reactive chemicals is minimal, this slight margin for error is not acceptable in SCL systems.[320] However, due to the limited volume of a CL, it is not possible to strengthen the battery encapsulation to prevent these defects. For the wireless power transfer, inductive power transmission and inductive sensors have been reported.[322,323] However, both are not practical for continuous operation of SCL systems due to the external requirement of power-transmitting devices. A more practical wirelessly flexible rechargeable battery/supercapacitor with an overall size and power density commensurate with potential SCL applications should be developed.

6.4. Intelligence and Programmability of SCL Wearable Platform

Intelligence and programmability are desirable attributes for future SCL systems. However, progress towards intelligent and programmable SCL is limited.[352,353] Therefore, the investigation of intelligent and programmable SCL systems should be continuous to focus on adopting appropriate tactics, including bio-inspired strategies, programmed functions, and machine learning (ML) to enable intelligent control and management.

ML has been found to be attractive for controlling various medical devices with the assistance of artificial intelligence (AI). AI devices can capture useful data, identify learned patterns, and make final decisions with no/minimal human intervention. Consequently, the integration of ML technologies into the control module is appealing for SCL systems, such as automatically controlled drug vehicles for drug-eluting SCLs. Moreover, ML algorithms can collect long-term data from CL sensors/biosensors and then transform them into scientific and/or clinically meaningful information to classify human health conditions and diagnose ocular abnormalities and diseases.[354,355] Furthermore, the AI-enabled SCL platform can get feedback from the built-in sensor module of the CL, eventually achieving closed-loop and/or autonomous control.

6.5. Bench-to-Bed Translations and Commercialization of SCL for Diagnostics and Therapeutics

Translations from lab research to marketized products present an essential path for SCL systems must take to have great societal impact. Representative examples that have been successfully commercialized with various design philosophies are as follows: usage for monitoring glucose level (e.g., Google) and detecting IOP (e.g., Sensimed Triggerfish); incorporation of AR (e.g., Samsung, Mojo Vision, InWith) and head-up display (e.g., Innovega); achievable drug delivery (e.g., Johnson & Johnson, OcuMedic, Leo Lens, CIBA Vision); UV-resistant/super wettability/ (Edmund Optics, BAUSCH+LOMB). The SCL products typically act passively as coatings or bulking agents at the current stage. In the current translational SCL market, long-term reliability is more important than the functional response capability in commercial applications.[356,357]

Understanding practical factors such as cost-effectiveness, raw material availability, scalable manufacturing, application scenarios, reliable performance, and safety can help researchers better design and engineer potentially marketable CL products from academia. Besides, the above-mentioned factors, composition, microbiology, toxicology, immunology, biocompatibility, shelf life, and clinical investigations also need to be evaluated by the US Food and Drug Administration (FDA) to assure the SCL's biological safety and effectiveness before commercialization.[358] Because CLs are susceptible to absorbing tears or proteins during use, prolonged use can cause dry eye and eye irritation. Hence, it is highly desirable to develop antibiotic and/or self-wettable CLs with the addition of hygroscopic salts or thin surface coatings, especially for users expecting long-term operation. Lastly, a good balance between user-centric design and proper cost management would be a win-win for manufacturers and customers.

6.6. SCLs for Antiviral Infection

In the field of ophthalmology, there have been several reports focusing on the relationship between ocular concerns and COVID-19.[359–361] In the early stages of the virus outbreak worldwide, Jones and co-workers reported no evidence showing an increased risk of COVID-19 infection for SCL wearers.[362] However, it has also been reported that an infected eye may be one route of transmission for the virus as COVID-19 patients may experience visual symptoms, and the virus may be present in tears and conjunctival secretions.[360] Consequently, the ocular transmission of SARS-CoV-2 should not be ignored.[363]

To the best of our knowledge, there are few reports of the use of therapeutic SCLs to combat COVID-19.[364] Among several future opportunities, the possible use of SCL may be to serve as a drug dissolution device in viral diseases such as COVID-19. The technical challenges may lie in two aspects: material selections, i.e., synthetic, or natural sources, and the SCL designs, i.e., the drug-eluting strategy. Advances in materials processing allow the application of a variety of fabrication techniques to develop therapeutic SCLs that can fight against viral infections. Additionally, inspired by advanced drug delivery technologies, drug-eluting SCLs can be employed to transport bioactive antiviral agents such as mRNA and proteins from the ocular surface to the site of action in the body, opening up opportunities for functional SCLs in antiviral therapeutic applications.

6.7. Challenges of SCLs

The field of SCLs faces a variety of challenges when being developed for healthcare settings. Because these devices are considered as biomedical devices in contact with mucous membranes, they require extensive testing before translation into human application. The diversity of technologies and the amount of testing required prior to clinical applications limit the translation of products from the lab to the market.

The first challenge is to evaluate whether the device is sufficiently "safe" for clinical application. ISO 10993 (Biological evaluation of medical devices) and ISO 9394 (Ophthalmic optics) both cover the testing of CLs.[365,366] Since CLs are devices in contact with mucosal membranes, they require testing for cytotoxicity, hypersensitivity, irritation,

and implantation effects. Animal testing on rabbit eyes is also required before further animal testing. After establishing the criteria for biological testing, the devices may be placed into clinical trials. Advances in contact lens technology take considerable time due to the length and cost of the testing and testing process, which causes very few products to translate from lab benches to market.

MiSight's daily lens product was FDA-approved in 2019 for SCLs that slow myopia in children while correcting vision using a concentric ring design.[367,368] According to the NIH, the clinical approval period for this SCL was six years. Another SCL device on the market is the SENSIMED Triggerfish, which performs IOP sensing and received FDA approval in 2017.[369] This clinical trial had to pass two years of safety and tolerability tests and four years of multicenter sensor efficacy trials. The aforementioned examples' time-to-market timelines exemplify how complex the process of approving and bringing SCLs to market is complex.

The second challenge in SCL development is shelf life and reproducibility. As the technology advances, products can become more complex and may include chemical and biological sensors and/or drug delivery modalities. Due to this biological/chemical complexity, the sterilization, packaging, and shelf life of the final product are important factors that can affect the scalability of SCL.[95] Changes in biochemical sensor quality during storage and transport may induce inaccurate data measurements, which can lead to false negatives and erroneous medical consequences. In addition, in the case of drug delivery SCL, denaturation of the drug incorporated with SCL can cause not only a decrease in efficacy but also unwanted side effects, which can lead to a more serious issues. Since the 1980s, there are several drug-eluting CLs that have been used in clinical trials, including lenses with chloramphenicol, gentamicin carbenicillin, and some other drugs.[370–372] However, over the past 40 years, there have been few market launches due to issues related to shelf life and drug stability. Another aspect related to shelf life is the power of electronic components. Batteries and power sources not only affect the shelf life of the product, but may also cause special storage conditions.[373] An SCL, which includes more functions, such as sensing and drug delivery, and informatics aspects, compared to the existing CL, demands further development in the realm of safety and shelf life as well as more accurate functionality.

7. Conclusion

In the present age, the development of wearable devices is faster than ever. Along with technological developments such as the miniaturization of electronics, development of artificial intelligence, and popularization of AR, increasing public interest in personalized medicine is accelerating the development of wearable devices. In this respect, it can be said that the SCL, a "visible device", has reached an important point more than ever. Through this comprehensive review article, we reviewed the development of SCLs from material synthesis, device design and fabrication, and functionalization to diagnostic and therapeutic applications. As we demonstrated in Sections 3 and 4, SCLs are being tested as minimally invasive, daily-use biomedical devices. As we discussed throughout the article, the development of such SCL technology is not simple from one field of bioelectronics that

affects miniaturization/wearable, but include 1) development of biocompatible materials, 2) development of intuitive interfaces, and 3) development of integration technologies capable of SCL research, our comprehensive review can serve as a guiding light for those pursuing SCL research.

Acknowledgements

Y.Z., S.L., and J.L. contributed equally to this work. The authors gratefully acknowledged funding by the National Institutes of Health (CA214411, AR074234, GM126571, TR003148). Finally, the authors acknowledge our colleagues from the Terasaki Institute for Biomedical Innovation, the University of California, Los Angeles, the University of California, San Diego, and the University of California, Riverside, for the excellent collaboration.

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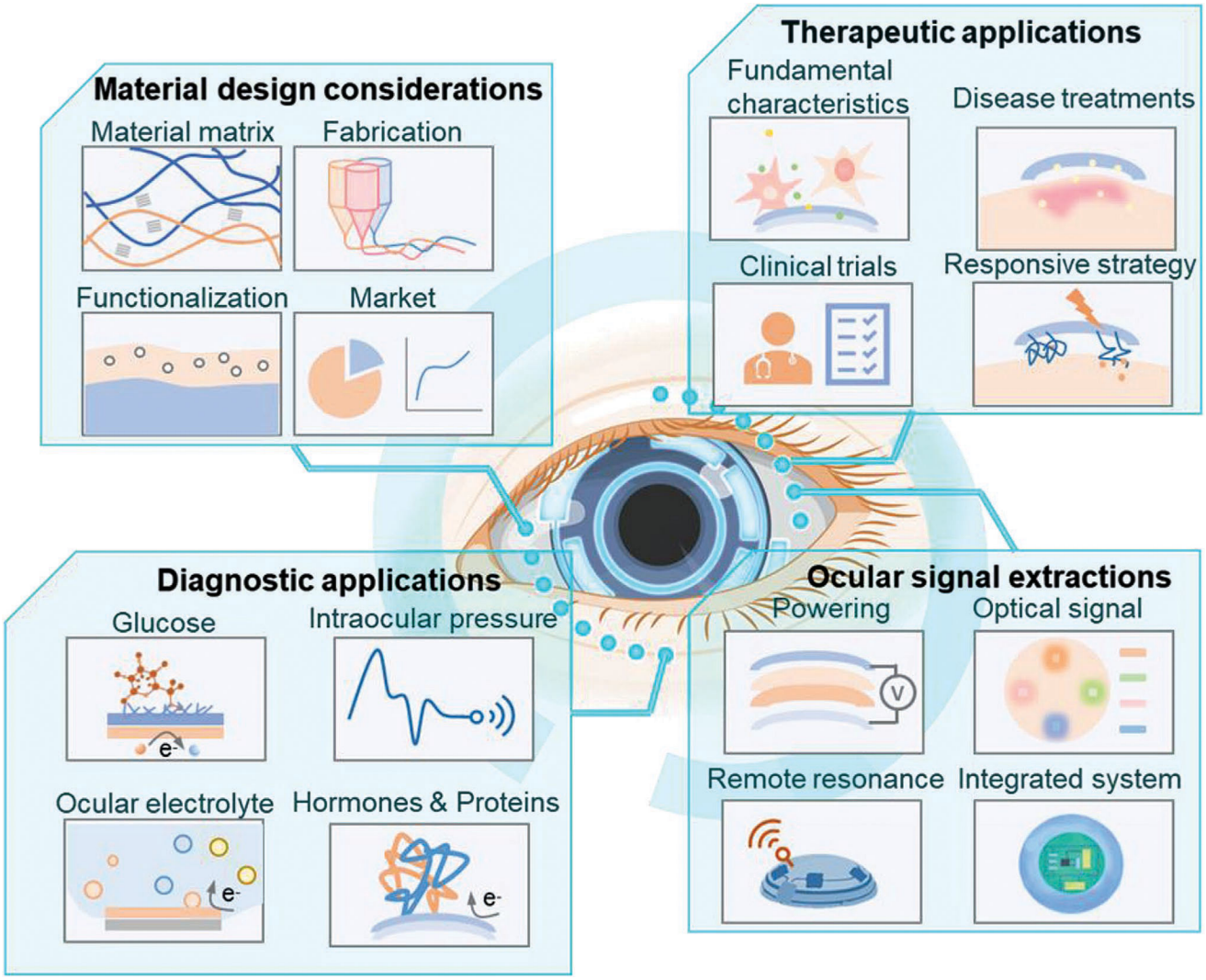

Figure 1.

Lab-on-a-contact lens. A wearable SCL platform integrated with flexible power transfer systems is employed to wirelessly monitor physiological signals (intraocular pressure, corneal temperature, and pH), biomarkers (glucose, proteins, ions, and virus), and controlled drug release in diagnostic and therapeutic applications.

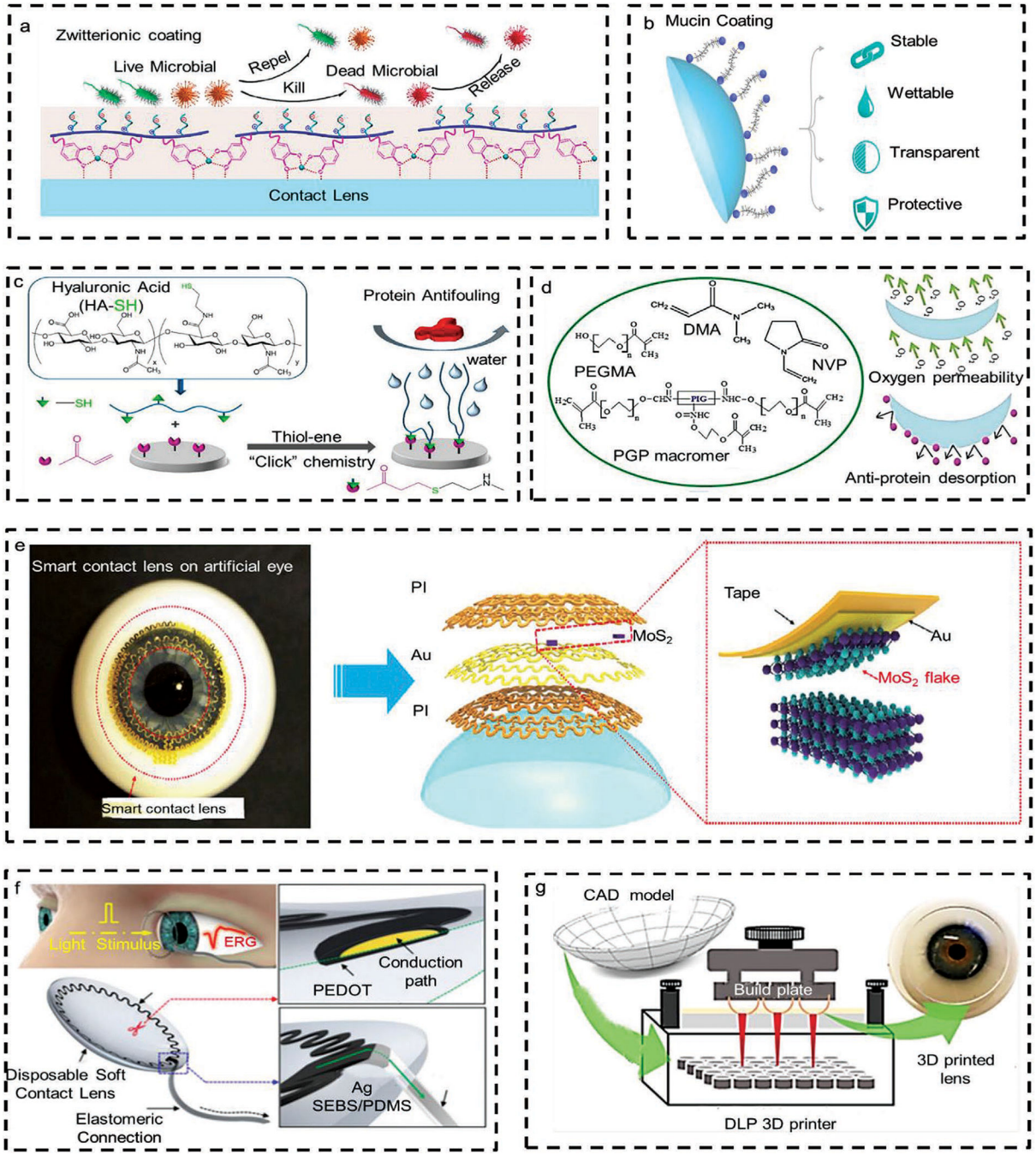

Figure 2.

Material innovations and device fabrication of SCLs. a) The zwitterionic coating on the CL exhibited antimicrobial and antifouling properties. Adapted with permission.[57] Copyright 2020, American Chemical Society. b) Highly stable mucin coating improved the wettability and tribology. Adapted with permission.[58] Copyright 2020, American Chemical Society. c) The hyaluronic acid (HA)-grafted coating enabled CL antifouling. Adapted with permission.[59] Copyright 2019, American Chemical Society. d) Copolymerization of hydrophilic polymers and PDMS to make silicone CLs become protein-antifouling without

cytotoxicity. Adapted with permission.[60] Copyright 2021, Elsevier. e) Ultrathin MoS_2 transistor-based SCL was used to monitor glucose levels. Adapted with permission.[35] Copyright 2021, Cell Press. f) The all-printed stretchable SCL sensor based on poly(3,4-ethylene dioxythiophene) (PEDOT) coating. Adapted with permission.[61] Copyright 2021, Nature Group. g) Schematic illustrations of the 3D-printed CL. Adapted with permission.[19] Copyright 2021, American Chemical Society.

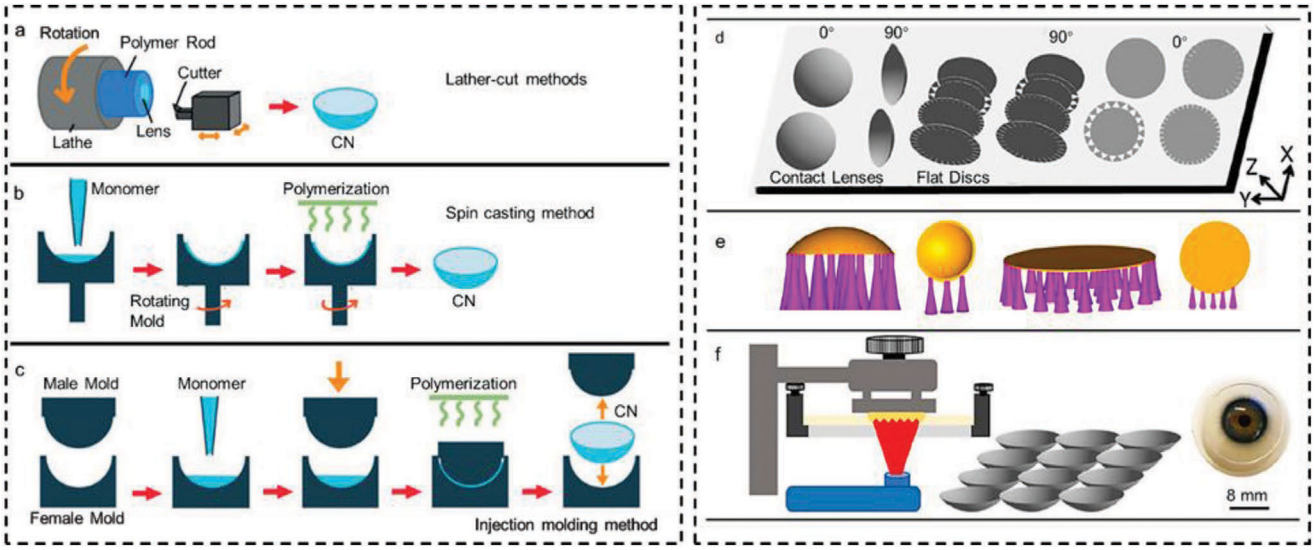

Figure 3.

Summary of the conventional manufacturing methods and the emerging 3D printing techniques. a–c) Traditional CL manufacturing methods: a) lathe-cut method, b) spin casting method, and c) injection molding method. Adapted with permission.[99] Copyright 2019. Wiley. d–f) Schematic representation of advanced 3D printing method using DLP. d) Production of the model of the lens, e) preparation of 3D printer readable files, f) DLP 3D printing of CLs. Adapted with permission.[19] Copyright 2021. American Chemistry Society.

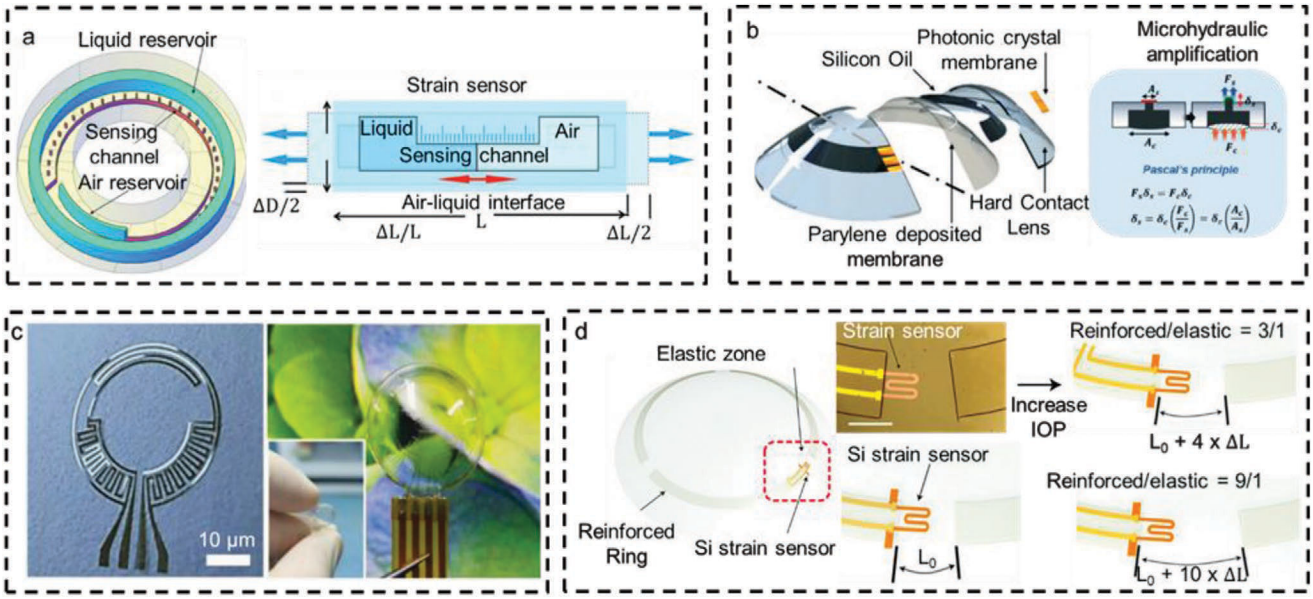

Figure 4.

SCLs with IOP monitoring. a) The microfluidic strain sensor-based contact lenses (MSS-CL) for IOP measurement and the illustration of the working mechanism. Adapted with permission.[157] Copyright 2018, Royal Society of Chemistry. b) Cross-section of the photonic crystal-incorporated SCLs and the description of Pascal's principle behind the signal amplification process. Adapted with permission.[162] Copyright 2020, Royal Society of Chemistry. c) Self assembly graphene (SAG) Wheatstone bridge strain gauges, and the self-assembly graphene CLs (SAG-CLS) with flexible printed circuit board (FPCB) connection with insert showing the bent CLs. Adapted with permission.[167] Copyright 2021, Wiley-VCH. d) Schematic of the CL-based IOP monitoring with its strain sensor, the elastic region, and working mechanism. Adapted with permission.[96] Copyright 2021, Springer Nature.

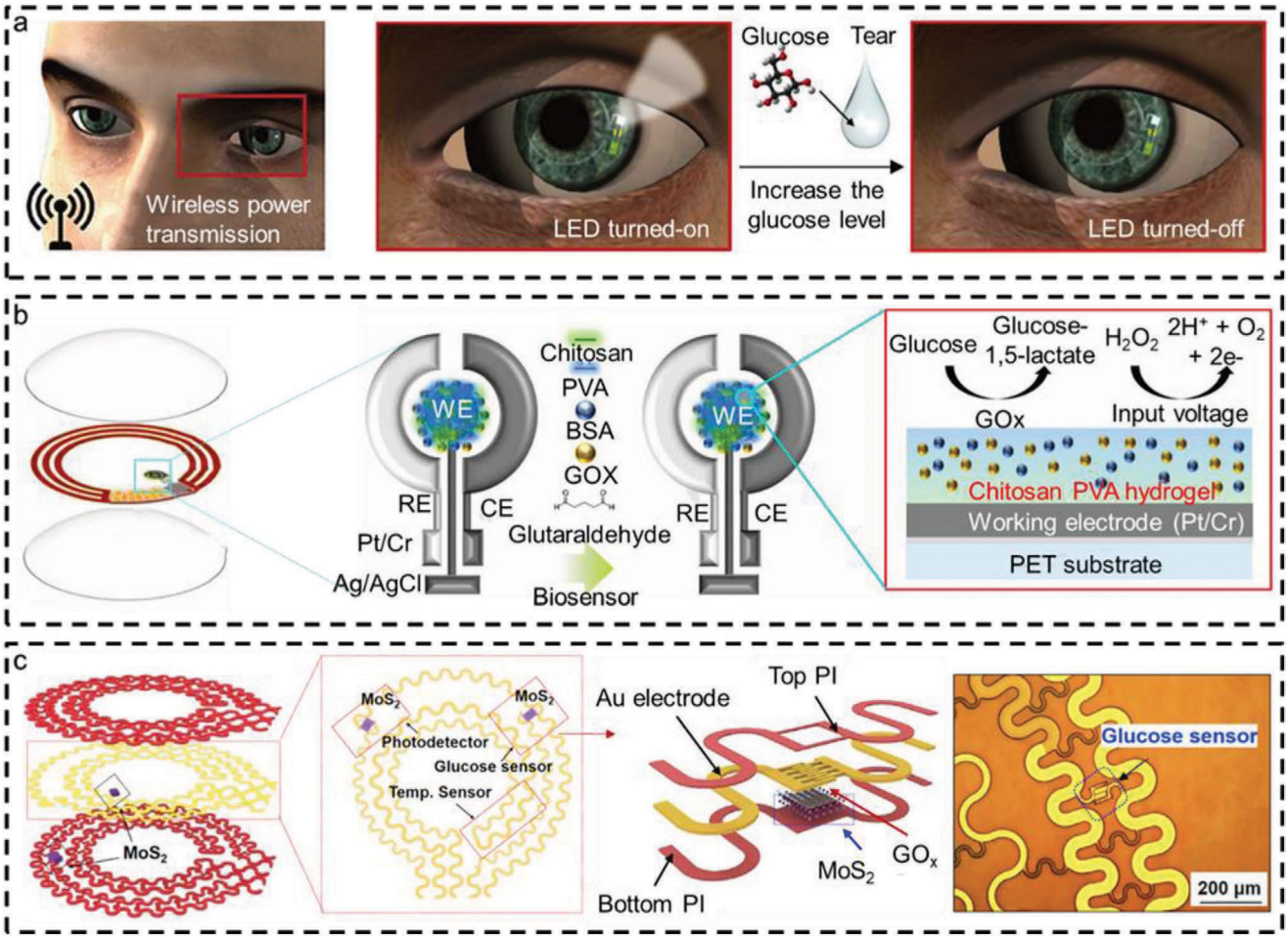

Figure 5.

SCLs with glucose monitoring. a) Schematic of the wireless LED incorporated contact lens glucose sensor, with on/off states of the LED indicator. Adapted with permission.[38] Copyright 2018, AAAS. b) Schematic of the SCL embedded with a biosensor, a flexible drug delivery system (f-DDS), and a transmitter, with the inset showing the biosensor components and working mechanism. Adapted with permission.[94] Copyright 2020, AAAS. c) Schematic illustration of the multifunctional sensor placed on the serpentine circuit and the integrated glucose sensor. Adapted with permission.[35] Copyright 2021, Elsevier.

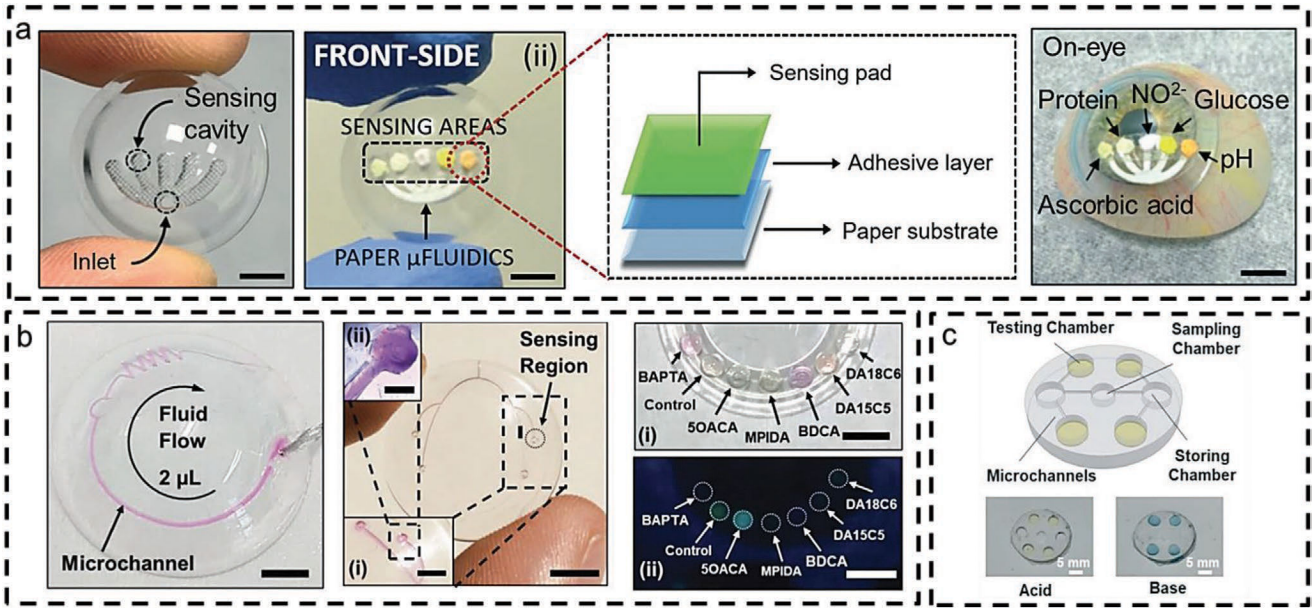

Figure 6.

SCLs for the monitoring of pH, ions, and small molecules. a) From left to right, the image showing the laser-inscribed microfluidic system CL, image with the embedded paper microfluidic chip inside the inscribed cavities for ascorbic acid, protein, NO_2, glucose, and pH detection, schematic illustration showing the paper integration for ion sensing and the full functioning sensor on an artificial eye model. Scale bar represents 2 cm, and image reproduced with permission. Adapted with permission.[195] Copyright 2020, The Royal Society of Chemistry. b) From left to right, the image showing the fluid flow of the multiplexed scleral lens for ion detections, the photograph of the microchannel integrated lens in increasing magnification, and finally LED excited image (top) and fluorescence image (bottom) showing the ion-sensitive fluorescence probe integrated scleral lens. Reproduced with permission.[197] Wiley-VCH. c) Schematic illustration of the PHEMA microchannel CL for pH sensing. Reproduced with permission.[53] The Royal Society of Chemistry.

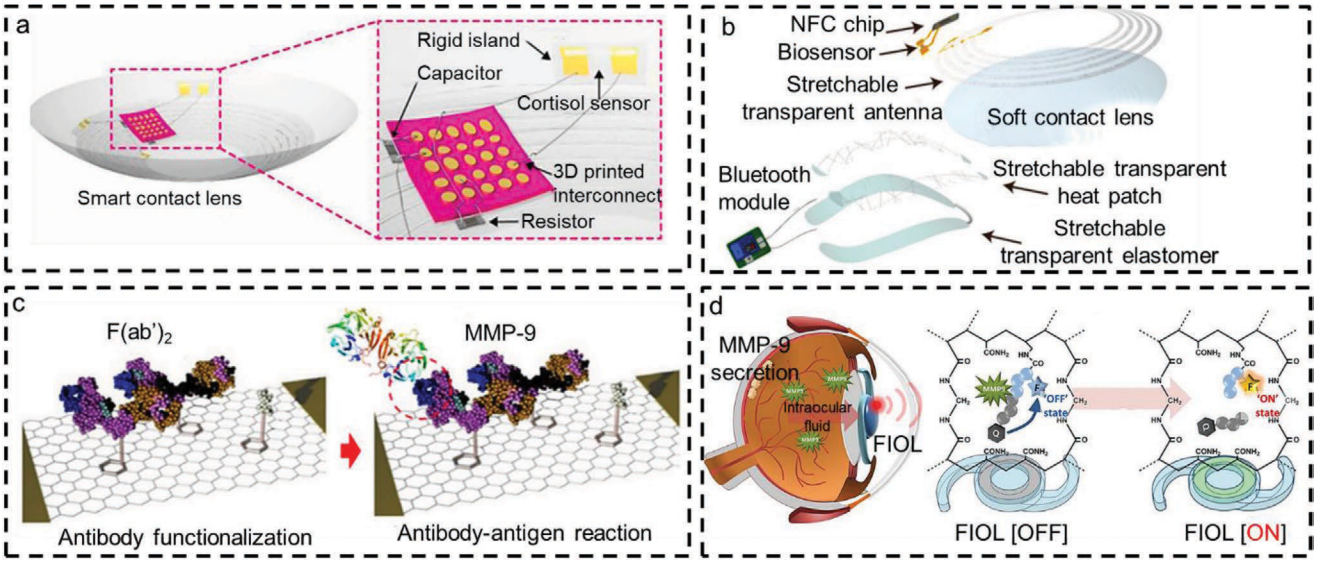

Figure 7.

SCLs for the monitoring of hormones, enzymes, and cytokines. a) Schematic showing the cortisol CL biosensor integrated with the 3D printed stretchable interconnects, antenna component, capacitor, and resistor. Adapted with permission.[13] Copyright 2020, AAAS. b,c) Schematic showing the incorporation of a near-field communication (NFC) chip, biosensor, stretchable transparent antenna on a soft CL, integrated with a Bluetooth-controlled heat pad, and an illustration showing the detection mechanism of the antibody-functionalized SCL platform. Adapted with permission.[206] Copyright 2021, Elsevier. d) Graphical representation showing the working principle of matrix-metalloproteinase-9 (MMP-9) hydrogel sensor. Where a hydrogen matrix is crosslinked to MMP-9 specific peptides, and it will be cleaved in the presence of MMP-9, resulting in detectable fluorescence. Adapted with permission.[211] Copyright 2020. Elsevier.

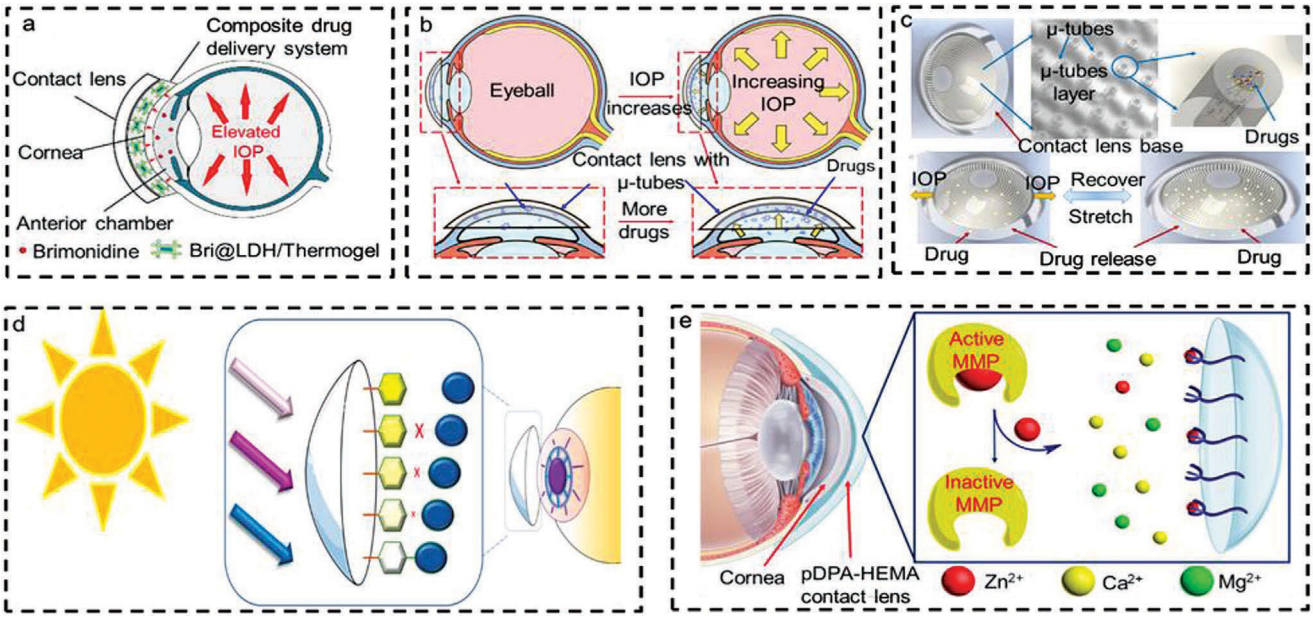

Figure 8.

Drug-eluting SCLs for therapeutic applications. a) The double-layered hydroxide (LDH) nanoparticle/thermogel composited drug delivery system for sustained brimonidine (Bri) release. Adapted with permission.[226] Copyright 2017, American Chemical Society. b) A self-adaptive CL embedded with μ-tubes as the drug container for the treatment of glaucoma. Adapted with permission.[230] Copyright 2020, American Chemical Society. c) The illustration of the PDMS μ-tubes-embedded drug container and delivery system with self-adaptive drug release ability. Adapted with permission.[230] Copyright 2020, American Chemical Society. d) The illustration of the coupled timolol to the CLs' polymer compositions with the photo-responsiveness (400–430 nm) to achieve the daylight-mediated sustained timolol release to treat glaucoma. Adapted with permission.[229] Copyright 2018, American Chemical Society. e) The illustration of the mechanism of deactivating MMPs through the pDPA-HEMA-based CLs. Adapted with permission.[246] Copyright 2019, American Chemical Society.

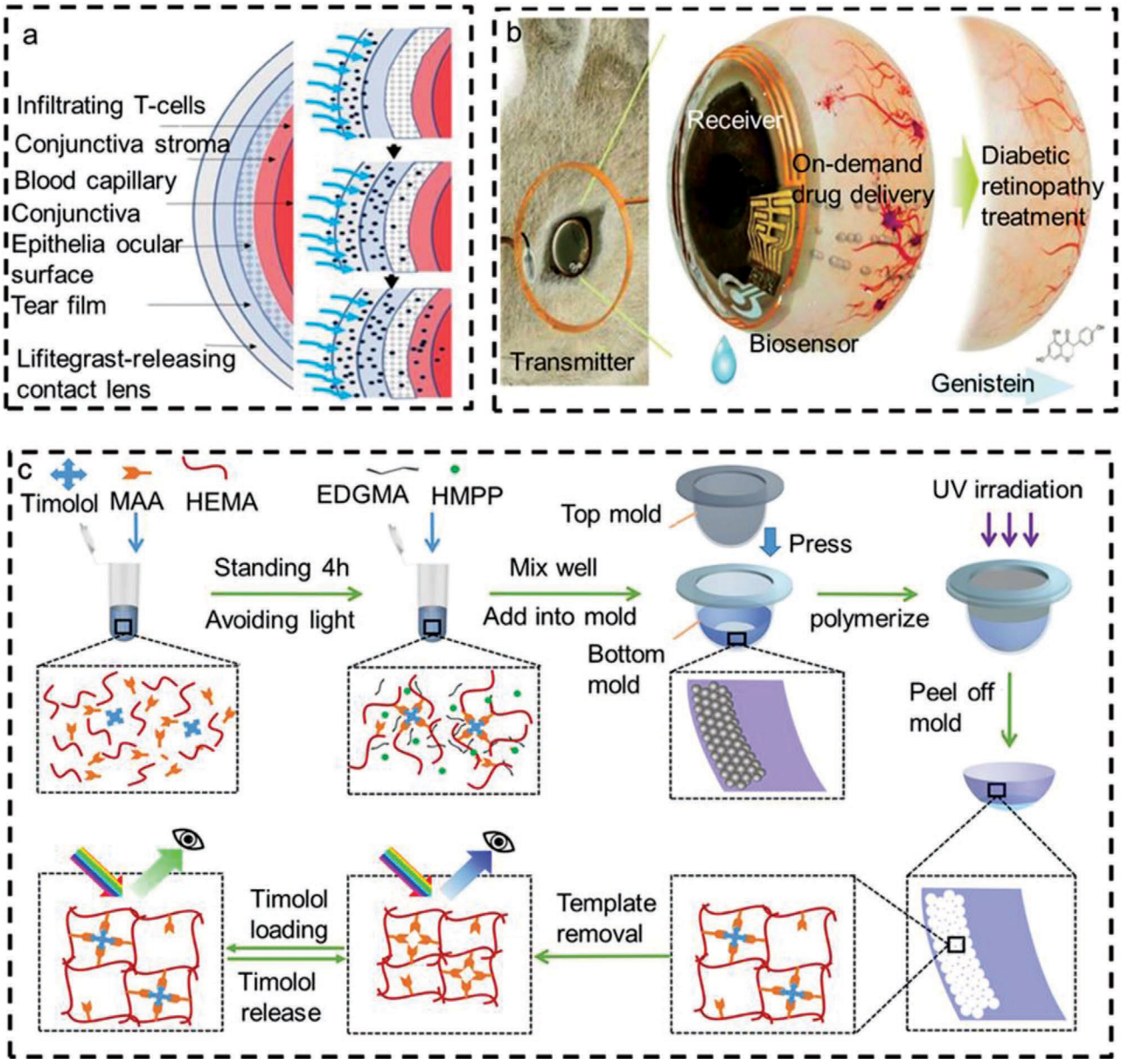

Figure 9.

Examples of the therapeutic SCL with responsiveness. a) Left: The illustration of the engineered CL with its structure on the anterior eye. Right: The CL releases therapeutically effective lifitegrast during exposures to indoor daylight (400–430 nm). The photoreleased lifitegrast molecules demonstrate a progressive diffusion-based manner from the lens hydrogel to reach the tear film and the conjunctiva stroma. Adapted with permission.[238] Copyright 2021, Marriott et al. b) The illustration of the SCL for real-time diabetic diagnosis and therapy with electrically-controlled drug release design. Adapted with permission.[94] Copyright 2020, AAAS. c) The molecular imprinting technology used in CL design gave the CL considerable blue shift with accumulative timolol release. Adapted with permission.[228] Copyright 2018, American Chemical Society.

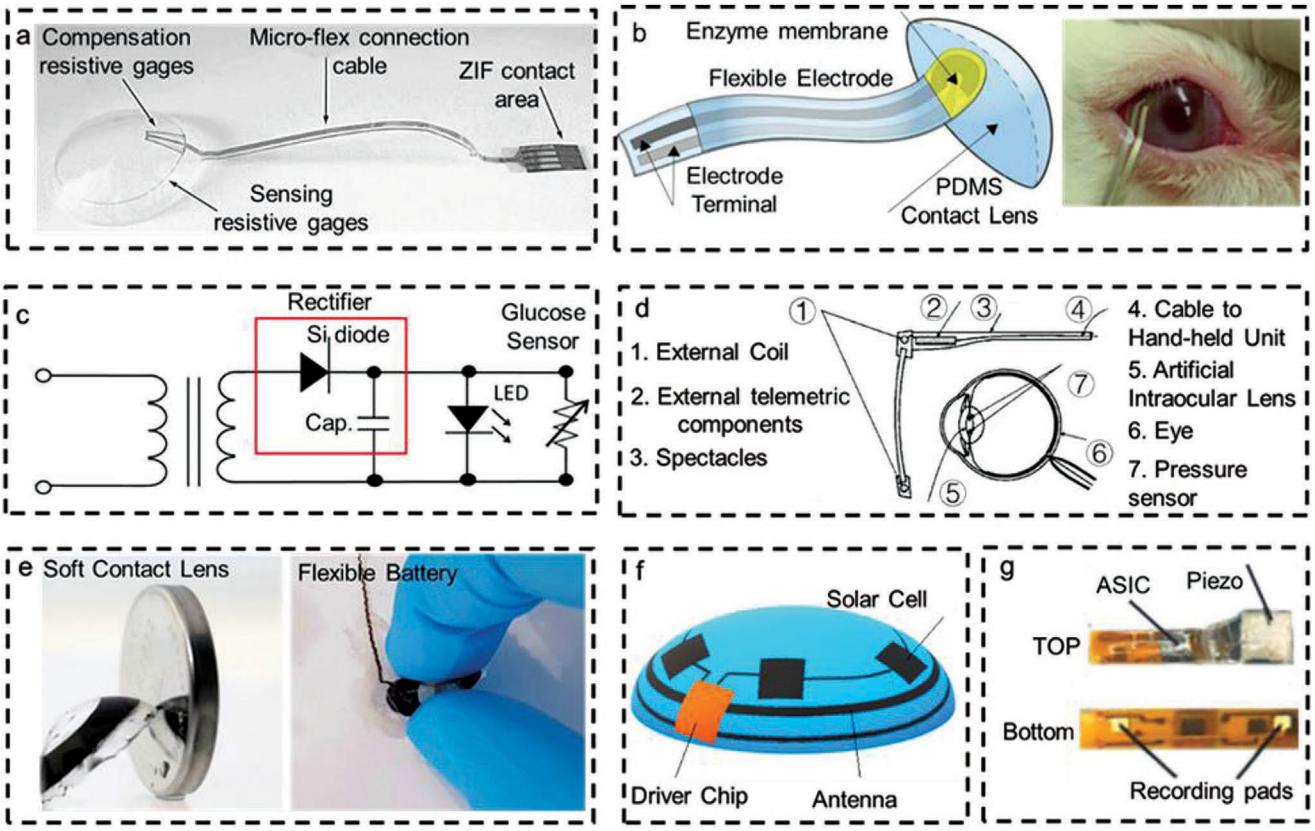

Figure 10.

Wearable powering methodology for SCL. a) The SCL is integrated with sensing resistive gages and micro-flex interconnections. Adapted with permission.[326] Copyright 2004, The Association for Research in Vision and Ophthalmology. b) The flexible electrode bonded onto the PDMS CL as an electrical interconnection for glucose sensing. Adapted with permission.[328] Copyright 2011, Elsevier. c) Typical circuit diagram for the RF signal coupling and the conversion to DC voltage. Adapted with permission.[38] Copyright 2018, AAAS. d) Schematic illustration for the integrated TOP sensor in the artificial intraocular lens. Adapted with permission.[329] Copyright 2001, IEEE. e) The bio-fuel battery integrated CL. Adapted with permission.[320] Copyright 2021, American Chemical Society. f) Schematic of the self-powered CL with hybrid energy harvesters. Adapted with permission.[63] Copyright 2020, IEEE. g) The wireless ultrasonic power receiver unit, originally for neural stimulations. Adapted with permission.[332] Copyright 2016, Elsevier.

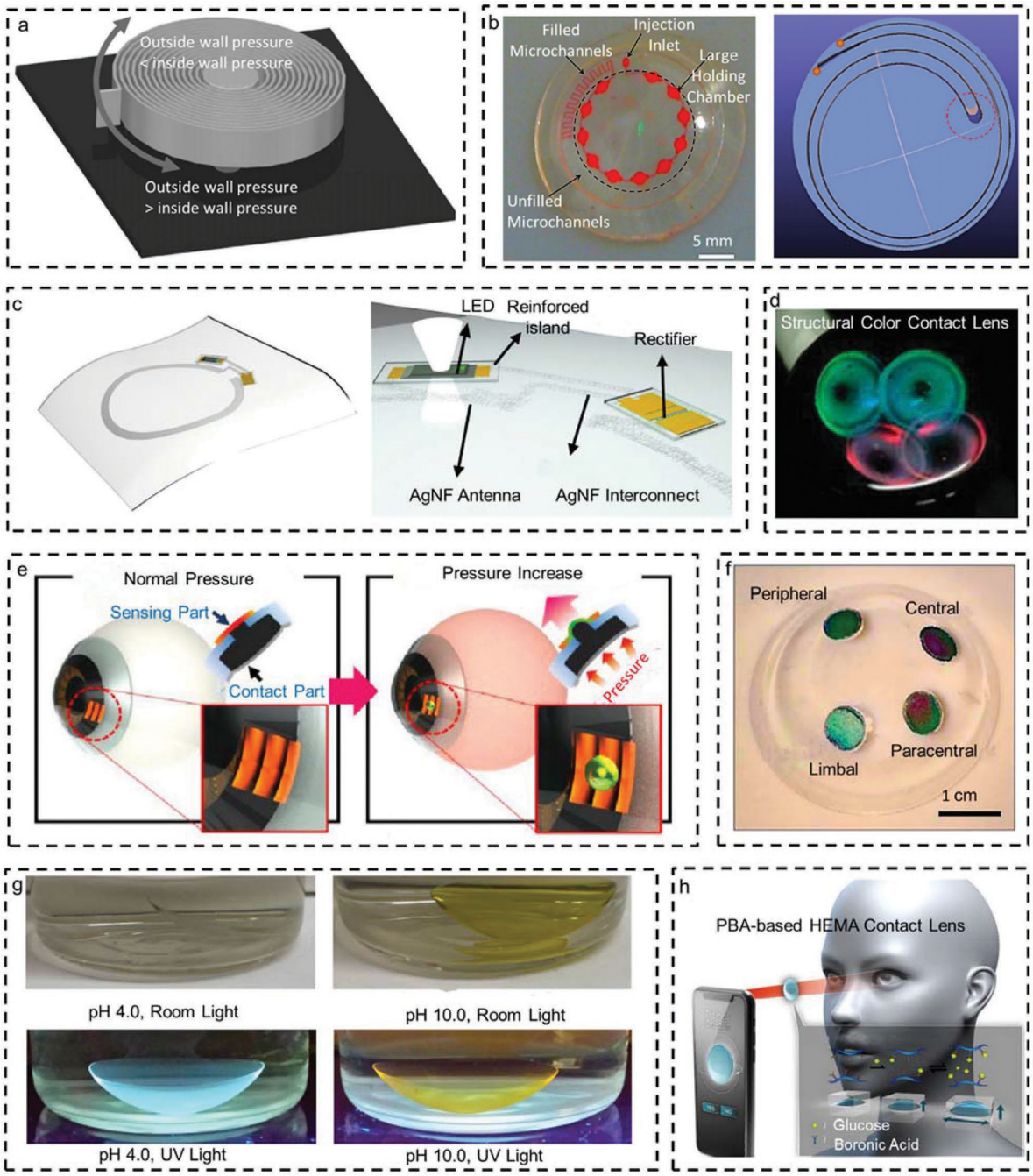

Figure 11.

Ocular signal extraction based on optical methods. a) Rotation of the pointing tip for the high-aspect-ratio Partlene tube. Adapted with permission.[333] Copyright 2006, Elsevier. b) Two represented types of microfluidic-based IOP sensors. (Left) Adapted with permission.[334] Copyright 2011, IEEE. (Right) Adapted with permission.[335] Copyright 2020, Wiley. c) Schematic of the wireless display circuit, including rectifier, LED units, the transparent antenna, and electrical interconnections. Adapted with permission.[38] Copyright 2018, AAAS. d) Camera images of the structural colored CL for the ophthalmic health

monitoring. Adapted with permission.[160] Copyright 2020, the Royal Society of Chemistry. e) Illustration denoting the operation principles of the SCL. Adapted with permission.[162] Copyright 2020, Royal Society of Chemistry. f) Photographs of CL for corneal temperature mapping. Adapted with permission.[337] Copyright 2019, Royal Society of Chemistry. g) Digital photos of 6HQ-18 labeled biofinity CL in various pH under room light or UV light. Adapted with permission.[196] Copyright 2018, Elsevier. h) Integrated system for detecting the thickness of the PBA-based HEMA CL. Reproduced under the terms of the CC BY license.[338] Copyright 2018, The author(s). Published by MDPI.

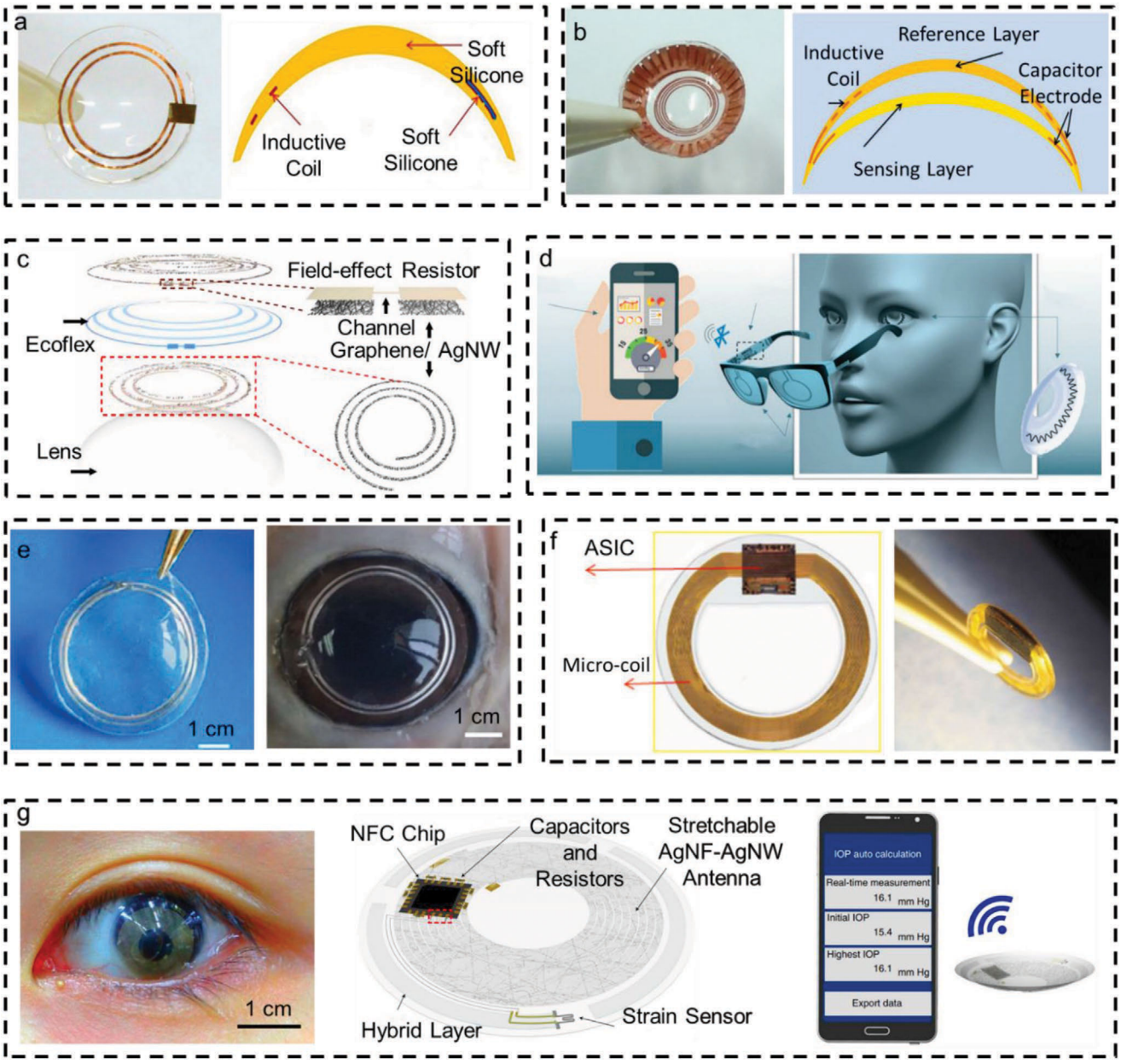

Figure 12.

Signal extraction based on remote resonance detection and integrated ASIC chip. a) The SCL with sensing components is embedded in a silicone rubber CL. Adapted with permission.[324] Copyright 2014, Elsevier. b) Photograph and cross-section of the contact lens sensor for IOP monitoring. Adapted with permission.[250] Copyright 2013, Elsevier. c) Schematics of the wearable CL platform integrated with glucose and IOP sensing. d) The soft CL sensor for the IOP monitoring. Adapted with permission.[340] Copyright 2020, Royal Society of Chemistry. e) Camera images of the liquid-metal-based pressure sensor on the CL. Adapted with permission.[72] Copyright 2021, IOP Publishing. f) IOP monitoring with a pressure transducer. Adapted with permission.[343] Copyright 2011, Association for Research in Vision and Ophthalmology. g) Schematics of a fully integrated

system, including a strain sensor, stretchable AgNF-AgNW antenna, NFC chip, passive elements, and the stretchable EGaIn interconnects on a rigid-soft hybrid film. Adapted with permission.[96] Copyright 2021, Springer Nature.

Table 1.

Summary of the pros and cons of commercial CL materials.

Material	Strengths	Weaknesses	Market share	Major manufacturer(s)
PMMA	Durable; Easy to manufacture	Low gas-permeability; Limited hydrophilic property	1%	Bausch + Lomb
PHEMA	Highly flexible; Hydrophilic; Being able to be copolymerized	High protein absorption; Good gas-permeability	22%	CooperVision Bausch + Lomb Vistakon
Silicone	Gas-permeable; Durable; Modifiable	Innate hydrophobicity; High modulus	64%	Alcon CooperVision Bausch + Lomb
PVA	High tensile strength; Antibiofouling; Highly adjustable	Not fully researched; Low gas-permeability	2%	CIBA Vision

Table 2.

Examples of CLs on the market.

FDA-approved Product[a)]	Manufacturer/ Sponsored institution	Featuring characteristics	Material	Water content	Refs.
1 day Acuvue Moist	Johnson & Johnson	Decreased friction; Retained soft feeling; Enhanced visual accuracy; Blocking over 82% of UV-A/ 97% of UV-B radiation	Etafilcon A	58%	[115,116]
Acuvue Oasys with Transitions	Johnson & Johnson	Seamlessly adapting to changing light; All-day/soothing vision	Senofilcon A	38%	[117]
Air Optix Night & Day Aqua	Alcon	Oxygen permeability to pass through the lenses	Lotrafilcon A	24%	[118]
Air Optix Aqua	Alcon	Up to five times more oxygen to reach the eyes compared to other CLs; Smooth surface to resist protein deposits;	Lotrafilcon B	33%	[119]
Dailies Total 1	Alcon	The first and only contacts with a water gradient composition; Great breathability	Delefilcon A	33%	[120]
Dailies AquaComfort Plus	Alcon	Being super thin; Slowly released moisturizing ingredients	Nelfilcon A	69%	[121]
Biofinity	CooperVision	High oxygen permeability and a naturally wet lens material; High water content with a soft lens; No need to use additional wetting drops throughout the day	Comfilcon A	48%	[122]
Frequency 55 Aspheric	CooperVision	Varying curvatures over the CL surface; Extended focus range right to the edge of the lens and increased contrast sensitivity	Methafilcon A	55%	[123]
Avaira Vitality	CooperVision	Enhanced water content; Blocking more than 90% harmful UVA and 99% UVB rays; Great breathability, allowing for longer wear times;	Filofocon A	55%	[124]
Proclear 1 Day	CooperVision	Aspheric design with varying amounts of curvature on different lens areas	Omafilcon A	60%	[125]
ULTRA for Presbyopia	Bausch&Lomb	All-day comfort and great vision; Hydrating, breathable comfort for up to 16 h; Excellent longevity	Samfilcon A	46%	[126]
ULTRA for Astigmatism	Bausch&Lomb	95% of lens moisture for 16 h; All-day comfort; Stable, clear vision;	Samfilcon A	46%	[127]
SofLens Toric	Bausch&Lomb	Great comfort; High permeability to oxygen and moisture	Alphafilcon A	66%	[128]
Biotrue ONEday	Bausch&Lomb	Being similar to the outer layers of the eye, making it practically imperceptible; Same water content as the cornea; The long-standing moisture over the day. Excellent breathability to provide the cornea with sufficient oxygen.	Nesofilcon A	78%	[129]

[a)]Indicates data accessed in January of 2022.

Table 3.

Examples of SCLs on the market. Definition: passive method refers to: the generation of power from the energy, collected from electromagnetic waves; active method refers to relying on a battery-storage device.

Manufacturer/ Applicant[a)]	Product platform/Patent	SCL material	Powering method	Features	Refs.
Sony	U.S. Patent Application No. 14/785249)	N/A	Electromagnetic induction; Radio wave; Electromagnetic field resonance	Image pickup and recording; Piezoelectric sensor for eye movements	[130]
Google	U.S. Patent Application No. 17/096072	N/A	Passive; Active	Detection of a user's gaze; Millimeter waves-compatible communications	[131]
Innovega Inc.	eMacula and iOptik	N/A	N/A	Combination of glasses and SCLs; Being light and comfortable; AR/VR/MR configuration	[112]
Samsung	U.S. Patent Application No. 14/644488	N/A (SU-8, PMMA passivation layer)	Capacitor	AR function; Manufacturing and operation; Eliminating movement effects of wearers.	[132]
Mojo Vision Inc.	Embedded microLED display	N/A	Solid-state battery	Vision correction; AR configuration, etc.	[111]
SENSIMED Triggerfish	Continuous ocular monitoring system	Silicone	N/A	FDA-approved, CE-markedly 24 h IOP monitoring; Bluetooth-enabled data transfer; Guiding glaucoma treatments, etc.	[133]
Aleksandr Shtukater	U.S. Patent Application No. 15/442674	N/A	RF antenna, battery, capacitor, etc.	Designs of generating many display outputs by using embedded display component of SCLs; Eye position tracking; Smart UI designs, etc.	[134]

Abbreviation: SCL: smart contact lens; EMI: electromagnetic induction; LED: light-emitting diode; FDA: U.S. Food and Drug Administration; CE: IOP: intraocular pressure; VR: virtual reality; AR: augmented reality MR: mixed reality; SU-8: SU-8 is the epoxy-based negative photoresist; PMMA: poly (methyl methacrylate).

[a)]Indicates data accessed in January of 2022.

Table 4.

Summary in SCLs for the detection of ions in tear fluids.

Bioactive molecule	Target	Sensitivity	Detection range	Refs.
Benzenedicarboxylic acid	H^+ (pH)	0.12 pH	pH 5.0–9.0	[197]
6-hydroxyquinoline-C18 alkane	H^+ (pH)	–	pH 4.2–10.0	[196]
Methyl red	H^+ (pH)	12.23 nm per pH	pH 4.3–6.2	[194,195]
Phenolphthalein	H^+ (pH)	12.23 nm per pH	pH 8.2–12.0	[194]
6-methoxyquinolinium-C18 alkane	Na^+	–	–	[196]
Diaza-15-crown-5 conjugated 2’7’-dichlorofluorescein	Na^+	15.6×10^{-3} M	$6.7–12 \times 10^{-3}$ M	[197]
Diaza-18-crown-6 conjugated 2’7’-dichlorofluorescein	K^+	0.8×10^{-3} M	$1–50 \times 10^{-3}$ M	[197]
1,2 biz(o-aminohenoxy) ethane-N,N-N’,N’-tetraacetic acid	Ca^{2+}	$0.02–0.05 \times 10^{-3}$ M	$0–2 \times 10^{-3}$ M	[197]
5-oxazolecarboxylic acid	Mg^{2+}	$0.01–0.03 \times 10^{-3}$ M	$0.1–2.0 \times 10^{-3}$ M	[197]
Fluorescent N-(2-methoxyphenyl) iminodiacetate	Zn^{2+}	0.001×10^{-3} M	$0.005–0.05 \times 10^{-3}$ M	[197]
Sodium green poly-$_L$-lysine	Cl^-	$0.2–0.7 \times 10^{-3}$ M	$0–100 \times 10^{-3}$ M	[199]

Table 5.

Examples of therapeutic SCLs for treating various ocular diseases

Main ingredients	Active agent	Mechanism	Characteristics	Disease	Refs.
Chitosan	Brimonidine tartrate	Chitosan film swelling controlled diffusion	Simple and ecofriendly fabrication; Low toxicity; Excellent biocompatibility/ biodegradability; High cornea permeability	Glaucoma	[222]
HEMA, NVP, TRIS, EGDMA	Betaxolol hydrochloride	pH responsive	Excellent stability during storage in PBS buffer with ignorable drug loss; Sustained in vivo drug release for over 240 h in tear fluid; 53 times increase in mean residence time of drug in rabbits compared to soaked contact lenses	Glaucoma	[223]
EGDMA, DMA, NVP, siloxane and HEMA	Timolol, bimatoprost and HA	Diffusion/dissolution	Adoption of implantation technology to passively deliver drugs at therapeutically relevant doses without high burst release; Smooth CL surface; Reduction of IOP for 120 h; Sustained drug release for 72 h with a low burst release	Glaucoma	[224]
EGDMA, HEMA, NVP, TRIS	Betaxolol hydrochloride	pH responsive	Ion-exchange resin as a carrier; Increase drug loading amount; Sustained drug release; Prevent drug leakage during storage in PBS with low ionic strength	Glaucoma	[225]
PLGA-PEG-PLGA copolymer	Brimonidine	Step I: Brimonidine released from LDH NPs to thermogel matrix Step II: Diffused from matrix to the tear film	Dual-control release system based on a thermogel incorporated with Bri@ LDH to deliver brimonidine to the ocular surface continuously; No cytotoxicity to human corneal epithelial cells; Good biocompatibility; In vitro sustained drug release for up to 144 h; In vivo sustained drug release for at least 7 d	Glaucoma	[226]
Silica NPs, HEMA, MAA	Timolol	N/A	Usage of molecular imprinting technology for sustained timolol release; Selfreporting ability for the release process: conversion of the drug release into a readable signal by color changes	Glaucoma	[227,228]
HEMA, EGDMA, NVP	Timolol	Light-responsiveness (exposures of the lens to the 400–430 nm)	Patient controllability over the amount of timolol released from CL throughout the day; Disposable; Daily use; Low-cost manufacturing	Glaucoma	[229]
PDMS	Timolol	Diffusion; IOP-triggered release	Combination of a ball-mold fabrication process and soft lithography; High bioavailability/ lower risk for adverse effects; A simple, noninvasive, sustained drug release up to 45 d; Self-adaptive drug release without human intervention	Glaucoma	[230]
PDMS	Timolol	Diffusion	All-in-one design: power-free soft CL device to measure IOP; Extended in situ drug release (up to 30 d); Glaucoma biomarker detection; Optically transparent/biocompatible material-anodic AAO thin film	Glaucoma	[231]
N/A	Gentamicin sulfate	Bacterial-caused pH responsiveness	Self-assembly of antibiotics loaded ADA-GS/PEI multilayered films on CL surface; Bacterial-responsive release; Fast antibacterial property	Corneal bacterial infections	[68]
HEMA, MAA, EGDMA	Moxifloxacin HCl & HA	HA/Moxifloxacin HCl release; Diffusion in the release media	In vitro release for moxifloxacin HCl/HA up to 96 h; in vivo drug release with the significant improvement compared to eye drops; Successful application of the implantation technology to codeliver moxifloxacin HCl/HA to treat conjunctivitis	Bacterial conjunctivitis	[102]
HEMA, VP	Pranoprofen	Pranoprofens-release	Incorporation of a zwitterionic polymer to suppress protein and bacteria adsorption; The “hot-melt press method” involves poorly water-soluble pranoprofen into the CL	Allergic conjunctivitis	[232]
Methafilcon A	Tobramycin	Lens surface reaction	Sonochemical modification; Antibacterial/antifungal; Enhanced wettability; Anti-adhesion ability of platelets and proteins; Antioxidant capacity; Good cytocompatibility	Keratitis	[79]
HTCC/Ag/GO	Voriconazole & AgNPs	Diffusion (Vor adherent to GO)	Mechanically robust cross-linked CL formation via electrostatic interactions between GO and HTCC; In vivo experiments proved biocompatibility; Increased drug loading	Keratitis	[233]

Main ingredients	Active agent	Mechanism	Characteristics	Disease	Refs.
			capacity/extended drug release time due to the hydro-phobicity of Vor and the physical uniqueness of GO; Incorporation of AgNPs to enhance the antifungal activity/expand the antimicrobial spectrum		
HEMA/Glycerol/ EGDMA	Diclofenac	Diffusion from inclusion complexes of β-CD-crHA: and diclofenac	Advantages of inclusion of β-CD-crHA: Improved surface hydrophilicity; Water uptake ability; Oxygen permeability; Great flexibility/light transmission; Enhanced drug encapsulation capacity/ sustainable delivery.	Conjunctivitis	[234]
TRIS, HEMA, NVP, EGDMA	Moxifloxacin hydrochloride	N/A	Suitable hydrophilic property. High transmittance; Increased ionic permeability. Low surface roughness/adequate stiffness. Molecular imprinting technology was applied with AA as a functional monomer to recognize MXF specifically. Sustained drug release. No cytotoxicity and no potential ocular irritancy effect.	Bacterial-related ocular disease	[235]
HEMA/EGDMA, MAA/Pluronic F127	Cyclosporine	pH responsiveness	Sustained release of cyclosporine up to 156 h at therapeutic rates; No drug leaching during sterilization/storage period; Maintaining optical/physical properties of CLs; In vivo drug release up to 336 h in tear fluid	DES	[236]
HEMA, EGDMA	Cyclosporine	N/A	Significant improvement in wettability/mechanical strength with maintained optical transmittance; In vitro cyclosporine release/controlled delivery for over 12 d; Approved therapeutic effect on DES by Schirmer tear test etc	DES	[237]
HEMA, MMA, DMAA	Lifitegrast	Light responsiveness	Sustained passive delivery lifitegrast at a therapeutic level for a long time; Improved drug utilization at a lower cost; Easily integrated technology for daily-use CLs	DES	[238]
PVA	HA	Diffusion	Excellent light transmittance/biostability when exposed to eye shear stress; Sustained HA release from the ring implanted CL up to 14 d; No corneal epithelial cell cytotoxicity and no cell attachment on the device	DES	[239]
Nelfilcon A	HA	Diffusion	Adoption of biomimetic imprinting technology (molecular imprinting); No structural and property change; Controlled release of HA over 24 h	DES	[240]
Siloxane, DMA, NVP,EGDMA, HEMA	Epalrestat	N/A	Deliver hydrophobic epalrestat to the anterior and posterior side of the eye without affecting the critical lens properties; In vitro release studies showed low burst release and sustained release up to 196 h; High epalrestat accumulation in the various ocular tissues	DED	[241]
HEMA; Silicone-containing monomers of TMSPMA,TRIS, EGDMA	Genistein metformin	Electrical control (on-demand)	(Noninvasive) electrically controlled (on-demand) drug delivery combined with real-time glucose monitoring; Wireless power management; Wireless communication; Biocompatibility with ultrathin, flexible electrical circuits, and a microcontroller chip	DR	[94]
PDMS	Gaseous tritium light sources	Light responsiveness	A first phototherapeutic SCLs to manage diabetic retinopathy by reducing retinal metabolism via suppression of rod cell dark current; Being qualified with FDA guidelines for overnight wear; Comfortable and reliability	DR	[175]
ACUVUE OASYS CLs (purchased from Johnson & Johnson)	Pirfenidone	Diffusion	50 times higher drug in the lens to cornea compared to eye drops; Suppression of gene expressions of inflammatory cytokine and profibrotic growth factor treated with pirfenidone SCLs; Significant improvement in a corneal haze after the treatment of pirfenidone CLs	OSI	[137]
Methafilcon	Dexamethasone	N/A	Sustained in vivo drug delivery for seven days; No ocular irritation; No toxicity; Prevention of suture-induced corneal neovascularization/ inflammation for seven days and lipopolysaccharide-induced anterior uveitis for 5 d	OSI	[242]
N/A	N/A	Wireless communications with programmed applications	Real-time monitoring of a biomarker for OSI and serve as a therapeutic device; Usage of smartphones to achieve an instantaneous diagnosis of OSI and automated hyperthermia treatments; Great wearability/ reliability as a noninvasive, mobile healthcare device proved by in vivo experiments using live animals and human subjects; New opportunities	Chronic OSI	[243]

Main ingredients	Active agent	Mechanism	Characteristics	Disease	Refs.
			to clinical information and the potential capability for machine learning in diagnosing disease		
PLGA	Bromfenac	N/A	Usage of ultrasonic spray technology to develop a drug-eluting IOL; Sustained drug release, being able to bypass the corneal barrier and directly reach the posterior capsule with excellent biocompatibility; In the rabbit cataract surgery: the IOL exhibited superior PCO prevention and inflammation suppression effects	PCO	[244]
PEGMA	Doxorubicin hydrochloride	MMP-2 enzyme responsive release	In vitro LEC proliferation inhibition; Great PCO prevention; Excellent intraocular biocompatibility.	PCO	[245]
HEMA	Dipicolylamine	Removal of zinc ions to deactivate excessive expression of zinc-dependent MMPs that cause corneal melting	Effective prevention of cornea degradation; DPA specifically binding to a zinc ion among all (biological) metal ions decreases the chance of side effects resulting from the depletion of other metal ions; Synthesis production on a large scale at a low cost; No adverse impact on the viability of keratocytes and corneal epithelial cells; Minimizing the risk of severe nonspecific side effects.	Corneal Melting	[246]
HEMA, NVP, MAA	Ceria NPs	CeNPs to effectively eliminate ROS	The intrinsic ROS-scavenging property of the incorporate CeNPs mimicked superoxide dismutase and catalase; High transparency with excellent extracellular ROS-scavenging properties. Enhanced viabilities of human conjunctival epithelial cells and human meibomian gland epithelial cells in the presence of CeNP-CLs.	OSD	[90]
EGDMA, HEMA	Diclofenac sodium	pH responsiveness	Storability in PBS without noticeable drug loss and changes in drug release; Safe with minor ocular irritation. In vivo sustained drug release for over 24 h in tear fluid with improvement in drug residence time	Swelling of the eye	[247]
PLGA	Dexamethasone	Diffusion out of the matrix	Sustained drug delivery to the retina at therapeutic levels; Great biocompatibility; 200 times retinal drug concentrations greater compared to hourly drop use; Lower dexamethasone concentrations in blood serum.	RVI	[248]

(Abbreviation: CL: contact lens; HEMA: 2-hydroxyethyl methacrylate; NVP: 1-vinyl-2-pyrrolidinone; TRIS:3-[tris(trimethylsiloxy)silyl] propyl methacrylate; EGDMA: ethyleneglycol dimethacrylate; DMA: N,N-dimethyl acrylamide; PLGA: poly(lactide-co-glycolide); MAA: methacrylic acid; PDMS: polydimethylsiloxane; VP: 4-vinylpyridine; PVA: poly(Vinyl Alcohol); HTCC: quaternized chitosan; AgNPs: Silver nanoparticles; GO: graphene oxide; AAO: anodic aluminum oxide; AA: acrylic acid; LEC: lens epithelial cell; OSD: ocular surface disease; RVI: retinal vascular leakage; PCO: posterior capsular opacification; OSI: ocular inflammation; DR: diabetic retinopathy; DES: dry-eye syndrome; HA: hyaluronic acid; PEGMA: poly(ethylene glycol) methacrylate; MMP: matrix metallopeptidase; ROS: reaction oxygen species; CeNPs: ceria nanoparticles; NVP: N-vinylpyrrolidone; PBS: phosphate-buffered saline; TMSPMA: 3-(trimethoxysilyl)propyl methacrylate).

Table 6.

SCLs in clinical trials

Title (NCT number)[a)]	Sponsored institution/ personnel	Application/objective	Investigated condition(s)	Phase	Refs.
LSH Silicone Soft Hydrophilic CLs for Daily Wear (NCT01735045)	Szabocsik and Associates, Inc.	To evaluate the performance of the LSH (mangofilcon A) soft silicone CLs for myopia correction	Myopia	Phase III	[309]
TCLDDS in Patients With Recurrent Cystoid Macular Edema (NCT04225611)	Massachusetts Eye and Ear Infirmary	To investigate the safety, tolerability, and feasibility of a dexamethasone-eluting TCL-DDS for the treatment of recurrent cystoid macular edema	Cystoid Macular Edema	Phase I/ Phase II	[310]
Latanoprost Eluting CL for Treating Glaucoma and Ocular Hypertension (NCT04500574)	Massachusetts Eye and Ear Infirmary	To assess the safety, comfort, and feasibility of lowering IOP using a novel CLDDS with latanoprost	Glaucoma/Ocular Hypertension	Phase I	[311]
Prolongation of CL Comfortable Wear Duration by CLM2 Topical Gel (NCT03994406)	Glia, LLC	To investigate comfortable wear duration time of CLs; test versus control	CL-induced CD/CFS; CL acute red eye	Phase II	[312]
The Impact of CL CoF on the Development of LWE (NCT03209505)	University of Houston	To determine the amount of LWE induced in subjects after SCL fitting that do not have LWE at study enrollment	LWE	Phase IV	[313]
Safety Study of a CL With Ketotifen in Healthy, Normal Volunteers (NCT00889252)	Vistakon Pharmaceuticals	To evaluate the safety of SCL in healthy regular volunteers	Allergic Conjunctivitis	Phase III	[314]
Anesthetic Impregnated Bandage Soft CL in Pain Management After PRK (NCT04283331)	Beeran Meghpara, MD	To explore the potential of an anesthetic soaked bandage SCL in reducing pain levels compared to a bandage SCL alone after PRK	Myopia/ Hypermetropia/RE/ Astigmatism	Phase IV	[315]
Evaluating the Impact of JJVC Senofilcon A – Based CL With New UV-blocker on Day and Night Driving Performance (NCT03330275)	Johnson & Johnson Vision Care, Inc.	To evaluate the effect of JJVC Senofilcon A-based CLs with a new UV-blocker on day and night driving performance	VP	Phase II	[316]
A Clinical Study Comparing the Comfort of Three Commercially Available CLs (NCT02298400)	ORA, Inc.	To compare the comfort of three commercially available CLs	CL Complication	Phase IV	[317]

(Abbreviation: TCL-DDS: therapeutic contact lens drug delivery system; LWE: lid wiper epitheliopathy; PRK: photorefractive keratectomy; CoF: coefficient of friction; CD: corneal disorder; CFS: corneal fluorescein staining; RE: refractive errors; VP: visual performance).

[a)] Indicates data accessed in August of 2021.