CLEAR - contact lens technologies of the future

Lyndon Jones, FCOptom, DSc, FBLCA[1,2]
Chau-Minh Phan, PhD[1,2]
Alex Hui OD, PhD[3]
Michael Leonard Read, MCOptom, PhD, FBCLA [4]
Dimitri Azar, MD[5,6]
John Buch, OD, MS[7]
Joseph B. Ciolino, MD[8]
Shehzad Anjam Naroo, FCOptom, PhD, FBCLA[9]
Brian Pall, OD, MS[7]
Kathleen Romond, MPH[5]
Padmaja Sankaridurg, BOpt, PhD[3,10]
Cristina M. Schnider, OD, MSc, FBCLA[11]
Louise Terry, PhD[12]
Mark Willcox, PhD[3]

1. Centre for Ocular Research & Education (CORE), School of Optometry & Vision Science, University of Waterloo, Waterloo, Canada.
2. Centre for Eye and Vision Research (CEVR), Hong Kong
3. School of Optometry and Vision Science, UNSW Sydney, Sydney, New South Wales, Australia, 2052
4. Eurolens Research, Division of Pharmacy and Optometry, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester M13 9PL, United Kingdom.
5. Department of Ophthalmology and Visual Sciences, University of Illinois College of Medicine, Chicago, IL, USA
6. Verily Life Sciences, San Francisco, CA, USA
7. Johnson & Johnson Vision Care, Jacksonville, Florida
8. Department of Ophthalmology, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, MA, USA
9. School of Life and Health Sciences, Aston University, Birmingham, B4 7ET, UK
10. Brien Holden Vision Institute, Sydney, Australia
11. C Schnider Insights & More, Brush Prairie, WA, USA
12. School of Optometry and Vision Sciences, Cardiff University, UK

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Acronyms

CE	Conformité Européenne
ConA	Concanavalin A
DEAA	*N,N*-diethylacrylamide
DED	Dry eye disease
Dk/t	Oxygen transmissibility
ECP	Eye care professional
EGDMA	Ethylenglycol dimethacrylate
FDA	Food and Drug Administration
HEMA	Poly (2-hydroxyethyl methacrylate)
HPMC	Hydroxypropyl methylcellulose
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IL	Interleukin
IOP	Intraocular pressure
LED	Light emitting diode
MAA	Methacrylic acid
MMP	Matrix Metalloproteinase
PEG	Polyethylene glycol
PLGA	Poly (lactic-co-glycolic acid)
PMMA	Polymethylmethacrylate
PoC	Point-of-care
PoLTF	Post-lens tear film
ROS	Reactive oxygen species
TFOS DEWS II	Tear Film & Ocular Surface Society Dry eye workshop II
TNF	Tumor necrosis factor
UV	Ultraviolet

Abstract

This review examines the use, or potential use, of contact lenses aside from their role to correct refractive error. Contact lenses can be used to detect systemic and ocular surface diseases, treat and manage various ocular conditions and as devices that can correct presbyopia, control the development of myopia or be used for augmented vision. There is also discussion of new developments in contact lens packaging and storage cases.

The use of contact lenses as devices to detect systemic disease has mostly focussed on detecting changes to glucose levels in tears for monitoring diabetic control. Glucose can be detected using changes in colour, fluorescence or generation of electric signals by embedded sensors such as boronic acid, concanavalin A or glucose oxidase. Contact lenses that have gained regulatory approval can measure changes in intraocular pressure to monitor glaucoma by measuring small changes in corneal shape. Challenges include integrating sensors into contact lenses and detecting the signals generated. Various techniques are used to optimize uptake and release of the drugs to the ocular surface to treat diseases such as dry eye, glaucoma, infection and allergy. Contact lenses that either mechanically or electronically change their shape are being investigated for the management of presbyopia. Contact lenses that slow the development of myopia are based upon incorporating concentric rings of plus power, peripheral optical zone(s) with add power or non-monotonic variations in power. Various forms of these lenses have shown a reduction in myopia in clinical trials and are available in various markets.

Contact lenses in the future will likely have functions other than correction of refractive error. Lenses designed to control the development of myopia are already commercially available. Contact lenses as drug delivery devices and powered through advancements in nanotechnology will open up further opportunities for unique uses of contact lenses.

1 Introduction

Contact lenses were invented to correct refractive error and they have become a successful, convenient and widely used commodity for this purpose. However, looking forward into the not-so-distant future, the potential applications for these devices are proliferating to uses where vision correction *per se* is often not the main intention. Industries as far ranging as bio-sensors, pharmaceuticals, defence and the entertainment sector could all potentially apply contact lens-based technologies to achieve solutions to problems for their specific unmet needs. This review will explore some of these innovations and consider how these efforts will change the way contact lenses are used in the future.

2 Diagnosis and Screening for Systemic Disease

Historically, the quantification of analytes in the tear film has primarily focused on the diagnosing and monitoring of ocular conditions. However, it is increasingly apparent that the tear film contains a wide range of biomarkers that may help diagnose systemic disease for a range of conditions [1]. A contact lens-based diagnostic device would allow a biosensor to be placed in close proximity to the ocular tissue and be bathed in the tear fluid, which is known to reflect pathophysiological changes in several systemic and ocular diseases, as described in Table 1.

Table 1: Systemic disease biomarkers found within the tear film

Disease	Potential tear biomarkers
Alzheimer's disease	Increased levels of dermcidin, lacritin, lipocalin-1 and lysozyme-C [2]
Cancer	Increased levels of lacryglobin [3, 4], changes in combination of specific proteins [5]
Cystic fibrosis	IL-8 and IFN-γ [6], MIP-1α [7] and MIP-1β [8]
Diabetes	Increased levels of glucose [9], advanced glycation end products [10], cytokine changes [11]
Multiple sclerosis	Oligoclonal bands of IgG [12, 13] and α-1-antichymotrypsin [14]
Parkinson's disease	TNF-α [15] and oligomeric alpha-synuclein [16]
Thyroid disease	IL-1β, IL-6, IL-17, TNF-*α* [17] and IL-7 [18]

IL – Interleukin; IFN – Interferon; MIP – Macrophage inflammatory protein; TNF – tumor necrosis factor; IgG – Immunoglobulin G.

Biochemical tear film sensing technology is rapidly evolving, allowing the incorporation of either electrochemical or optical sensing technologies into future diagnostic contact lenses [19]. This approach offers distinct advantages over direct tear sampling, as a contact lens enables the cumulative detection of biomarkers during the wearing period, potentially increasing assay sensitivity [20]. In addition, a range of sensing technologies is now available which could be incorporated into future diagnostic contact lenses to monitor clinical ophthalmic biomarkers, including blink tracking [21], eye movement tracking [22], pupillary responses [23] and retinal vessel pulsation/imaging [24]. In addition, due to the relatively large surface area of the contact lens, there is potential for multiplexing to monitor various biomarkers at the same time via a single device [25, 26]. Future research will likely focus on identifying and refining the key biomarkers for these conditions, establishing the specificity and sensitivity of the biomarkers for the particular diseases, and developing tear film capturing and sensing technologies to allow such analysis to be truly diagnostic. This will allow the potential for simple contact lens-based

technologies that could diagnose systemic disease at an earlier stage, allowing prompt management and improved clinical outcomes.

Two specific examples of research in this area relate to diabetes monitoring via tear film glucose detection and detection of cancer-markers within the tear film.

2.1 Diabetes monitoring via tear-film glucose detection

Diabetes, a chronic condition characterised by high levels of blood sugar, affects more than 463 million people worldwide and is on the rise [27]. As there is currently no cure, effective monitoring and control of blood glucose levels are critical in managing the condition and its complications. The gold standard for blood glucose monitoring is the finger-prick method, where a lancet is used to pierce the skin of a finger or another site to obtain a blood sample that is read by a glucose meter. This procedure can cause discomfort and is inconvenient, while also raising the risk of loss of sensation and secondary infection in repeatedly sampled areas [28]. Non-invasive methods for glucose detection have thus been proposed to alleviate these complications and improve patient quality of life.

The tear fluid is a potential site for non-invasive glucose monitoring due to its relative accessibility. The concentration of tear glucose is higher in diabetics than healthy individuals [9] and several groups have proposed contact lens-based biosensors to measure tear glucose levels [29-41]. This concept would open up the possibility of continuous tear glucose monitoring rather than the “snapshots” which are provided by monitoring through finger prick testing.

2.1.1 Mode of detection

Glucose detection using a biosensor can be broadly categorised into either optical or electrochemical methods (see Table 2 for examples).

2.1.1.1 Optical detection methods

For optical detection, the binding of glucose to the sensors typically results in a colourimetric or fluorescence change which is measured using an external reader such as a photodetector or a smartphone. Optical sensors are relatively inexpensive

and simple to fabricate since they do not require any additional embedded circuits for power or communication. However, optical detection can be somewhat subjective and prone to errors influenced by elements such as lighting conditions and detector distance.

2.1.1.2 Electrochemical detection methods

Electrochemical sensors are more complex, requiring additional micro-components such as a power source, microprocessor and an antenna for external communication. The underlying mechanism of glucose detection in these systems is a redox reaction of glucose by a catalyst into hydrogen peroxide, which is then oxidised at an electrode to release free electrons [42-44]. The free electrons produce an electric current that is proportional to the amount of glucose present in the system. The catalyst can be an enzyme [42-44], a metal [35-37] or another glucose-binding molecule [45].

The advantages of the electrochemical approach is that these systems are highly accurate and can provide continuous and seamless real-time monitoring of tear glucose. The challenge of such a system lies in methods harnessing the electric current, translating it into a quantifiable signal and creating the accessory micro-components to an electrochemical sensor. Previous work has discussed the development of a contact lens platform that coupled the current from the glucose sensor with an antenna and microprocessor [29, 30, 46]. This system was powered entirely wirelessly using radio frequencies, solving the difficulties involved with powering the individual micro-components [29, 30, 46]. This concept spurred several startup companies that have tried to develop a so-called “smart” glucose contact lens, the most prominent example being led by the tech giant Google (Mountain View, CA, USA) in 2014, followed later by a collaboration between Google and Novartis (Basel, Switzerland) [34].

2.1.2 Glucose sensor types

Several forms of glucose-sensors exist in the contact lens-based glucose sensors proposed (see Table 2 for examples).

2.1.2.1 Boronic acid-based glucose sensors

Boronic acids reversibly bind to carbohydrates, particularly diol-containing molecules such as glucose. These acids have unique optical properties when bound to glucose, resulting in a colourimetric or fluorescence change, depending on the specific boronic acid derivative used [47, 48].

2.1.2.2 Concanavalin A-based glucose sensors

Concanavalin A (ConA) is a lectin or carbohydrate binding protein. A ConA competitive binding assay biosensor has been applied to a contact lens system [32, 49]. In the absence of glucose, ConA is bound to a ligand, such as fluorescein-labelled dextran and produces minimal fluorescence [32, 49]. In the presence of glucose, the ligand is displaced and glucose instead binds to ConA, resulting in an increase in fluorescence related to the amount of glucose present, with the change in fluorescence measured using a handheld fluorometer [32, 49, 50].

2.1.2.3 Enzymatic glucose sensors

Enzymatic detection of glucose by glucose oxidase, which specifically targets glucose, has both high sensitivity and selectivity [35, 51]. In the presence of water and oxygen, the enzyme converts glucose to gluconic acid and hydrogen peroxide. The hydrogen peroxide is then oxidised at the anode of an electrochemical probe to produce a current corresponding to the amount of glucose in solution [51].

The significant advantage of enzymatic sensors lies in their specificity for the molecule in question, but a challenge lies in the integration of the microelectronic components into a contact lens platform. Other drawbacks relate to stability, especially for long term storage [35, 43] and that the sterilisation methods typically used by the contact lens industry (such as autoclaving) will generally denature the enzymes.

2.1.2.4 Metal-based glucose sensors

The stability problems associated with enzymatic sensors can be overcome by using metals such as platinum [35], gold [37], copper oxide [36], zinc or nickel oxide [52] and molybdenum disulfide [53]. However, these sensors are less specific and sensitive to glucose than enzymes such as glucose oxidase.

2.1.3 Challenges to contact lens-based glucose sensors

Aside from the technical challenges associated with integrating a glucose sensor (whether optical or electrochemical) into a contact lens, other issues also challenge the viability of these devices. There is approximately 20 minutes lag time between changes in blood glucose and tear glucose levels [54-56]**.** For patients with insulin-dependent diabetes that require real-time information to accurately calculate and administer insulin to avoid hyper- and hypo-glycemia, the discordance between tear and blood glucose levels [57, 58] may be fatal. Thus, for severe diabetics, a contact lens-based glucose sensor which only measures levels of glucose in the tears may not be relied upon as the only glucose monitoring device. There will also be market challenges related to the adoption of these smart contact lenses, due to their cost and practicality, in addition to regulatory hurdles to obtain approval for the use of such diagnostic devices. The initial hype towards the commercialisation of a contact lens-based glucose sensor has waned since Google and Novartis put aside their joint venture in 2018, citing a variety of technical challenges [59]. However, the outlook remains positive as the fields of biosensors, microelectronics and nanotechnology continually advance and converge.

Table 2**:** Examples of glucose biosensors developed for contact lenses

Mode of detection	Glucose sensor	Reader
Fluorescence [60]	Boronic acid, Concanavalin A	External detector
Colourimetric [47]	Boronic acid	Colour chart
Fluorescence [61]	Boronic acid	Photodetector
Fluorescence, colourimetric [62]	Boronic acid, Concanavalin A	External detector
Fluorescence, colourimetric [63]	Boronic acid, Concanavalin A	Photodetector
Fluorescence [64]	Boronic acid, Concanavalin A	External detector
Light emitted [65]	Boronic acid	Photodetector
Electrochemical [45]	Boronic acid	Electrode

Fluorescence, luminescence [66]	Boronic acid	External reader
Light emitted [31]	Boronic acid	Smart phone
Optical [33]	Boronic acid	External reader
Absorbance [50]	Concanavalin A	Spectrophotomer
Fluorescence [49]	Concanavalin A	Handheld photofluorometer
Fluorescence [32]	Concanavalin A	Handheld photofluorometer
Electrochemical [46]	Glucose oxidase	Electrode
Electrochemical [29]	Glucose oxidase	Smart phone
Electrochemical [30]	Glucose oxidase	Handheld reader or smart phone
Electrochemical [67]	Glucose oxidase	External receiver
Electrochemical [38]	Glucose oxidase	On lens display
Electrochemical [68]	Metal oxides	External receiver

2.2 Cancer detection

The tear film is well suited to the detection of cancer biomarkers as it is less biologically complex than blood [69, 70] and tear sampling is also relatively non-invasive compared with collecting blood samples.

Early work in tear film cancer detection highlighted the presence of a tear film protein called lacryglobin [71] that has similarities to mammaglobins upregulated in breast cancer [72]. Lacryglobin is present in the tear film of patients with colon, lung, breast and prostate cancer, as well as patients with a family history of cancer [3]. A protein analogous to lacryglobin is also present in the tear film of dogs suffering from a range of cancers [4]. Lebrecht and colleagues used time-of-flight mass spectroscopy to compare the tear film of cancer patients and healthy controls, identifying differences in 20 tear film biomarkers [73-75].

Contact lens technology may play a key role in offering a platform for sensing these cancer biomarkers, either via a direct measurement using an electronically-active biosensor mounted on a contact lens [76] or by the natural accumulation of tear components within a contact lens material during wear, which could then be analysed following contact lens removal. Such contact lens-based technology would allow early diagnosis, improved monitoring and gauge susceptibility to a range of cancers, aiding the clinician in providing improved patient care.

3 Diagnosis and Screening for Ocular Disease

3.1 Intraocular pressure monitoring for glaucoma

Glaucoma is a leading cause of blindness globally and thus developments in improving intraocular pressure (IOP) monitoring are of great interest to clinicians. However, methods of measuring IOP in clinical practice are suboptimal and do not reflect its dynamic nature, including its circadian variation and short-term fluctuations [77]. Current gold standard tonometry techniques provide an estimate of the IOP only over a matter of seconds, are generally only available during typical clinic hours and take the reading in an upright, seated position. However, studies have suggested that large IOP fluctuations, in particular nocturnal pressure spikes not captured with conventional tonometry, could have a direct impact on glaucoma progression [78, 79]. The use of continuous monitoring over a 24-hour period would therefore provide a more holistic description of the patient's IOP profile and contact lens sensors have been suggested as a suitable vehicle for this purpose [80].

3.1.1 Contact lens-based devices to monitor IOP

The Triggerfish contact lens sensor (Sensimed, Switzerland) (Figure 1) is a commercially available contact lens device that permits extended monitoring of IOP. This flexible silicone-based contact lens was first described in 2004 [81] and has received both CE marking and FDA approval for 24-hour measurement of IOP. Rather than measuring IOP directly, the device measures minute dimensional changes in corneal shape, which correspond to changes in ocular biomechanical properties and volume, as well as IOP [82]. This is based on the principle that a change in IOP of 1 mmHg elicits a change in corneal curvature of 3 µm, for an average corneal radius of 7.8 mm [82, 83]. Initial results demonstrated good

reliability of the device during ocular pulsation and against known induced IOP changes in porcine eyes [83].

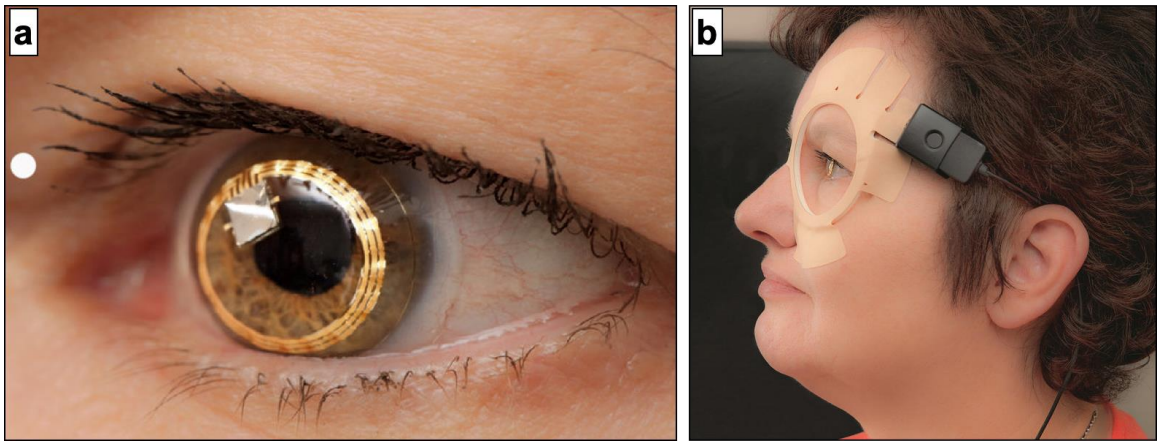

Figure 1. (a) Contact lens sensor (SENSIMED Triggerfish) on the eye; (b) The sensor transmits the information gathered when in situ to an antenna, which is connected to a portable recorder. (Sensimed AG).

The Triggerfish device has an embedded circumferential sensor consisting of two strain gauges that measure dimensional change. The gauges sit in a circular arc of 11.5 mm diameter, which is the typical position of the corneo-scleral junction, where maximal corneal deformation due to IOP change is assumed to occur [80]. Measurements are recorded for 30 second periods every 5 minutes during wear, providing 288 datapoints over a 24-hour period [82]. The readings are transmitted wirelessly to an adhesive antenna patch placed around the eye and then through a wired connection to the portable receiver worn by the patient. Since the device is wearable, the patient can perform their daily activities as normal with minimal interruption, although device instructions suggest avoiding driving and contact with water. The device is available in three base curves to aid in achieving an appropriate fit and has an oxygen transmissibility (Dk/t) of 119 units to facilitate overnight wear.

Many clinical studies have demonstrated that the Triggerfish device has good safety and tolerability in both healthy and glaucomatous eyes [82, 84-87]. The most common adverse effects seen in clinical trials include transient blurred vision, conjunctival hyperaemia and superficial punctate keratitis. These mild effects are common, being present in up to 95% of wearers [82, 85], but typically resolve within

24-48 hours. A reduction in best corrected visual acuity during and after wear has been noted, possibly due to orthokeratologic effects of intentionally tight-fitting lenses (to minimise lens mobility) [88, 89]. Studies report that the device captures reproducible 24-hour IOP profiles [90-92], although its validity in estimating IOP remains unknown [93]. The device outputs measurement in 'mV equivalent' units, which are relative to its initial baseline measurement. These outputs are not comparable to tonometric measurements in mmHg, making direct evaluation of accuracy difficult [90] and further work is warranted to explore the accuracy of the device and its relationship with conventional IOP measurement. Continuous IOP monitoring has enabled further investigation of several factors beyond what is possible with conventional measurement techniques, including the effects of topical medication and surgical interventions, certain activities and body position (e.g. supine versus seated), and circadian rhythm [80].

The Triggerfish is likely to be the first in a generation of commercially available contact lens-based devices to monitor ocular biomarkers of disease. However, there are a number of limitations with the current device, principally driven by the bulky microprocessor and strain gauge assembly, which when encapsulated within the contact lens results in a 325 µm centre thickness, which is 2 to 3 times thicker than a typical contact lens. Consequently, to ensure sufficient oxygen is able to pass through the lens, particularly during overnight wear, the lens is manufactured from a highly oxygen permeable silicone elastomer material. This combination of a thick lens and relatively stiff material may potentially negatively impact the sensitivity of the strain gauge system and comfort during wear [94]. The need for an external adhesive patch to power and monitor the system would also ideally be addressed in a less obtrusive manner, either by integration into a spectacle frame or by on-lens power systems.

These limitations have led to a range of different technologies being studied in order to develop future systems that are less invasive and more effective at monitoring IOP. A metal strain gauge electrode with an integrated Wheatstone bridge circuit has been developed allowing a thinner lens design and improved sensitivity, although it lacks integration of the control electronics or aerial and evaluation was limited to laboratory testing only [95]. The use of a flexible, highly piezoresistive organic bilayer

film sensor has been proposed, which was reported to improve sensitivity to the subtle changes in ocular surface curvature (3-10 times greater sensitivity in comparison with metal strain gauges) [96]. The prototype film sensor was mounted on a rigid contact lens annulus with a wired connection to the external monitoring equipment. Evaluation in a laboratory and clinical setting (single participant) highlighted the ability of the system to monitor change in IOP. The incorporation of a graphene woven fabric into a contact lens has been described [97], demonstrating excellent sensitivity to ocular surface deformation due to large changes in resistivity in the stretchable fabric when IOP changes altered corneal curvature. The graphene woven fabric material was also reported to have reasonable transparency and biocompatibility, although evaluation was limited to laboratory testing with tethered resistance measurements.

An alternative to monitoring IOP with resistive strain sensors is the use of capacitive sensors, which are generally thought to have a higher sensitivity and lower power consumption [98]. These sensors monitor subtle changes in corneal curvature by measuring the resulting change in capacitance due to altered capacitive gap spacing. When combined with an inductor, this change in capacitance influences its resonant frequency allowing this passive device to be read wirelessly [99]. In addition, capacitive sensors are more compact, with a lens thickness of around 100 µm achievable [100]. Graphene-silver nanowire technology has been sued to form a capacitance sensor within a silicone elastomer contact lens [99]. Recently, a passive doughnut-shaped IOP sensor has been developed which consists of a microfabricated capacitor and variable inductor (in the form of a stretchable serpentine wire) that serves as both the sensor and antenna [101]. Near field electromagnetic coupling is used to wirelessly monitor the resonant frequency of the sensor, enabling continuous monitoring of change in corneal curvature induced by IOP variation. This relatively simple passive device avoids the need for lens-mounted electronic chips, with laboratory testing suggesting good sensitivity, although the authors are yet to report on any clinical evaluation.

With many of these IOP monitoring systems, an obvious limitation is that the sensor measures changes in corneal curvature as a proxy for IOP. This means that the measurements are dependent on the biomechanical properties of the human eye

and their output is not a direct measure of pressure. In an attempt to address this, a novel IOP sensing contact lens has been developed which operates on the basis of applanation rather than topographical change [102]. This silicone hydrogel lens contains a capacitive pressure sensor mounted into an annular recess in the mid-periphery of the lens. This annular recess causes the underlying portion of the lens to protrude and experience a reactive deformation when pressed into the cornea by the blinking action of the lids or during sleep. The deformation is detected by the capacitive sensor and wirelessly monitored by a portable external controller. This system is claimed to provide profiles of IOP change in actual pressure values (mmHg) and is reportedly less influenced by the mechanical behavior of the cornea and the sclera [103]. The system has undergone pilot clinical testing, with the device reported to be able to track IOP changes whilst causing only low levels of discomfort [104].

Due to the complexity of integrating electronics within a contact lens, microfluidic and optical technologies have also been considered. Microfluidic contact lenses typically contain a network of enclosed microchannels, with a fluid level indicator that tracks changes in internal volume due to variations in corneal curvature or IOP. It is envisaged that these microfluidic IOP sensors could be read directly by the clinician or imaged using a mobile phone camera [105, 106]. An alternative approach is based on the generation of optical nanostructures using laser processing on a commercial contact lens, which forms a holographic optical sensor [107]. This type of sensor would be read by observing the spectral shift of reflected light due to changes in corneal curvature or IOP [105, 106]. Although these optical and microfluidic sensors lack the ability to track IOP during sleep or on a continuous basis, their relative simplicity may allow for more rapid sensor development and a lower cost device than electronically active systems [105].

Rapid progress is being made in developing a broad range of biosensing technologies to support the development of biocompatible minimally invasive contact lens for IOP monitoring. However, with the exception of the Sensimed Triggerfish lens, many of the proposed sensors have had limited, if any, clinical evaluation. This likely relates to (i) the complexity of integrating electronics within a contact lens, (ii) the early stage of development of many of these new sensors and (iii) the costs

associated with medical device development and clinical evaluation. However, the latest IOP sensor technology from Sensimed AG (known as “Goldfish” (Clinicaltrials.gov number: NCT03689088)), highlights continuous monitoring of IOP in humans over a 24-hour period [108] using a micro-electro-mechanical system pressure sensor technology, offering an exciting glimpse into the potential impact contact lens-based technology could have on the future of glaucoma diagnosis and management.

3.2 Dry eye disease diagnosis and monitoring

The diagnostic approach proposed for confirmation of dry eye disease (DED) in the TFOS DEWS II report involves a screening questionnaire and measurement of various homeostasis markers, including non-invasive tear break-up time, tear film osmolarity and ocular surface staining [109]. Due to the placement of contact lenses on the ocular surface, contact lens-related technology has the potential to provide additional clinical information to aid in the diagnosis and monitoring of DED. A full description of the ocular surface anatomy, which may be useful to refer to, is given in the CLEAR Anatomy and Physiology of the Anterior Eye report [110].

3.2.1 Osmolarity

Tear film osmolarity is an important tool in the diagnosis and management of DED [109, 111]. Point-of-care (PoC) osmometers, based on lab-on-a-chip technology, are now available that measure the osmolarity of microscopic tear film samples using electrical impedance [112]. Given the importance of osmolarity to the development of DED, a number of research groups have studied the feasibility of measuring this via contact lens technology. Researchers have developed a prototype contact lens which can evaluate tear osmolarity, tear evaporation rate and ocular surface temperature [113]. The authors aim to apply this technology in a clinical setting to assist in DED diagnosis, evaluate the effectiveness of clinical treatments and monitor clinical performance. This approach has the advantage of providing a continuous assessment of these clinical metrics. However, it is relatively complex, requiring external power induction and the integration of complex electronics within the contact lens.

An alternative approach to determining the electrolyte composition of the tear film uses coloured or fluorescent dyes that are integrated within the contact lens material. A microfluidics system has been developed [26], where a number of fluorescent chemical sensors were multiplexed in cavities engraved into a scleral lens. A handheld fluorescence imaging device was also developed to read the sensors and provide quantitative measurements. A similar approach has been used [25], where a hydrophobic ion-sensitive fluorophore was bound into commercial silicone hydrogel lenses, allowing individual ion concentrations in tears to be quantified. These fluorophore-based systems appear to avoid much of the complexity of an electronic sensor approach and are more specific about the concentration of each ionic species in tears than conventional osmometers. However, significant clinical work is required to better understand how these sensors would work in the chemically complex tear film environment, to review the safety of these dyes in a clinical setting and to understand how these dyes might otherwise influence clinical performance.

Finally, holographic grating sensors, which have previously been used to monitor analytes such as metal ions, glucose, water content and pH, have also been proposed as contact lens osmolarity sensors [47, 114-117]. When a holographic sensor comes into contact with its analyte, the polymer within the sensor grows or shrinks, resulting in a change in the colour of the hologram (with the wavelength of the reflected light proportional to the analyte concentration). Holographic sensors can be produced on a commercial contact lens by direct laser processing for the sensing of sodium ion concentrations [107]. This approach is appealing as these sensors are purely optical, relatively low cost, compatible with hydrogel lens materials and require no complex electronics. However, they are yet to undergo any significant clinical evaluation and it is not fully understood how they are likely to perform in the biologically complex tear film environment.

3.2.2 Inflammatory cytokines and other biomarkers

In DED, a range of cytokines/chemokines are elevated in the tears, including TNF-α, IL-6, IL-17a and IL-8 [118]. Although no contact lens-integrated cytokine sensor currently exists, the feasibility of integrating antibody functionalised sensors into thin flexible polymer membranes for continuous studying of analytes (in this case

monitoring IL-6 using a wearable diagnostic sweat biosensor) has been described [119]. This type of technology, integrated into a contact lens, would allow the development of a continuous monitoring system for tear film cytokines, in addition to PoC diagnostics, both potentially useful tools in the diagnosis and monitoring of DED, contact lens discomfort and other ocular surface diseases.

Immunoglobulin proteins found in the tears are also known to vary in concentration in a range of ocular surface diseases [120-123]. Optical biosensing, using a photonic nonporous crystal structure within a hydrogel, has been described for use in the detection of IgG antibodies [124]. The binding of IgG to these photonic sensors results in a refractive index change, with a change in colour from green to red with increasing IgG concentration. This type of photonic crystal sensor is simple, low-cost, label-free and requires a simple imaging system for the detection of immunoglobulin proteins, meaning that it is well suited to PoC testing. This technology could also potentially be integrated into contact lenses to form wearable biosensors [124], although improvements in sensor sensitivity may be required to detect trace amounts of biomarkers within tears [19], unless changes in the concentration of sIgA are diagnostic, as this is in relatively high concentration in tears [125].

An alternative approach for tear film biosensing is the use of contact lenses to collect biomarkers for PoC diagnostics. An example of this approach is the development of a portable reader to quantify lysozyme, using a contact lens as the sample collector [126]. An example of this system has been described in the literature, where a balafilcon A lens was worn for 15 minutes and then washed in a microtube containing a reaction buffer. The lens was then discarded and the solution mixed with a fluorophore, with the fluorescence monitored over time using a mobile phone-based well-plate reader. The presence of lysozyme in this assay reduces the degree of fluorophore quenching, with the degree of fluorescence proportional to the activity of lysozyme. This type of PoC technology could enable the clinician to diagnose and monitor diseases such as dry eye or Sjögren's syndrome, where reduced concentrations of tear film proteins such as lactoferrin and lysozyme occur [127]. In addition, this technique could be adapted to detect the presence of pathogens such

as *Staphylococcus aureus*, viruses that cause conjunctivitis or *Acanthamoeba* [126]. Indeed, it may be that the material and/or design of a contact lens could specifically be developed to extract analytes of interest from the tear film, particularly where they are present in only trace quantities. This PoC approach has the potential for advanced health diagnosis and monitoring and for personalised medicine-related applications.

3.2.3 Blink monitoring, material dehydration and ocular surface temperature

Blinking frequency and completeness are known change during contact lens wear [128] but are also important clinical metrics in the diagnosis and management of both DED and contact lens discomfort [129-131]. Although blinking can be studied in a clinical setting, the integration of a blink sensor within a contact lens would allow continuous monitoring of blink dynamics whilst undertaking real-world activities. In addition to IOP monitoring, the commercially available Sensimed Triggerfish lens has been reported to be capable of tracking basic blinking characteristics during lens wear, due to a spike in resistance associated with blinking [132]. However, the increased thickness and modulus, and the invasive nature of the external antennae are likely to interfere with natural blinking dynamics. A contact lens-based blink monitoring system has been described [21], where transient reductions in light falling on an integrated photo-sensor would allow the frequency and completeness of eyelid blinking to be monitored, although this idea currently appears to be only conceptual in nature.

Another technology with potential application in diagnosing and monitoring DED is a structurally coloured contact lens sensor to detect changes in moisture and pressure by altering its colour [133]. These lenses were manufactured by dispensing silica particles onto the concave section of the contact lens mould, forming a highly ordered ring-like crystalline template, which was then polymerised into a hydrogel contact lens material. The contact lens was then placed in acid to etch the silica particles and subsequently washed with deionised water. The resulting contact lens had an inverse opal structure and displayed brilliant colour in the lens periphery. During material dehydration, polymer shrinkage reduces the spacing of the inverse opal structures, with the lens periphery displaying a visible shift in colour, which can be quantified using a spectrophotometer. In addition, the material is sensitive to

pressure, due to the associated decrease in structure spacing, leading to a decrease in the reflectance wavelength. This may have diagnostic value in highlighting surface desiccation and/or increased pressure applied to the contact lens due to inadequate lubrication in DED (in addition to the potential of monitoring IOP). Although these devices have yet to undergo clinical testing, their simple approach to measuring the variation in hydration and pressure, suggests that this type of sensor holds promise for PoC diagnosis and monitoring of conditions such as DED and contact lens discomfort.

Ocular surface temperature has also been studied in relation to DED, as an unstable tear film is thought to increase tear film evaporation, resulting in a relative cooling of the ocular surface [134-137]. An optical temperature sensor has been developed, where temperature-sensitive liquid crystals incorporated into a contact lens exhibited a fully reversible temperature-dependent colour change [138]. An alternative approach [139] relates to the incorporation of an electronic temperature sensor into a contact lens, with the change in temperature over the interblink period reported to be useful in diagnosing DED. Depending on the placement of these sensors, it may be possible to independently sample the temperature of the underlying ocular surface (which is potentially raised in DED due to inflammation) and the temperature at the contact lens/pre-lens tear film interface (which is potentially reduced in DED due to evaporative cooling).

3.3 Monitoring of ocular vasculature

Monitoring of the vascular system is critically important in the medical management of a wide range of health conditions. Historically, devices to measure characteristics such as heart rate, oxygen saturation and the hyperaemic response of tissue were medical instruments, but this technology is increasingly being found in consumer technology, such as mobile phones and wearable technology. The eye is an ideal site to monitor the vascular system, as it allows an unobstructed view of the blood vessels in both the retina and conjunctiva.

3.3.1 Retinal vasculature

Typically, retinal imaging is performed using ophthalmic instrumentation in a clinical setting, but a recent patent [140] has proposed the incorporation of an ultrasonic transducer within a contact lens to allow retinal vascular imaging during wear. This patent describes the incorporation of an annular ring within a contact lens, which would contain the power system, control electronics and a piezoelectric element, whilst allowing the central portion of the lens to be transparent. The device would emit an ultrasonic pulse that would travel through the ocular media towards the retina. The returned ultrasonic signal would then detect pulsation of the retinal vessels and generate an image of these vessels. It is primarily envisaged that this technology would be applied to monitor general vascular health, with warnings provided to the wearer if the device detected a cardiac rhythm and/or rate of blood vessel displacement outside of a normal range. The patent also discusses its potential for monitoring ocular disease by analysing specific regions of the retinal vasculature, such as the macula or optic nerve head. Such data could either be continuously logged for later review by the clinician, provide live alerts to the wearer (either wirelessly or via an audio/visual alert via micro-acoustic/micro-photonic elements) or communicate directly with a concurrent drug delivery apparatus. Although there are numerous technical challenges in developing such a system and the patent seems to report on a concept rather than a working model, it does highlight the potential for an electronically active contact lens to monitor retinal vasculature.

3.3.2 Conjunctival response to contact lens wear

Conjunctival blood vessels are typically evaluated during an ophthalmic examination, with hyperaemia associated with ocular disease, inflammation and irritation [141]. A patent describes the incorporation of an optical sensor within a contact lens, which emits light onto the conjunctiva to allow detection of characteristics such as pulse rate and blood oxygen levels [142]. Although the proposed device is primarily intended for monitoring systemic vascular characteristics, this type of device has a range of potential uses in monitoring ocular health, including detecting hyperaemia of the bulbar and/or tarsal conjunctiva. Monitoring hyperaemia in a continuous fashion would allow a clinician to review changes in vasculature over a prolonged period of time to more appropriately manage a range of clinical conditions, including allergic

conjunctivitis, DED, uveitis and contact lens complications. In addition, the device could either highlight to the lens wearer if hyperaemia was detected (via a visual or auditory stimulus [142]), could prompt a consultation with their eyecare practitioner (ECP), or act as a trigger to dispense a therapeutic agent from a drug-delivering contact lens.

The range of approaches and technologies currently being studied as potential contact lens and PoC biosensors highlights the huge interest in the area. These biosensors, however, should not necessarily be viewed as independent technologies, as it is likely that many of these sensors provide complementary information and, in the future, these differing technologies may be brought together into a single diagnostic lens, with the capability to monitor a wide range of characteristics. Alternatively, key biosensors may be incorporated into standard contact lenses as a routine feature of the lens, such as is now the case with ultraviolet (UV) blockers or lens inversion indicators.

4 Treatment and Management of Ocular Conditions

The use of contact lenses in the treatment and management of ocular diseases is a relatively routine part of clinical practice. From providing pain relief in cases of corneal abrasion, corneal protection for trichiasis, to promotion of wound healing in neurotrophic keratitis, contact lenses are employed by clinicians for a broad variety of anterior segment conditions. However, the application of contact lenses for disease indications beyond what is currently undertaken in clinical practice has been a subject of significant research. The CLEAR Medical Use of Contact Lenses report provides a detailed review of the use of other aspects related to this section [143].

4.1 Dry eye disease

Dry eye disease is one of the most common conditions managed by ECPs and some novel contact lens options offer alternatives to the use of traditional therapies such as ocular lubricants. However, to date all of the options described have little, if any, clinical data to support their use in the management of DED and further clinical studies are required.

4.1.1 Dehydration resistant materials

A novel approach to avoiding ocular surface desiccation is the use of electro-osmotic flow [144]. This involves using an ionic contact lens material (such as a HEMA/methacrylic acid (MAA) copolymer), which serves as the fluid conduit for electro-osmotic flow generation. The placement of an arcuate anode and cathode in the lens surface allows an upward electro-osmotic flow of tear fluid within the contact lens when an electrical current is applied. This electrical current could be applied either by wireless induction or using biocompatible battery technology. The laboratory prototype described appears able to compensate for evaporative water loss and maintain post-lens tear film thickness by driving fluid flow through the lens material.

Another potential method to minimise dehydration is based around the use of an ultra-thin graphene layer on the anterior lens surface [145]. Graphene has long been hailed as a 'wonder material' and its possible uses in the field of contact lenses include its potential to act as an electromagnetic interference shield [145], as a clear flexible electrical conductor [146, 147], as a means to enhance contact lens night vision [148] and as an antimicrobial material [149]. In its application to combat desiccation, the applied graphene layer is proposed to act as a barrier to water loss from the contact lens material. In DED, the ocular surface typically shows signs of desiccation due to an unstable tear film, infrequent /incomplete blinking and subsequent air exposure [150]. Therefore, an engineered material that is resistant to dehydration does offer a potential solution.

4.1.2 Lacrimal gland stimulation

An alternative approach to the treatment of DED focuses on increasing tear production by incorporation of an electrical stimulator into a contact lens. This concept is based on a similar intranasal stimulator technology (TrueTear, Allergan, CA, USA) which delivers an intranasal electrical stimulus to stimulate tearing [151] and promote goblet cell secretion [152]. A recent patent highlighted the potential for this type of technology to be manufactured in the form of a contact lens [153]. The patent details the incorporation of a stimulator chip, which would generate an electric waveform to stimulate the cornea, conjunctiva and/or sub-conjunctiva, resulting in activation of reflex pathways and an associated increase in tear production [153].

The proposed design is envisaged to receive energy wirelessly from an external power source, potentially in the form of an external infrared light source and a contact lens mounted photodiode. To date, this appears to be conceptual, with no publicly available clinical studies. It is unclear whether such technology would produce a sub-threshold stimulus or whether the stimulus would be felt by the wearer, as is the case with the TrueTear stimulator, and whether the stimulus would be continuous or intermittent. Clinical evidence does support this neurostimulation approach to enhancing tear secretions [151, 152] and therefore if a compact and comfortable contact lens-based treatment could be developed this would be exciting technology, offering an alternative option to new and existing contact lens wearers struggling with dryness symptoms.

4.1.3 Scavenging of reactive oxygen species and matrix metalloproteinases

Oxidative stress and the presence of reactive oxygen species (ROS) at the ocular surface have been proposed to play an important role in the development of DED [154, 155] and studies have indicated that decreasing ROS at the ocular surface is a potential treatment strategy [156, 157]. However, eye drop-based ROS-scavenging/antioxidant therapeutics are likely to be rapidly eliminated from the ocular surface [158] and require frequent reapplication [157]. A soft contact lens which incorporates Ceria nanoparticles [159], which are used for their known ROS-scavenging properties [160], has recently been described. Unlike antioxidant therapeutic drops that can potentially act on intracellular ROS, these antioxidant nanoparticles are tightly embedded within the lens matrix, exhibiting their effects through the reduction of extracellular ROS levels. These lenses exhibited good transparency, biocompatibility and effective extracellular ROS-scavenging properties in an ocular surface animal model [159].

Another group of biomarkers commonly observed in ocular surface disease are the Matrix Metalloproteinases (MMPs) and a potential treatment in these conditions is the topical application of MMP inhibitors [161]. A hydrogel material containing dipicolylamine, which has a high affinity for zinc ions has been developed [162]. Sequestering of zinc results in a loss of essential ions from MMPs, resulting in their deactivation and this technology has the potential to treat conditions associated with

excessive MMP activation, such as that found with increased amounts of MMP-9 in DED [163-165].

4.2 Limbal stem cell deficiency

An intact and healthy corneal epithelium is required to achieve an effective barrier against infection and maintain the transparency required for clear vision. To achieve this, the epithelium is continuously regenerated by the limbal epithelial stem cells. Destruction of the stem cell niche in conjunction with dysfunction or depletion of the limbal epithelial stem cells, through trauma or conditions such as aniridia, leads to limbal stem cell deficiency, a debilitating condition characterised by painful chronic ulceration, inflammation and vascularisation of the cornea. Limbal stem cell deficiency may be managed by using scleral lenses, as outlined in the CLEAR Scleral lenses and CLEAR Medical use of Contact Lenses reports [143, 166]. Conventional corneal grafts are typically ineffective for managing limbal stem cell deficiency and the therapeutic aim is to boost the limbal epithelial stem cell population through transplantation of donor tissue [167]. However, this method risks damaging the limbal epithelial stem cell population in the donor eye if the fellow eye of the recipient is used in unilateral cases of limbal stem cell deficiency, or graft rejection and the need for immunosuppression if a non-self donor is used [168].

Human amniotic membranes are the substrate commonly used for culturing and delivering limbal epithelial stem cells to the ocular surface [169]. However, this process requires expensive donor screening and manipulating and securing the substrate can prove difficult [168]. The use of contact lenses as a stem cell delivery device has been demonstrated, with the contact lens vehicle doubling as a protective bandage following grafting [170]. limbal epithelial stem cells have been shown to reliably transfer from the contact lens to the ocular surface [171, 172] and an initial study of three patients with limbal stem cell deficiency reported a 100% success rate at a 12-month follow-up [173].

Contact lenses are beneficial in that they are synthetic and non-immunogenic, eliminating the xenobiotic infection risk from donor tissue. However, the risk of infection resulting from overnight contact lens wear should be considered and to

date, no clinical trials have compared the delivery of stem cells via contact lenses and amniotic membrane, and this is warranted before large-scale implementation can take place.

4.3 Pupil or iris defects

Liquid crystal cells have been recently combined with miniaturized electronic circuits forming smart platforms in order to replicate the functionality of the pupil and iris arrangement [174, 175]. This may be useful for iris defects (aniridia and coloboma), transillumination of the iris (ocular albinism), high order aberrations (keratoconus) and high sensitivity to light (dry eye syndrome and chronic migraine). Such devices are intended to enhance the iris functionality by filtering incoming light autonomously controlled by application specific integrated circuits and on-lens light sensors and power directly by near magnetic fields and rechargeable micro-batteries [175].

The smart platforms are build-up by means of microsystems technology (photolithography, sputtering, etc.), flip-chip of discrete components and thermoforming into a spherical shape fitting the contact lens body [176]. The platforms can be embedded inside soft contact lenses, thus avoiding contact with the surface of the eye and maintaining the conventional refractive correction of the ophthalmic device [177]. The device was also protected against saline solution (at least for 25 weeks) and withstood mechanical bending forces [177]. Contrasts of 1:2 between ON/OFF (effectively blocking 50% of the light at least between wavelengths of 500 nm and 600 nm) were able to be achieved, producing a pin-hole effect, and simulated results of the light filter with a 2 mm pupil diameter embedded inside a scleral contact lens with data from patients with aniridia gave maximum depth-of-focus values of 3D, 2D and 0.75D for light levels of 1000 cd/m^2, 10 cd/m^{2}and 1 cd/m^2 [174]. Contrast values higher than 1:2 will be required in order to protect eyes with big pupils from excessive light.

4.4 Diabetic retinopathy

Diabetic retinopathy is the leading cause of blindness in the working age population and is a disease of ischemia leading to microvascular retinal damage. Oxygen consumption of the rod photoreceptors is greatest during dark adaptation [178],

potentially causing hypoxia in the diabetic retina and driving further disease progression [179]. To minimise hypoxia during sleep, researchers have considered various methods of delivering light to the retina during eye closure [180] and the development of a phosphorescent contact lens for treatment of diabetic retinopathy has been described [181]. This novel silicone elastomer contact lens incorporates 24 radioluminescent gaseous tritium light sources arranged in a radial pattern, with a clear central 3 mm aperture. This design allows unobstructed vision under photopic conditions, whilst under scotopic conditions the enlarged pupil allows the retina to receive the phototherapeutic dose.

The tritium light source is well suited to use in a contact lens, due to its compact size (300 µm by 2000 µm), safety profile (it emits no ionising radiation) and long life (12-year half-life). The therapeutic benefit of this concept is debatable, with electroretinogram testing in an animal model highlighting suppressed rod dark adaptation with this contact lens technology, whilst a large multi-centre randomised clinical trial, evaluating a similar mask-based technology, found no therapeutic benefit [182]. This contact lens approach, however, has several advantages over the mask-based system, as the lens moves with the eye, avoiding issues associated with Bell's phenomena, the light does not pass through the lid (thus the light intensity reaching the retina is more consistent), the presence of light is less bothersome (due to Troxler neural adaptation) and the wavelength better controlled [181]. Future clinical trials are clearly required to investigate whether this contact lens-based approach is able to reduce the long-term risk of diabetic retinopathy and diabetic macular oedema.

4.5 Colour vision deficiency

Colour vision deficiency is the result of an abnormality or absence of one or more of the three classes of cone photoreceptors in the normal human retina that are responsible for the perception of colour. Having abnormal colour vision may impact virtually all facets of modern life from childhood to adulthood, with implications extending across sports, driving, education, occupation and health and safety issues. For these reasons, exploring and understanding technologies that remove some of these limitations are of keen interest.

Enhancement of colour perception in patients with colour vision deficiency has been mostly limited to using colour filters, which enhance colour discrimination by tuning the brightness, saturation and hue through selective absorption of certain wavelengths. The first contact lens example to use this concept was the X-Chrom lens, a red contact lens placed over one eye [183]. This long-pass filter works by darkening yellow-green objects and making orange objects appear more red and slightly darker and appears more effective for anomalous trichomats than dichromats [184]. The X-Chrom concept was modified by Harris to develop the ChromaGen lens, a soft lens system with seven hues and light, medium and dark densities [185]. Tint selection is based on patient subjective response and their use significantly reduced error rates on Ishihara plates, the D-15 test, and an improvement in subjective colour perception, though it did suffer from reports of poor vision in dim light [186].

The most recent contact lens development concerns a metasurface-based approach [187]. A large-scale plasmonic metasurface was embedded on a gas permeable contact lens to address deuteranomaly, the most common class of colour vision deficiency. These metasurfaces are engineered surfaces made of subwavelength building blocks that enable a tuneable control over their optical response, in this case, utilising the wavelength-selective features to overcome colour vision deficiency. The fabrication process utilises an electron beam lithography technique to fabricate a 40nm thick metasurface of gold building blocks on an indium-tin-oxide-coated glass. They then spin-coat a thin (~350nm) layer of polymethylmethacrylate (PMMA) and bake it to adhere the metasurface and use hot deionised water to separate the PMMA matrix with the embedded metasurface from the glass substrate. This membrane is then thermally fused to a plasma-treated gas permeable lens. Using a variety of matrices, researchers were able to demonstrate a shift in the perception of a test pigment in the case of deuteranomaly closer to the pigment viewed in cases of normal vision and were able to demonstrate contrast restoration using a simulated Ishihara plate perception test [187].

Clinical evaluation of commercial filters designed to enhance colour discrimination or “correct” colour vision deficiency indicates either no enhancement or substantial performance trade-offs. As a result, the potential benefits of the application of

spectral filtering to mitigate colour vision deficiency are uncertain. Moreover, subjective anecdotes indicate that some colour vision deficiency subjects appreciate certain spectral filters, but the mechanism is not well understood. The metasurface contact lens technology holds some promise in that it may allow “tuneable” spectral filtering functionality into contact lenses to achieve an improved success rate over a range of patients with colour vision deficiency.

5 Drug Delivery to the Ocular Surface

Drug releasing soft contact lenses have been widely studied and continue to show promise, primarily by overcoming the current limitations associated with delivering ophthalmic medications via an eye drop.

The primary disadvantage with eye drops is their low bioavailability of less than 5% [188], which is attributed to high tear turnover rates, blinking, nasolacrimal drainage, non-productive absorption by the conjunctiva, and low permeability of the cornea [189, 190]. Thus, improving bioavailability by increasing the residence time of the drug on the ocular surface remains an important area of research. When placed on the eye, a contact lens splits the tear film into the pre-lens tear film overlying the lens and post-lens tear film (PoLTF) between the back surface of the lens and the ocular surface. This compartmentalisation is beneficial to drug releasing contact lens as the PoLTF is very thin with a relatively low turnover rate [191]. When a drug releasing lens elutes its medication into the PoLTF the low tear turnover rate promotes an increased concentration of the drug behind the lens, in addition to an increased residence time, leading to potentially greater bioavailability of the drug and increased ocular penetration [190, 192]. Additional benefits include decreased frequency of drug administration, minimised systemic absorption and a more controlled drug release profile [190].

Drug delivering contact lenses may offer more accurate dosing over eye drops [193], provided the drug volume and release profile is consistent from lens to lens. Once the lens is placed on the eye, the medication will elute from the lens with few external factors influencing the release profile. Contrary to this, there are multiple factors that can affect the variability of dosing via eye drops. With conventional eye

drop bottles, patients are required to tilt their head back and keep their eye open while simultaneously positioning the inverted bottle directly over their eye and squeezing the dropper bottle with the precise amount of force and with accurate aim in an attempt to deliver the prescribed amount of medication. Not only is there variability in how successful patients are in their aim but also in the drop size itself based on the bottle tip, amount of drug in the bottle and angle at which the bottle is held [194].

Incorporating drug-releasing technology into a soft contact lens may also significantly improve treatment compliance over eye drops. The compliance rate with the routine administration of eye drops is low [195] and while the reasons are likely multifactorial, patients may simply have difficulty incorporating their eye drop therapy into their daily routine. However, assuming a contact lens technology can provide a sustained release over multiple days, a patient can wear the lens (or have it applied for them) and have their medication continually delivered over a predetermined period of time. If a drug releasing contact lens is loaded with a daily dose of medication, the vision correction function of the contact lens may improve compliance, particularly in habitual contact lens wearers, as inserting contact lenses are already part of their daily routine.

Many topical ophthalmic drops require preservatives such as benzalkonium chloride to provide antimicrobial protection and maintain drug stability. However, even at low concentrations they can result in corneal and conjunctival epithelial cell toxicity [196, 197]. Contact lenses are terminally sterilised and so the use of preservatives with drug-releasing contact lens technology is not required.

While there are potential benefits to delivering ophthalmic medications via a contact lens, there are many challenges that must be overcome for this technology to become a commercial reality.

a) Choosing a lens/drug combination to optimise the uptake and release profile

The first consideration is in selecting the specific drug and contact lens material that will allow for a therapeutically meaningful uptake and release profile. A key attribute of the drug under consideration is its chemical nature. A more hydrophilic molecule will be more easily incorporated in a more hydrophilic hydrogel lens material, while a more lipophilic molecule will be more easily absorbed by a relatively hydrophobic silicone hydrogel material. However, if a drug molecule has an exceptionally high affinity for the lens material, then it could result in an unacceptably prolonged drug release profile once the lens is placed on the eye [189]. The molecular weight of the drug may also impact the ultimate uptake and release of the drug [198].

The efforts to identify various technologies to influence drug uptake and release from a contact lens have led to some compelling results from *in vitro* experiments. However, it is important to note that the correlations between *in vitro* models and *in vivo* results are not always strong, due to the difficulty in simulating continuous tear flow, eyelid blinking mechanics, and the morphology of the ocular surface. Thus, the drug release kinetics demonstrated in the laboratory may not be replicated when the drug releasing lens is placed on the eye [199].

b) Drug viability during manufacturing

On the path to commercialisation, once the specific drug and contact lens material has been selected and an optimal method for incorporating the drug into the lens matrix obtained, the combination must remain viable throughout the lens manufacturing process. The drug can be incorporated into the lens monomer mix, facilitating a relatively homogenous distribution throughout the manufactured lens. However, this requires that the drug withstand the lens curing steps (typically via a light or thermal curing process). Once cured, the lens then typically goes through a series of monomer extraction and lens hydration steps using aqueous and/or solvent solutions. Depending on the chemical nature and stability of the drug, these curing and extraction steps could have a significant impact on the final loaded drug concentration or may even accelerate drug degradation. To protect the drug from the lens manufacturing environment, the drug could be added after the lens has been fully polymerised and hydrated. In this scenario, the challenge is then to find the optimal method of drug incorporation, resulting in the desired drug uptake and

release profile, in addition to incorporating a consistent amount of drug within the lenses. Finally, since most contact lenses are terminally sterilised via an autoclaving process, the selected drug would ultimately need to be able to withstand a period of intense heat (over 120 degrees Celsius).

c) Impact of lens design on drug uptake

While the consistent release of the drug is a key benefit of a drug releasing contact lens, a prerequisite of this is that a consistent amount of drug is taken up by the lens. The challenge in this comes from the multiple lens designs and range of lens powers that are required to provide this vision-correcting technology to a broad patient base. The different lens powers require subtle differences in lens shape, resulting in a change in lens volume. For example, a hyperopic lens has a greater centre thickness than a myopic contact lens. Similarly, the designs for toric contact lenses often have an increased thickness profile across specific regions (due to the stabilisation zones) as compared to a spherical power lens. Thus, to maintain a consistent and efficacious dose being released to the eye, the drug uptake must be tailored to each lens power and lens design during the manufacturing process, which is complex and likely to add cost and time to the production process.

d) Impact on contact lens properties

The incorporation of a drug into a contact lens cannot significantly alter the contact lens properties and parameters or have a detrimental impact on comfort, vision and handling. The tear film uptake profile is also an important consideration, as the chemical nature of the drug could result in tear film lipids and proteins to have a greater affinity to the lens. The lens also needs to maintain an acceptable base curve radius and diameter to ensure an optimal fit, as well as sufficient oxygen permeability based on the intended wear modality.

e) Regulatory issues

Another substantial hurdle relates to the clinical trials required to demonstrate the safety and efficacy of the drug releasing lens. The scope and timing associated with

these trials can be influenced by multiple factors, including the disease state being evaluated, the endpoints required to demonstrate efficacy, the intended lens wear modality (such as daily wear or extended wear), the existing safety profile of the drug and contact lens material, as well as the regulatory pathway for product approval, as combination products require both pharmaceutical and device review [200].

The lens wear modality of a drug releasing contact lens is obviously an important factor as it will dictate the required release profile necessary to provide a therapeutic benefit. For chronic disease states or patients who may otherwise not wear contact lenses, an extended wear or monthly replacement daily wear modality may seem logical. In these cases, the drug release profile would be tailored to elute the medication over multiple days or weeks. However, if intended to be worn on an extended wear modality, the drug releasing lens would likely require extensive clinical testing to support an acceptable safety profile [200]. If the lens is designed for a frequent replacement, daily wear modality, then the drug-lens combination would need to be able to withstand the daily rubbing, rinsing, and overnight soaking steps associated with the use of multipurpose cleaning and disinfecting solutions. A daily disposable lens wear modality may provide some advantages by avoiding the interactions with lens care solutions, but to be commercially viable, the manufacturing process would need to be scaled up to allow for a sufficient quantity of lenses to be produced.

f) Long-term stability

A packaged drug-releasing contact lens is required to demonstrate long term stability with minimal drug degradation and with a consistent amount of drug in the lens over time [201]. This can be challenging, as soft contact lenses need to remain hydrated and are usually immersed in solution in their primary packaging container. Once manufacturing and packaging are complete, the lenses are then shipped and stored in distribution centres, ECP offices, or in patient's medicine cabinets for many months prior to use. During this time, the medicated lenses can be exposed to a wide range of temperatures, which can impact the stability of the product. Therefore the packaging solution and primary packaging must be compatible with the drug-lens combination to protect it from degradation over time [201].

5.1 Ocular drug delivering technologies

A wide variety of technologies have been established in an attempt to develop commercially viable methods to deliver drugs to the ocular surface from contact lenses.

5.1.1 Contemporary contact lens materials

Contemporary contact lens materials are commonly used as part of the therapeutic management of conditions such as corneal abrasions and recurrent corneal erosions via their so-called use as “bandage lenses” [202, 203], often in conjunction with concurrent use of topical pharmaceutical management agents such as antibiotics and steroids [204]. Despite this common clinical practice, few studies have investigated the impact of concurrent pharmaceutical and contact lens use on clinical outcomes or safety, or of the degree to which topical drugs are delivered to the eye when combined with commercially available contact lens materials.

Almost every major class of ophthalmic medications in use has been investigated *in vitro* for their uptake and release into commercially available contact lenses, from anti-allergy [205, 206], antibacterials [207-213], antifungals [214], anti-inflammatories [206, 211, 215], antimyopia [216], antiviral [217], anaesthetics [218-221], dry eye [211, 222, 223], non-steroidal anti-inflammatory agents [206] and glaucoma agents [224-227]. The influence of the *in vitro* testing conditions has also been explored across different studies, with the influence of aspects as broad as the concentration of the drug loading solution [228], the rate of replenishment or replacement of the drug release solution [217, 222], the composition of the drug release solution (saline versus a synthetic artificial tear analogue) [225-227] and mechanical effects of simulated blinking [229].

While there are some exceptions, general trends emerge from these studies. Commercially available contact lens materials do demonstrate significant amounts of drug uptake and release [205, 207]. The properties of the material and drug (particularly with respect to hydrophobicity, hydrophilicity and ionic charge) have significant impact on drug uptake. For example, the amphipathic antifungal drug

natamycin (which has both hydrophilic and hydrophobic components) is expected to interact with both the more hydrophilic conventional hydrogel polymers as well as the more hydrophobic silicone hydrogel polymers, and indeed the amount of drug uptake into the two materials is similar [214]. However, as the drug is relatively hydrophobic, it remains more tightly bound in the hydrophobic silicone hydrogel polymers, leading to proportionally less of the drug being released [214]. Surface charge effects are most prominently illustrated with the interaction between the negatively charged etafilcon A material with ciprofloxacin, which is positively charged in solution [207]. This led to a significant charge interaction between the drug and lens, leading to a significant uptake of the drug into the material compared to other materials investigated [207]. In contrast, the hydrophobic anti-glaucoma drug latanoprost was taken up and released to the greatest degree by the more hydrophobic silicone hydrogel materials compared to conventional hydrogel materials, further illustrating the importance of the drug polymer interaction characteristics [225].

The general characteristics of drug release from drug soaked commercially available contact lenses *in vitro* are uncontrolled, burst release over the course of minutes or, in rare instances, hours [205-207, 214, 215, 225, 228]. There is little evidence for sustained release from unmodified, commercially available lenses *in vitro*. Thus, it is likely that approaches that are more sophisticated than simply soaking commercial lenses in drugs are required to develop viable drug-delivering contact lens materials.

5.1.2 Nanoparticles

Due to their size, nanoparticles have been used as effective drug carriers for both the anterior and posterior segment of the eye [230, 231]. They can be made from a combination of natural and/or synthetic polymers, providing a wide array of properties that can also be further tuned for drug delivery applications, including enhanced drug loading, targeted delivery, increased residence time and sustained drug release [231].

Nanoparticles can be readily and usefully divided based on their size, properties or morphology [232]. Nanoparticles are broadly classified as molecules that range in sizes between 1 and 1000 nm [231, 233] and can include micelles, liposomes, metallic and polymeric nanoparticles [233-238].

The selection criteria for nanoparticles should include those which are biocompatible, safe and do not interfere with critical contact lens properties such as optical transmittance, water content or oxygen permeability [239-243]. The choice of nanoparticles is also dependent on the synthesis approach, with each process having its respective advantages and disadvantages [244]. For instance, synthesis of metal nanoparticles utilise different methods than those used for micelles or those used for polymeric nanoparticles [244]. Cost, safety, ease-of-use, repeatability and scalability are some of the critical factors researchers have to balance when applying this technology to contact lenses.

The combination of drug-nanoparticles with a contact lens produces a drug delivery platform that promises the benefits of both systems. Sustained drug release is often observed from a nanoparticle-laden contact lens [189, 245-247] because the encapsulated drugs have to diffuse through multiple barriers before reaching the tear film [248]. Table 3 provides some examples of nanoparticle technologies that have been developed and incorporated into contact lens materials.

Table 3: Examples of nanoparticle technologies for contact lens drug delivery

Drug	Nanoparticle	Synthesis method	Loading method	Average size (nm)	Release Duration
Ciprofloxacin [249]	Pullulan-PCL *micelles*	Dropwise addition of water to DMSO	Dispersion in pre-polymer solution and soaking	142 ± 12	3 – 4 days
Cyclosporine [250]	Brij surfactants *micelles*	Dissolution in water	Dispersion in pre-polymer solution	< 40	>15 days
Cyclosporine [243]	C-HA *micelles*	Dissolution in water and DMSO	Dispersion in pre-polymer solution	300	12 days

Ketotifen [242]	silica shell	Microemulsion	Dispersed in pre-polymer solution	104.2 – 126.54	10 days
Lidocaine [221]	DMPC *liposomes*	Microemulsion	Dispersed in pre-polymer solution	20	8 days
Loteprednol etabonate [251]	PCL/HEMA/PEG-DA	Surfactant-free mini-emulsion polymerisation	Dispersed in pre-polymer solution	52.3 - 83.4	12 days
Natamycin [252]	Dex-*b*-PLA *micelles*	Nanoprecipitation (DMSO to water)	Soaking	26.1 – 26.6	12 – 24 hours
Prednisolone [253]	PLGA	Emulsion-solvent evaporation	Dispersed in pre-polymer solution	294.5 ±1.8	24 hours
Timolol [254]	PVP-PNIPAAM	Electrohydro-dynamic atomisation	Dissolved in polymeric solution	52% of nano-structures < 200	24 hours
Timolol [241]	EC	Double emulsion	Dispersed in pre-polymer solution	261 - 340	168 hours

C-HA, cholesterol-hyaluronic acid; ***DA***, diacrylate; ***EC***, ethyl cellulose; ***Dex***, Dextran; ***DMPC***, dimyristoylphosphatidylcholine; ***DMSO***, dimethylsulfoxide; ***HEMA***, poly (2-hydroxyethyl methacrylate); ***PEG***, polyethylene glycol; ***PCL***, polycaprolactone; ***PLA***, polylactic acid; ***PLGA***, poly (lactic-co-glycolic acid); ***PNIPAAM***, poly (N-isopropylacrylamide); ***PVP***, poly(vinylpyrrolidone).

5.1.2.1 Incorporation of nanoparticles into contact lens materials

In general, two key steps are required to fabricate a nanoparticle-laden contact lens material: synthesis of the drug-loaded nanoparticle, followed by its incorporation into a contact lens polymer [246].

Two major methods exist to incorporate nanoparticles into contact lens polymers:

a) The drug-nanoparticles are mixed with the pre-polymerisation solution of the future contact lens material, entrapping the drug-nanoparticles within the polymer during the polymerisation process [189, 245-247]. The advantage of this approach is that the amount of drug loading can easily be controlled by varying the concentration of the drug-nanoparticle component. The drawback is that the process may result in unwanted side reactions, potentially affecting contact lens properties including optical transmittance, oxygen permeability and water content. It may also affect the integrity of the drug if it is sensitive to the polymerisation process.
b) Soaking an already formed contact lens with the drug-nanoparticles [238, 239, 249, 252, 255-257]. The advantage in this approach is that it can readily be applied to commercial contact lenses, which potentially greatly lowers the barrier for commercialisation. Additionally, this method is also compatible with drugs that may be sensitive to heat or ultraviolet radiation, which are both commonly used as part of the polymerisation process for hydrogel materials [252, 255]. The downside to this method is that there is less control over the amount of drug loading. The drug release duration may also be significantly shorter compared to drug-nanoparticles incorporated during the polymerisation step as the nanoparticles are located only on the lens surface.

5.1.2.2 Liposomes

Liposomes represent a unique class of vesicles made from a phospholipid bilayer. They can greatly vary in size, but liposomes less than 1000 nm are generally considered to be a type of nanoparticle. Liposomes consist of an aqueous core that can be used to incorporate water-soluble drugs and a lipid phase that can be exploited to dissolve hydrophobic drugs [221, 235]. A popular approach is to coat the exterior of the contact lens in liposomes. Dimyristoylphosphatidylcholine and cholesterol liposomes have been coated onto HEMA-based hydrogels by depositing a layer-by-layer polyion solution to electrostatically sandwich the liposomes in place [258]. The liposomes did not contain drugs themselves. Prior to deposition, the hydrogels had been soaked in levofloxacin. Both the polyelectrolyte layers and the liposomes acted as a barrier to release, decreasing the total amount of release without affecting the release rate [258]. Utilization of the high affinity avidin-biotin

binding has also been used to attach biotinylated polyethylene glycol containing liposomes to NeutrAvidin-coated contact lenses [259].

Attaching drug eluting liposomes to the contact lens has also been explored. PEGylated 1,2-Diasteroyl-sn-glycero-3-phosphocholine (DPSC) was attached to HEMA-based hydrogels. Multiple layers of liposomes containing a model drug (carboxyfluorescein) could be attached to the surface of the hydrogel. By AFM imaging, the liposomes could be visualised on the surface of the lens. The lenses could be stored for one month, without release of the liposomes from the lens [259].

Due to their similarities with cellular membranes, they are generally non-toxic, highly biocompatible and biodegradable [235]. To date, no *in vivo* or human studies using liposomes in contact lens drug delivery have been reported.

5.1.2.3 Polymeric nanoparticles

There is a large selection when it comes to polymeric nanoparticles, each with their own unique properties and advantages. The encapsulation of drugs in polymeric nanoparticles creates a diffusion barrier, which results in sustained drug release.

Hydrophobic polymers are often used to encapsulate hydrophobic drugs. Formulations of PLGA nanoparticles to deliver prednisolone, a corticosteroid, have been described [253]. In some cases, it may be beneficial to create nanoparticles with multiple different polymeric layers. Polycaprolactone in association with PEG to create nanoparticles to deliver loteprednol etabonate has been described [251]. Polymers used in contact lens materials, such as polyvinyl alcohol, can also be used to formulate nanoparticles. A novel ketone drug for treating microbial keratitis, phomopsidone, was encapsulated in polyvinyl alcohol nanoparticles. [255].

5.1.2.4 Metal nanoparticles

Metallic nanoparticles have been widely employed in nanotechnology because of their unique electrical, optical, magnetic and chemical properties [260]. For instance, silver and gold are well known for their antimicrobial and optical properties [260]. Furthermore, there are numerous approaches to functionalise metallic nanoparticles such that they can easily bind drugs, ligands and antibodies [260]. Metallic

nanoparticles, especially silver and copper, can be used as antimicrobial coatings on contact lenses [239].

Despite their numerous pharmaceutical advantages, nanoparticles can be toxic to humans and the environment [261]. Nanoparticles have a very high surface area, which provides more contact points to interact with cellular components [261]. In some cases, this design is advantageous when the interaction is intended, but in other cases it could lead to increased cellular toxicity. There are also other reasons contributing to the toxicity of nanoparticles, including their shape and their biochemical composition [261]. For these reasons, one of the main barriers to the commercialisation of nanoparticles and nanoparticle-laden contact lenses will be proving their safety and biocompatibility.

5.1.3 Microemulsions

Microemulsions are stable, isotropic and homogenous solutions of a polar substance, a non-polar compound, and a surfactant [262]. Microemulsions can be described as mixtures of oil in water, water in oil, or as bicontinuous phases.

Their ability to dissolve both hydrophobic and hydrophilic components simultaneously is tremendously advantageous in drug delivery. In particular, the interface between the oil and water allows for encapsulation chemistries to entrap drugs and other compounds [262]. Thus, microemulsions have been widely used as a method to synthesise a variety of nanoparticles [262] and other nanostructures [263]. Microemulsions are distinctively different from emulsions and nano-emulsions, which are unstable [264]. Since they require a high concentration of surfactants and co-surfactants for stabilisation, which may be toxic to the ocular surface [265, 266], careful considerations should be made in selecting biocompatible surfactants. Table 4 provides some examples of microemulsion-laden contact lenses that have been developed to date.

Table 4: Examples of the development of microemulsions for contact lens drug delivery

Drug	Oil	Surfactants	Loading method	Average size (nm)	Duration
Cyclosporine A [267]	Isopropyl myristate	Pluronic F68, Pluronic F127, Tween 20, Tween 80, Sodium caprylate	Dispersed in pre-polymer solution	53 - 168	15 days
Ketotifen [242]	Isopropyl myristate	Tween 70, Pluronic F127, OTMS	Dispersed in pre-polymer solution	104.2 – 126.54	10 days
Timolol [268]	CL polymer	PEO-R-MA-40, silicone surfactant	Dispersed in pre-polymer solution	10-250	72 hours
Timolol [269]	Ethyl butyrate	Pluronic F127	Dispersed in pre-polymer solution	20 - 35	< 4 hours

OTMS, Octadecyltrimethoxysilane; ***PEO-R-MA-40***, ω-methoxy poly(ethylene oxide) 40 undecyl α-methacrylate macromonomer

Most of the microemulsions used with contact lenses are oil in water microemulsions [267, 269-274]. These systems contain nanosized oil globules in the nanometre scales that are stabilised by surfactants, as shown in Figure 2 [262, 264]. The drugs, often hydrophobic, are entrapped within the oil phase, which then can slowly diffuse into the continuous water phase.

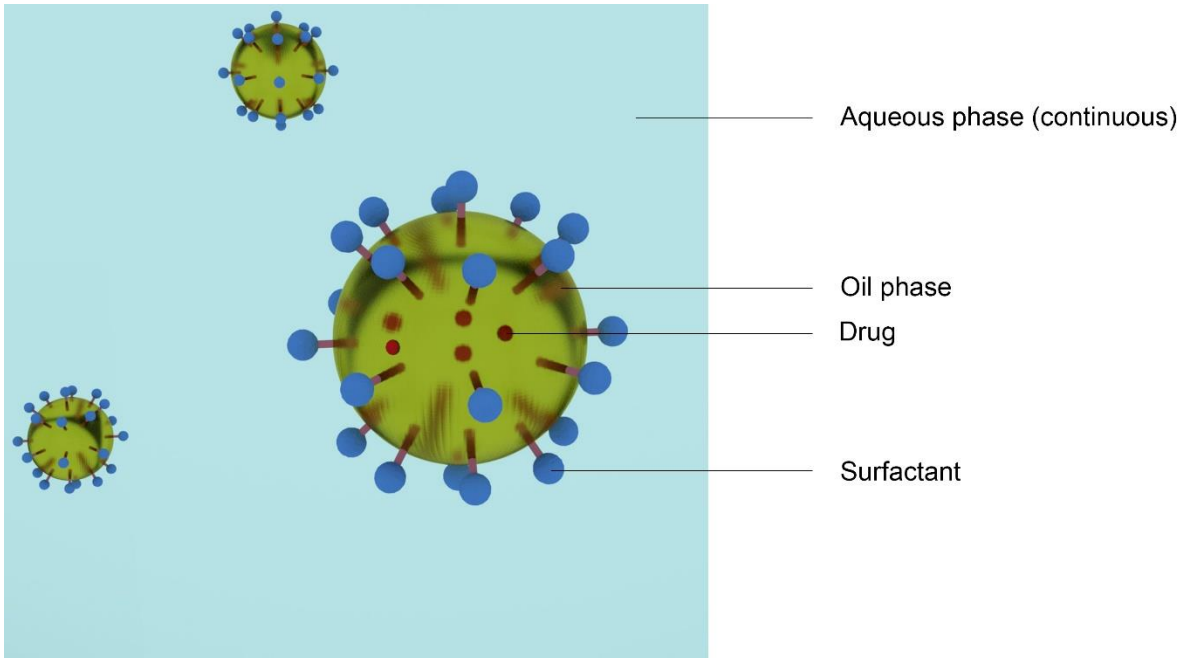

Figure 2: Schematic of an oil in water microemulsion with a dissolved hydrophobic drug

In an oil in water microemulsion, the surfactants act as a barrier to drug diffusion from the oil phase. The diffusion rate can, therefore, be tuned by changing the concentration [274] or properties of the surfactants, such as chain length [267] and ionicity [271]. Increasing the surfactant concentration, chain length and adding ionicity have been shown to create better diffusion barriers to slow release of the drug from the microemulsion [267, 271, 274].

The incorporation of microemulsions in a contact lens may affect critical properties such as wettability, and more importantly, optical transparency. Studies have noted that the stability of the microemulsions has an effect on overall transmittance [267, 269, 271]. Additionally, the size of the globules in the microemulsion can also have an effect, with smaller sizes having a better optical transmission than larger sizes [267, 271].

Microemulsion contact lenses present a promising strategy to improve drug delivery by increasing drug loading and prolonging the release duration. The release of surfactants from microemulsion contact lenses, however, should be evaluated

carefully, as a high concentration of surfactants may lead to ocular toxicity [265, 266]. Future studies should, therefore, also evaluate both the short and long-term safety of these devices.

5.1.4 Vitamin E

In an effort to reduce the initial drug burst and to prolong the duration of release, contact lenses have been soaked in a media containing Vitamin E along with the drug. Vitamin E is a biocompatible aliphatic compound and it is hypothesised that Vitamin E forms nanobarriers within the contact lens matrix, and that these nanobarriers impede drug release by slowing drug diffusion out of the lens [275]. Based on this approach, narafilcon and senofilcon contact lenses were soaked in a 0.07 g/mL Vitamin E-ethanol solution for 24 hours, then dried and immersed in a 0.3% solution of ofloxacin in PBS for 7 days. Lenses exposed to Vitamin E released ofloxacin longer *in vitro* than lenses lacking Vitamin E [276]. A similar approach was used to modify *in vitro* release of dexamethasone [277], timolol [278], bimatoprost [275], levofloxacin [279], ciprofloxacin [280], anaesthetics (lidocaine, bupivacaine and tetracaine) [219] and brimonidine [281].

Vitamin-E loaded contact lenses have been studied in several *in vivo* models. Pirfenidone and Vitamin E loaded contact lenses were evaluated in a rabbit model of alkali burn [282]. Rabbits wearing the contact lenses showed greater improvement in corneal haze and more down regulation in inflammatory markers compared to untreated eyes. Eyes treated with the pirfenidone-Vitamin E contact lenses had greater drug penetration into the aqueous humour than eyes treated with pirfenidone eye drops; this finding suggested that the contact lenses conferred greater bioavailability than the drop regimen [282]. Vitamin E was also studied as a means of prolonging the release of timolol from contact lenses for the treatment of glaucoma in a dog model [278]. The amount of timolol release from lenses was inversely related to the Vitamin E concentration. The results showed that IOP reduction from baseline by the contact lens on a daily basis was comparable with that by eye drops but with only 20% of drug dose, which suggested higher drug bioavailability for the Vitamin E-treated contact lenses than drops alone [278].

5.1.5 Molecular imprinting

Molecular imprinting is a polymerisation technique that creates shape specific and/or functional group specific areas or “memory” within a polymer on a molecular scale [283]. This typically involves the incorporation of template molecules and functional monomers as part of the pre-polymerisation mixture. The template molecules in the mixture represent the molecules of interest. While this often can be the actual molecule of interest, such as a drug to be released, in some instances this may represent only a part of a larger molecule [283]. The functional monomers in the mixture are typically small molecules that can be incorporated into the polymer and are chosen based on their ability to interact with the molecules of interest non-covalently, through forces such as hydrogen bonds or ionic forces. By including both the template and the functional monomers in the pre-polymerisation mixture, the functional monomers self-assemble around the templates, creating shape and functional specific “cavities” in the final polymer. Removal of the template afterward yields a polymer with high selectivity and affinity for the template and closely related molecules.

From a drug delivery perspective, the high affinity for the template molecule created during the molecular imprinting process is attractive as a means to increase the drug delivery period from a material [283]. Initial studies centred on the anti-glaucoma drug timolol imprinted in hydrogel systems, with a particular emphasis on drug loading and subsequent release under various *in vitro* parameters [284, 285]. *In vivo* testing of an optimised timolol molecularly imprinted DEAA-MAA-EGDMA material in a rabbit model demonstrated a substantially higher peak tear timolol concentration and area under the curve over time compared to non-imprinted materials or timolol eye drops [286].

Subsequent investigations into molecular imprinted contact lens drug delivery systems furthered the understanding of critical parameters, backbone monomers, functional monomers and crosslinker concentrations needed for systems designed for different ocular pharmaceuticals. Published examples included a wide variety of drugs, including anti-allergy [287, 288], antibacterial [289-292], anti-inflammatory [293-295], anti-glaucoma [296, 297] and dry eye [298, 299], all of which

demonstrated some substantial increase in drug loading and release times *in vitro* compared to non-imprinted materials.

Several studies have monitored tear drug concentrations with molecular imprinting use in animal models and compared them to levels found with eye drops or drug soaked non-imprinted materials [297, 300, 301]. A biomimetic inspired molecular imprinted contact lens for the release of ketotifen demonstrated upwards of 72 hours of release when tested *in vitro and* a mean residence time of approximately 12 hours in the tear film of New Zealand white rabbits, with a peak in concentration seen within four hours [301]. In contrast, non-imprinted lenses peaked at a lower concentration within four hours and had a calculated mean residence time of only approximately 3 hours [301]. Similar studies have been conducted with model silicone hydrogel materials for the anti-glaucoma drug bimatoprost, where the molecularly imprinted material demonstrated drug concentrations within the rabbit tear film for upwards of 12 hours [297].

One study has demonstrated the impact of molecular imprinted materials against *in vivo Pseudomonas aeruginosa* keratitis [291]. Ciprofloxacin releasing molecular imprinted silicone hydrogel materials with different acrylic acid functional monomer to ciprofloxacin template ratios were compared head to head with antibiotic eye drops and control lenses in a rabbit model of bacterial keratitis. Optimised imprinted materials with a 4:1 acrylic acid to ciprofloxacin ratio were able to significantly decrease the number of bacteria recovered from excised rabbit corneas after 24 hours of lens wear compared to non-imprinted lenses and the untreated controls. While the corneas were not sterilised as was seen with eyes treated with hourly ciprofloxacin eye drops, the treatment effect with the imprinted lenses was achieved by loading lenses with antibiotic concentrations 100 times lower than the conventional eye drop therapy, suggesting significant bioavailability when delivered via this method [291].

5.1.6 Ion interactions

Several ophthalmic drugs are ionically charged (or can be formulated as such), which can be exploited to form electrostatic interactions with a charged contact lens material. These ionic interactions, between a contact lens and a drug, have been

shown to improve drug loading significantly and achieve sustained release [205, 207, 302-306].

Several commercially available contact lens materials are ionically charged (balafilcon A; ocufilcon B; etafilcon A). Several studies have shown that such materials can improve the absorption and release of complementary charged drugs. For instance, etafilcon A and balafilcon A have been shown to have one of the highest uptake of ciprofloxacin-hydrochloride at low pH [207], at which the drug is positively charged [307]. Balafilcon A and etafilcon A had the highest uptake and release of ketotifen fumerate, a cationic drug, among various contact lens materials tested [205]. Unsurprisingly, these same contact lens types did not exhibit any electrostatic interactions for dexamethasone phosphate [215], a negatively charged molecule at physiological pH [302].

In addition to studies examining commercial materials, several studies have formulated ionic materials and investigated their ability to uptake and release ophthalmic drugs. The majority of studies have evaluated the performance of MAA, an anionic monomer that is used to increase the water content of common contact lens materials [308] and acrylic acid [290, 292, 296]. The negative charge on the carboxyl groups of acrylic acid and MAA imparts an overall anionic charge on the polymer at physiological pH [303, 309]. A study synthesised contact lens materials with acrylic acid and MAA to improve the loading of two ophthalmic drugs, ofloxacin and neomycin, in contact lenses [268]. At physiological pH, ofloxacin is neutrally charged while neomycin has a positive net charge. In order to ionise ofloxacin into its cationic form, the drugs were loaded into the contact lenses at pH 6.5. The electrostatic interactions between the contact lens polymer and drug significantly improved loading efficiency by 18 and 53 times for ofloxacin and neomycin respectively [303].

5.1.7 Cyclodextrins

Cyclodextrins are naturally occurring cyclic oligosaccharides used in a variety of pharmaceutical applications [310]. cyclodextrins form supramolecular complexes with small molecule drugs allowing for slower release. In addition, they can entrap poorly water soluble molecules, allowing for higher loading within a drug release

matrix. cyclodextrins are classified based on the number of structural units, the most common being α-cyclodextrins (6 units), β-cyclodextrins (7 units), or γ-cyclodextrins (8 units).

cyclodextrins have been incorporated into HEMA-based hydrogel discs and soaked in solutions of puerarin, an isoflavone found in a number of plants and herbs that is used to lower IOP. *In vitro* release studies showed that β-cyclodextrin-complexed hydrogels demonstrated slower release of puerarin than hydrogels lacking β-cyclodextrin-complexes. The amount of cyclodextrin loading corresponded to the duration of drug release [310]. In rabbits wearing the puerarin-cyclodextrin contact lenses, drug concentrations in tear fluid were greater than those from 1% puerarin eye drops. Concentrations of puerarin were detectable for up to six hours after administration compared to 3.5 hours from eye drops. The rabbits tolerated the contact lenses well. No adverse effects were reported [310].

In a separate study, HEMA and silicone hydrogels were functionalised with β-cyclodextrin and 2-hydroxypropyl-β-cyclodextrin (HP-β-cyclodextrin) and then soaked in natamycin, which is an antifungal drug. The *in vitro* release from HEMA-based hydrogel discs demonstrated no change in release duration, but an increase in loading compared to unmodified lenses. Compared to the addition of β-cyclodextrin, lenses functionalised with MHP-β-cyclodextrin exhibited an extended drug release for both HEMA and model silicon hydrogels within *in vitro* release testing studies [311].

5.1.8 Drug-polymer films

The inclusion of a thin film composed of drug and polymer has been shown to be effective for sustained contact lens drug delivery [312]. The film is encapsulated within the periphery of a standard contact lens hydrogel. The polymer provides an additional barrier to diffusion, allowing for slow release of the drug. By limiting the drug-polymer film to the periphery of the contact lens, the contact lens can be loaded with a therapeutic amount of drug while keeping the centre of the lens optically clear [313]. The drug release rate can be tuned by adjusting polymer concentration, drug concentration, drug-polymer ratio and characteristics of the polymer (molecular weight) [312]. Drug delivering HEMA-based contact lenses incorporating these drug

polymer films release therapeutic levels of ciprofloxacin [312], latanoprost [313, 314] and dexamethasone [315]. Unique formulations were used for each drug and each one demonstrated *in vitro* release for one week or more.

Contact lenses with PLGA films have demonstrated release in rabbits for up to one month for latanoprost [313] and one week for dexamethasone [315], with aqueous humour concentrations exceeding those of eye drops (0.005% latanoprost and 0.1% dexamethasone, respectively). Rabbits wore the contact lens for up to four weeks with no adverse effects. Efficacy of the dexamethasone-PLGA contact lens was demonstrated in a model of retinal vascular leakage [315]. Latanoprost-PLGA contact lenses lowered IOP in glaucomatous cynomolgus monkeys [314].

Lenses implanted with hyaluronic acid-HEMA-Moxifloxacin rings were worn by rabbits. Release measured from tear fluid endured over 48 hours, greater than the time from a 0.5% moxifloxacin eye drop. Efficacy studies in rabbit eyes infected with *S. aureus* demonstrated clinical signs improved by day four after the beginning of treatment compared to untreated eyes. The results were similar to those from rabbits receiving 0.5% moxifloxacin drops every four hours [316]. Similar lenses with timolol nanoparticles showed drug release in the tear film over one week [241]. For the treatment of dry eye, lenses were designed to contain and release hyaluronic acid, which has lubricating qualities [317]. The hyaluronic acid implanted rings demonstrated 15 days of release in tear fluid in rabbits. In a wound-healing model, rabbits wearing hyaluronic acid-implanted contact lenses had faster healing times than compared to untreated rabbits [317].

5.2 Drug delivery for the management of specific diseases

5.2.1 Dry eye

Dry eye disease is very common and a number of technologies related to either inserts or contact lens-based technologies exist.

5.2.1.1 Hydroxypropyl cellulose dissolvable insert

Lacrisert (Aton Pharma, Lawrenceville, New Jersey), a hydroxypropyl cellulose insert, is available commercially to aid with moderate to severe dry eye patients where conventional treatment with artificial tears is inadequate [318]. Each insert contains 5 mg of hydroxypropyl cellulose, which is slowly released into the tear film as the insert degrades after being placed in the inferior cul-de-sac and is replaced daily [318]. Findings from a registry of 520 patients who utilised the insert for four weeks showed good tolerability, with only 13% of participants discontinuing use, with the majority doing so due to blurred vision [319]. The inserts were able to reduce patient symptoms, as measured by the Ocular Surface Disease Index [318, 320] as well as signs of dry eye, including improving tear film breakup time, fluorescein staining and Schirmer values [318-321]. Approximately half of participants reported some difficulty with using the insert, although this tended to improve over time [318].

5.2.1.2 Lubricant releasing contact lens materials

Molecularly imprinted contact lens materials to enhance the loading and release of hyaluronic acid from contact lens materials have been developed [298]. These hydrogels exhibited improved loading of hyaluronic acid as well as an extended release profile, with 6 µg per hour being released for 24 hours when measured *in vitro* [298]. Another study investigated optimizing the use of an hyaluronic acid ring implanted into contact lenses of various thicknesses and crosslinker concentrations [317]. *In vivo* studies using New Zealand white rabbits showed hyaluronic acid release for 15 days into the tear film [317]. Molecular imprinting has also been used to manipulate the uptake and release of hydroxypropyl methylcellulose (HPMC), a rewetting agent utilised in many over the counter artificial tears [299]. Tailoring of the release rate of HPMC could be achieved under *in vitro* physiological flow rates, with release complete in 10, 13, 23 or 53 days achieved simply by varying the ratio of the functional monomer to template ratio [299]. Phospholipid replacement for dry eye therapy has also been proposed in the literature to address shortage of the lipid layer of the tear film in DED [322].

5.2.1.3 Cyclosporine releasing contact lens materials

Cyclosporine is a T-cell calcineurin inhibitor leading to decreased T-cell activity and topical ophthalmic formulations have been approved to improve Schirmer scores in

patients with moderate to severe DED [323]. Cyclosporine is a highly hydrophobic molecule and thus suffers poor solubility in aqueous solutions, requiring commercial eye drop formulations to be formed as emulsions [324]. Commercially available contact lenses show differences in cyclosporine release after loading depending on their base material. Etafilcon A lenses maintain release for only a day *in vitro*, while commercially available silicone hydrogels (which are comparatively more hydrophobic and better able to interact with cyclosporine) were able to release the drug without any further modification for upwards of two weeks [324]. Release from silicone hydrogel materials can be further enhanced through deposition of a coating of Vitamin E, with treated senofilcon A based silicone hydrogel lenses showing release of cyclosporine for more than one month *in vitro* [324].

Other means to load cyclosporine on to contact lenses involve the use of micelles [243], microemulsions and surfactants [274] or supercritical fluid techniques [325]. The surfactant Brij 97 (polyoxyethylene (10) oleyl ether) has also been explored to form microemulsions of cyclosporine to aid in cyclosporine loading within HEMA gels [274].

5.2.1.4 Anti-inflammatory releasing contact lens materials

Corticosteroids can be used to reduce inflammation associated with DED [326]. Dexamethasone sodium phosphate has been investigated for its uptake and release from commercially available contact lens materials, with uncontrolled release being observed from all materials *in vitro* [215]. Silicone hydrogel lenses can be modified to improve their release characteristics through varying the amounts of incorporated Vitamin E, which serves as a diffusion barrier [277, 327]. The rate of release could be tailored significantly, with total release times of up to 8 hours achievable with balafilcon A with large amounts of Vitamin E deposited and upwards of 3 weeks of release from senofilcon A lenses with 23% Vitamin E loading [327].

5.2.2 Glaucoma

Glaucoma is one of the leading causes of irreversible blindness and affects millions of people worldwide. The mainstay of therapy is topical drops that are self-administered 1 to 3 times a day to reduce IOP. Because adherence with glaucoma drop regimens is notoriously poor, a method of sustained drug delivery to treat

glaucoma has been described as one of the major unmet needs in ophthalmology. [314] Several fornix-based inserts and contact lens-based treatments have been described as a means of delivering glaucoma medications.

5.2.2.1 Inserts

From a drug-delivery perspective, the fornix-based approach enables inserts to have a larger size compared to devices that are placed on the cornea, in the punctum or inside the eye. The larger size can be used to store more drug or to contain mechanisms of controlling drug release.

Pilocarpine-releasing inserts were initially described in the 1970s. Ocusert delivered pilocarpine from an inferior fornix-based insert which diffused slowly through a semipermeable polymer membrane unit, releasing 20-40 µg of pilocarpine per hour for 7 days [328]. The clinical acceptance of the device was limited by discomfort, high rates of dislodgement and pilocarpine-related side effects [329]. No other topically placed ocular inserts or drug-eluting contact lenses have obtained FDA-approval or have become commercially available for the treatment of glaucoma.

A fornix-based insert composed of a HEMA matrix that contained timolol-loaded nanoparticles has been described in the literature [238]. *In vitro* studies demonstrated sustained timolol release for up to 3 months. A circular fornix-based insert that contains bimatoprost, a prostaglandin analog, has also been tested clinically [329]. The topical bimatoprost insert is a ring that is supported between both the inferior and superior fornix with varying sizes from (24 to 29 mm in diameter) to allow for customised fitting. The device was studied in a multicentre, double masked, randomised controlled clinical trial in 130 adult patients with glaucoma or ocular hypertension. Over 6 months, the retention rate was 88.5%.

5.2.2.2 Contact lens-based delivery

Modifications have been made to contact lenses or the contact lens manufacturing process in an effort to increase drug loading and the duration of drug release for the treatment of glaucoma.

- By incorporating timolol into the monomers during the manufacturing process, HEMA-MAA contact lenses were shown to absorb and release more timolol compared to lenses that were not made using the molecular imprinting process. In rabbits, these imprinted contact lenses released more drug into the tear film over the course of 90 minutes than non-imprinted contact lenses [286].
- Microemulsions have been added to contact lenses to increase drug loading and release rates [269]. Based on this approach, timolol loading was shown to be increased compared to lenses without microemulsions. However, in all cases, the release rate was faster for microemulsion-laden hydrogels. The authors proposed that the small size of the drug may have influenced its rapid release characteristics and that it was not impeded by the microemulsion system [269].
- Vitamin E has been studied as a means of controlling glaucoma drug release. Contact lenses were soaked in a solution containing Vitamin E and timolol [330]. The addition of Vitamin E increased the duration of drug release, but, conversely, decreased the drug loading.
- Drug polymer films have been encapsulated within the periphery of contact lenses to increase drug loading and to help modulate the drug release rates [312]. *In vitro*, contact lenses containing a latanoprost-PLGA film were shown to exhibit 1 month of drug elution. In rabbits that wore the lenses continuously for one month, the drug concentration in the aqueous humour was found to be greatest during a burst in the first day of lens wear. For the rest of the month, latanoprost concentration in the aqueous humour remained stable, with daily levels that exceeded that of daily latanoprost 0.005% drops [313].

Beyond improving compliance, there is some evidence that prescribing drug-eluting contact lenses could lead to better IOP reduction than glaucoma eyedrops [314]. However, little is currently known about the efficacy, safety, or patient acceptability of using drug-eluting contact lenses in a clinical setting.

Acceptance of drug delivery contact lenses for the management of glaucoma appears to be high among treating clinicians. US-based ophthalmologists who treat

glaucoma were specifically surveyed about using drug-eluting contact lenses as a management option. Ninety per cent answered that they would use the approach if it was available to treat their patients and 95% said they would use the devices to help differentiate lack of treatment efficacy from lack of patient adherence with drops [331].

5.2.3 Bacterial and fungal keratitis

Antibiotic solutions and ointments are commonly used to treat keratitis, conjunctivitis and to prevent infections following ocular surgeries or injuries, such as corneal abrasions and thus many researchers have explored antibiotic delivery through contact lens-based devices [332].

Antibiotic solutions are formulated at relatively high concentrations and are administered multiple times a day. For instance, moxifloxacin, is commercially formulated as a 0.5% (5 mg/ ml) solution. However, even at this concentration, moxifloxacin is often not sufficiently concentrated to treat many corneal ulcers, requiring the use of compounded antibiotics such as vancomycin at a concentration of 25 mg/ml. With regard to contact lens antibiotic drug delivery, the potency of a drug is important because contact lenses are relatively small devices, the drugs are frequently opaque and loading a clinically meaningful amount of drug into the lens has presented a historical challenge [207].

Contact lenses may be able to overcome the challenge presented by the relatively low potency of antibiotics by more efficiently delivering drugs to the target tissues than ophthalmic drops. Many studies used the drug absorption and release approach to load antibiotics into commercial contact lenses. As an example, etafilcon A lenses were bathed in lomefloxacin solution (3mg/ml) and then placed on rabbit eyes. Compared to hourly lomefloxacin solution, the presoaked lenses delivered a peak corneal concentration of 213 µg/g at 4 hours, compared to 31 µg/g for hourly drops at the same time point [213].

In a 10 patient study, HEMA-based lenses were soaked overnight in 0.5 % commercial gentamicin ophthalmic solution [333]. The contact lenses were worn for 96 hours. The tear film was sampled with paper tear strips at various times over the

4-day study. The concentration of gentamicin in the tear film was calculated indirectly by using a bioassay that measured the bacterial inhibition zone resulting from tear strips. The study found that the lenses were well tolerated and that gentamicin tear levels steadily decreased over the 4 days and remained above the minimum inhibitory concentration for all of the subjects for up to 3 days [333]. Another study found that presoaked lenses resulted in higher antibiotic concentrations in the aqueous humour compared to frequent drop administration [334]. The study investigated the drug flux from presoaked lenses into the aqueous humour of eyes that were to undergo cataract surgery. Vifilcon A lenses were loaded in 0.3% ciprofloxacin ophthalmic solution for 10-12 hours. The lenses were placed on the eyes of patients at different time points (3, 5-6 and 8-12 hours) prior to cataract surgery. During the surgery, the aqueous humour was sampled and the ciprofloxacin concentration measured at various time points. At the 3-hour time point, the measured ciprofloxacin levels were 3x greater than the maximum levels that were achieved by frequent administration of 0.3% ciprofloxacin drops [334].

Molecularly imprinted silicone-based contact lenses were loaded with ciprofloxacin and tested in a rabbit model of *P. aeruginosa* keratitis. Colony forming units in the cornea that were cultured from the corneas of rabbits that wore ciprofloxacin-loaded contact lenses were significantly less than lenses that were not loaded with ciprofloxacin [291]. Implanting contact lenses with moxifloxacin and hyaluronic acid semicircular rings has also been used to treat experimental bacterial conjunctivitis [316]. Rabbits wore the contact lenses and had tear fluid concentrations measured as various time points. Results were compared to a single 0.5% moxifloxacin eye drop. The contact lenses demonstrated a similar peak concentration as the eye drop, but a greater duration of release, with moxifloxacin still being detectable after 48 hours of wear.

Several reports exist on the development of poly-epsilon lysine containing bandage contact lenses which can bind other antimicrobials such as penicillin G, the antimicrobial peptide Mel4 or amphotericin B and be used to treat both fungal and microbial keratitis [335-338]. Poly-epsilon lysine is a naturally occurring antimicrobial peptide that is nontoxic, is used as both an emulsifier and food preservative, and is classified as “generally regarded as safe” by many regulatory authorities. Contact

lenses made of poly-epsilon lysine have activity against *S. aureus, Escherichia coli, P. aeruginosa* and *Candida albicans* in *in vitro* and *ex vivo* models [336, 337].

5.2.4 Ocular allergy

Ocular allergy is a pervasive condition that affects 20-40% of the population worldwide [339, 340]. Allergic conjunctivitis, the most common type of ocular allergy, is clinically defined as an IgE-mediated hypersensitivity response to exposure of the ocular surface to one or more allergens including tree or grass pollens, pet dander, or dust mite dander [339]. Allergic conjunctivitis can have a significant impact on productivity as well as on quality of life of patients [341, 342].

Currently, in the management of contact lens wearers with ocular allergies, patients may be encouraged to avoid or minimise lens wear due to an increase in contact lens-related discomfort [343]. Unfortunately, the concomitant use of topical anti-allergy eyedrops during contact lens wear is not advised, as the preservatives from the drops may be irritating to the ocular surface [343]. Furthermore, because the primary symptom of allergic conjunctivitis is itch, patients who naturally (and often, unconsciously) respond to ocular itch with eye-rubbing may cause both an exacerbation of their allergic symptoms and potentially risk damage to both their ocular surface and their lenses [344, 345]. An anti-allergic releasing contact lenses may also prove effective via two complementary mechanisms of action; while simultaneously delivering medication to the eye, the contact lenses may also act as a physical barrier to protect the ocular surface against airborne environmental allergens [346].

In vitro uptake and release studies evaluated the behaviour of the anti-allergy agents cromolyn sodium and ketotifen fumarate in commercially available hydrogel and silicone hydrogel materials [206]. Cromolyn sodium demonstrated a very rapid uptake and release across all lens materials, which was attributed to the relatively small size of the molecule and the relatively high water content of the lenses. In contrast, ketotifen fumarate demonstrated a much more gradual uptake and release profile and displayed some degree of sustained drug release. Ketotifen fumarate also showed a statistically significantly higher uptake and release in ionic versus

non-ionic lens materials, in hydrogel vs. silicone hydrogel lenses, and in higher water content versus lower water content lenses [206].

A subsequent set of *in vitro* experiments further established how both the chemical nature of the drug and the material characteristics of the lens influence the drug uptake and release [205]. In these experiments, 14 commercially available lens formulations were soaked in ketotifen fumarate and then drug uptake and release was measured. While all lenses were able to uptake and release ketotifen fumarate, the FDA group IV (ionic) materials showed the greatest uptake within the group of conventional hydrogel lenses tested. The only ionic silicone hydrogel evaluated, balafilcon A, also demonstrated the greatest uptake of ketotifen fumarate within the silicone hydrogel lenses tested. These ionic lens materials also showed significantly more drug release over time, but the drug release plateau occurred after only 2-4 hours. These data reinforced that the ionic charge of the contact lens material plays a key role in the uptake and release of ketotifen [205].

To better control the uptake of drugs by different lens materials (as well as prolong the duration of drug release), researchers have explored a variety of alternative technologies beyond simply soaking preformed materials.

- Molecular imprinting was used to load olopatadine into contact lenses and the uptake and release was modified using a combination of various monomers within the polymeric network, which result in a range of binding affinities with the drug. Several formulations demonstrated *in vitro* efficacy by inhibiting the release of histamine from cultured mast cells [288], while the consistent extended release of ketotifen fumarate from molecularly imprinted contact lenses has also been shown *in vivo* in New Zealand white rabbits [301].
- Drug loaded micro/nanoparticles have been used to attempt to sustain anti-allergy drug release from a polymer [347].
- Research incorporating ketotifen-containing microemulsions as well as silica shell nanoparticles into hydrogel contact lenses that were formulated using those same microemulsions demonstrated 9 days of ketotifen release *in vivo*,

while also having high optical transparency, good lens surface wettability and acceptable preclinical testing results [242].

Multiple clinical trials evaluating ketotifen-releasing contact lenses have been registered and include two safety studies [348, 349] in healthy normal volunteers and two evaluations of efficacy and safety [350, 351]. A review of the patent literature suggests that for these studies, the soak method may have been used to incorporate ketotifen into an FDA group IV hydrogel material (etafilcon A) post-polymerisation but prior to sterilisation [352]. The two efficacy studies reported the use of etafilcon A lenses with 19 µg of ketotifen as compared to etafilcon A lenses with no added drug (control). The studies utilised the conjunctival allergen challenge (CAC) model, which has been validated over many clinical trials and is an established standard for FDA approval of ophthalmic anti-allergy drugs. A combined total of 244 subjects were enrolled and, in both studies, the mean ocular itching scores in the eyes wearing the ketotifen-releasing contact lenses was significantly lower than the eyes wearing the control lenses for all time points. Between the two studies, there were 24 ocular adverse events reported in a total of 488 eyes (4.9%), with the majority of them being classified as mild in severity and not study related [353].

Thus, the results to-date would suggest that a commercially viable anti-allergy contact lens delivery device could be a valuable addition to the methods available to clinicians to manage allergic eye disease.

5.3 Potential future ocular drug delivery technologies

While novel technologies have been developed to improve sustained drug release from contact lenses, the overall release mechanism generally still depends on diffusion kinetics [198, 246]. The use of on-demand drug delivery systems or “smart” intelligent materials that release drugs in response to various stimuli offer innovative tools to control drug release [246, 354, 355].

5.3.1 Light-mediated release

Light-activated drug delivery systems have an advantage when it comes to ocular applications, as the eye is the only organ through which light can easily pass. These photoresponsive systems can be broadly classified into three groups (Table 5).

Table 5: Summary of photosensitive systems for drug delivery

Types of systems	Mechanism	Representative photo compounds
Photochemical	Photocleavage of the bond between polymer and drug	*o*-nitrobenzyl, courmarin, pyrene [354, 356]
Isomerization	Light-induced transition between on-off states	azobenzene, spiropyran [354, 356, 357]
Photothermal	Light-induced thermal reaction which causes drug release	gold nanoparticles, poly (N-isopropylacrylamide) (PNIPAAm) as a thermo-responsive polymer [354]

For photochemical drug delivery materials, exposure to light is sufficient to irreversibly cleave the covalent bonds between the material and the drug. Commonly used photolabile groups for these applications include derivatives of *o*-nitrobenzyl, coumarin, or pyrene [354, 356]. In photoisomerization, the light exposure causes reversible conformational changes, which transitions the material between an “on” and “off” state. Azobenzene and spiropyran derivatives are commonly employed for this application [354, 356, 357]. For photothermal systems, thermal energy or heat is produced when the material is photoexcited. These systems are composed of two elements, a chromophore that is able to convert light energy to heat and a thermoresponsive polymer [354]. Gold nanoparticles are widely used as a chromophore for this application as they are inert, non-toxic and exhibit tuneable optical and photothermal properties [354]. A well known thermoresponsive polymer

is poly (N-isopropylacrylamide), which transitions between reversible states; it is a hydrophobic polymer at low temperatures (entrapping drugs) and a swollen hydrogel at higher temperatures (releasing drugs) [354].

Potential limitations of such systems relate to the wavelength of light required for activation. Ultraviolet light is highly energetic, whereas near infrared light is energetically weak but can easily penetrate tissues [354]. Most of the light-responsive drug delivery systems require energy in the UV spectrum or high-energy visible light to work [354]. This is problematic, since prolonged exposure to UV light can damage the eye [358, 359] and near infrared exposure has been linked to the development of cataracts [359].

To date, there are no FDA approved light-activated systems for drug delivery [354]. Concerns include how to control the amounts of drugs released when exposed to varying levels of light. For instance, there would be significant differences in the doses released for people who spend the majority of their time indoors compared to those wearing their lenses primarily outdoors. Nonetheless, considering that a light-adaptive photochromic contact lens (Acuvue Oasys with Transitions Light Intelligent Technology; Johnson & Johnson) has been FDA approved, variations of light mediated drug release contact lenses may become a commercial reality.

5.3.2 Temperature triggered release

Thermoresponsive polymers, which alternate between two reversible states in response to changes in temperature, have been widely employed as smart materials for a number of applications [360]. This is advantageous for on-demand drug delivery systems, whereby the systems can be controlled using an “on-off” temperature. For biomedical applications, the activation temperature typically ranges between 25˚C to 37˚C, corresponding to ambient temperature and body temperatures, respectively [361]. The underlying mechanism involves changes in the miscibility of their polymer chains in aqueous solution at various temperatures [361]. The transition temperature at which these changes occur is defined as the lower critical solution temperature or the upper critical solution temperature. Below the lower critical solution temperature threshold, the polymer chains are hydrophilic and miscible in solution, the gel is hydrated and swells. Above the lower critical solution

temperature, the chains begin to aggregate, resulting in phase separation, the gel becomes hydrophobic, expels its water and dissolved contents and changes its properties [361-363]. The opposite effect is observed for upper critical solution temperature , whereby cooling the temperature results in phase separation [361]. The majority of thermo-responsive polymers are lower critical solution temperature-types, one of the most popular being derivatives of poly (N-isopropylacrylamide), which can be copolymerised with polymers such as HEMA and readily adapted into contact lens-viable materials [362-366].

5.3.3 Enzyme triggered release

Enzymatic triggered drug release only occurs in the presence of a set concentration of a specific enzyme. The human tear film contains a relatively high concentration of protein compared to other body fluids, with lysozyme, lactoferrin, albumin, lipocalin and lipophilin comprising the majority of the proteins found in basal tears [367]. Chitosan-poly (acrylic acid) nanoparticles were developed and demonstrated a breakdown and decrease in particle size in the presence of lysozyme [368]. These nanoparticles were then incorporated into polyvinyl alcohol-based contact lenses before being immersed in solutions containing lysozyme at physiological concentrations [368]. The nanoparticles were then released from the lenses over the course of 28 hours, which did not occur in the absence of lysozyme. The authors proposed that the nanoparticles can serve as vehicles for drugs, which could then be released by lysozyme degradation [368].

Another study utilised diamond nanogel embedded contact lenses. Nanodiamond particles were formed into nanogels containing timolol and coated with chitosan, which were then incorporated into the matrix of HEMA-based contact lens materials [369]. Degradation of the chitosan by lysozyme exposure led to the release of timolol from the nanodiamond particle. The timolol was shown to be biologically active, demonstrating that the encapsulation process and enzymatic release from the particle did not adversely affect the drug [369].

6 Antimicrobial contact lenses

Microbial adhesion to contact lenses is a risk factor for developing microbial keratitis, contact lens acute red eye and contact lens peripheral ulcers [370]. These adverse events occur more frequently with lenses worn on an extended wear schedule compared to those worn on a daily wear basis. It is estimated that as many as 1 in 500 wearers per year will develop microbial keratitis while using extended wear contact lenses [371-373]. Reduction in bacterial adhesion to contact lenses using antimicrobial coatings/treatments could thus be a viable means of reducing these potentially sight threatening complications. For these types of antibacterial contact lenses to be viable, several criteria should be considered:

- Efficacy against a broad spectrum of microbes implicated in contact lens-related infection and inflammation, including Gram-positive and Gram-negative bacteria
- Ability to maintain efficacy after exposure to the eye and potential lens cleaning regimes
- Biocompatibility with the ocular tissue
- Stability under typical contact lens sterilization and storage conditions
- Scalable synthesis process and required lens properties

The addition of silver or the use of antimicrobial peptides has received the greatest attention for this application. The CLEAR - contact lens wettability, cleaning, disinfection and interactions with tears report [374] reports more fully on the details of antimicrobial lenses. An overview only is given in this section.

Several contact lens manufacturers, including CIBA Vision (now Alcon), Sauflon (now CooperVision) and Marietta Vision (Marietta, GA, USA) have already incorporated silver into contact lens storage cases to prevent microbial contamination [375]. Silver integrated by various means into contact lens materials is effective at reducing colonisation by *P. aeruginosa*, *S. aureus* and *Acanthamoeba castellanii* [375-377]. However, it has also been noted that silver can be cytotoxic if released from the contact lens polymer [376] and at high concentrations may also impact various contact lens properties [378].

Considerable success in fabricating an antimicrobial contact lens has been seen through incorporation of antimicrobial peptides. The antimicrobial peptides melimine, Mel4 and Esculentin-1a have been incorporated into lenses either by soaking or via a covalent linkage using an (1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride) reaction [379-381], or an acrylic plasma coating technique to coat SiHy contact lens materials (senofilcon A, comfilcon A, somofilcon A, lotrafilcon A and lotrafilcon B) [382]. In all of the approaches described, the incorporation of the peptides did not impact contact lens parameters such as diameter, lens thickness, base curves, wettability, or deposition [381, 382]. These lenses can reduce the adhesion of several microbes including *P. aeruginosa*, *S. aureus, Fusarium solani* and *A. castellanii* which can cause contact lens-induced microbial keratitis [379-383]. Mel4-coated lenses are non-toxic in animal eyes and well tolerated in human trials [384].

Fimbrolides, also known as furanones, are derived from a marine red alga *Delisea pulchra*. They can reduce the adhesion of microbes by inhibiting quorum sensing and other signalling systems [385-389]. A synthetic fimbrolide coated onto lotrafilcon A lenses using gas plasma polymerization and reductive amination produced no notable changes in the lens parameters but was able to reduce adhesion of *P. aeruginosa*, *S. aureus*, *Serratia marcescens* and *Acanthamoeba* sp. [390]. These lenses were generally well tolerated in animal models or humans although it was noted that the volunteer subjects reported a higher degree of lens-awareness for the fimbrolide-coated contact lenses [390].

Microbial adhesion can occur on contact lens surfaces that have been coated by the tear film during wear [370]. For example, the deposition of albumin on lenses modulates bacterial adhesion [391]. Lenses that are resistant to tear film deposition, or biofouling, may therefore also show some degree of resistance to microbial contamination. A clinical study has shown that the incorporation of poly(ethylene oxide) on lotrafilcon A can reduce the biofouling of contact lenses by the tear film [392]. It may be beneficial in the future to explore other biomaterials that are resistant to biofouling as another strategy to develop antimicrobial contact lens materials.

7 Theranostics

Theranostics is a multi-disciplinary field of medicine that combines therapeutics and diagnostics. This rapidly growing area has produced new avenues of research, facilitating discoveries in disease mechanisms as well as drug and medical device development. Theranostics applies knowledge and techniques from nanotechnology, molecular and nuclear medicine, as well as pharmacogenetics, to achieve such tasks as *in vitro* diagnostics and prognostics, *in vivo* molecular imaging and therapy and targeted drug delivery [393]. Its personalised approach to medicine has enabled patient care to shift from defensive towards offensive strategies and from more traditional trial-and-error towards predictive treatments [394].

Potential theranostic contact lenses can be combined with currently available sensing technology and microfabrication techniques. These smart lenses would release appropriate therapeutics based on input from continuous monitoring methods, which would traditionally require invasive procedures for device placement. This emerging field has thus far produced relatively few papers, but theranostic contact lenses have been proposed for the detection and/or management of dry eye, glaucoma and diabetes.

7.1.1 **Dry eye detection and management**

There is growing interest in the changes in biomarkers on the ocular surface in DED, with particular focus on tear proteases such as MMP-9 and protease inhibitors [367]. Utilisation of a facile surface nanoengineering method on the surface of a contact lens could allow continuous monitoring of MMP-9 levels through a similar method as a commercially available PoC immunoassay (InflammaDry, Quidel, San Diego, CA) [367]. The inherent enzymatic activity of MMP-9 could be harnessed to enzymatically stimulate release of appropriate drugs to the ocular surface when their levels are elevated.

7.1.2 **Glaucoma detection and management**

IOP contact lens-based sensors for glaucoma monitoring have been widely studied [94, 97, 105]. The Sensimed Triggerfish contact lens utilises an embedded strain gauge within a contact lens attached to a processing unit and radiofrequency

transmission unit to report information to a receiver worn around the patient's neck [395] (see section 3.1.1). Given this application, it is relatively easy to envision a lens which combines this detection technology with a drug release technology, so that an increase in IOP triggers a tailored amount of a drug to be released to maintain pressure within a set of parameters. Given the mechanical nature of IOP detection with the Triggerfish, drug release could potentially also be tied to this change in physical property.

7.1.3 **Diabetic retinopathy detection and management**

Glucose monitoring sensors for contact lenses, which measure concentrations of glucose and lactate in tear fluid, have been proposed (see section 2.1) [38, 54, 396, 397] . These devices may use a number of sensing principles, including fluorescence, holographic, electrochemical sensing and colloidal crystal array [398].

A recent study has taken steps to expand diagnostic and sensing contact lens technology to include therapeutic elements. Electrically controlled drug delivery with a smart contact lens device has been described [399]. Flexible, ultra-thin electrical circuits and a microcontroller were embedded on a biocompatible polymer and achieved continuous glucose monitoring and drug delivery for diabetic retinopathy in rabbit models. Tear glucose levels were continuously monitored, which enabled triggered release of drugs from treatment reservoirs. The success of this device was made possible through the use of soft bioelectronics and a recently developed semiconductor implantable drug delivery device [399, 400].

Contact lens theranostics will likely expand in the coming decade due to recent advances in contact lens drug delivery innovations and those in the field of smart contact lens sensing. Future theranostic contact lenses will go beyond merely sensors in the contact lens itself, but include both sensing and drug delivery. However, the sensors that would provide the feedback for triggering drug delivery will likely be located outside the contact lens as it may not be feasible for them to be embedded into the same contact lens platform that delivers the drug itself.

8 Optical Enhancements

8.1 Customised optics for aberrated or diseased eyes

Aberrations within the eye are categorised as low order and higher order, with low order aberrations being those corrected with conventional optical corrections. Corneal pathology, such as keratoconus, creates significant amounts of higher order aberrations and spectacle lenses are unable to correct the aberrations created by the ectatic cornea. A standard soft contact lens simply drapes over the distorted shape and is unable to correct the high order aberrations, although customised soft contact lenses have been developed in an attempt to correct these [401, 402]. A rigid contact lens could be used, as the tear lens between the contact lens and cornea neutralises the irregular shape, creating a uniform refracting surface [403, 404].

Measurement and correction of high order aberrations have become more commonplace since the development of customised refractive surgery options that attempt to optimise vision correction during the surgical process, by reducing high order aberrations through individualised ablation of the corneal tissue [405-407]. Several studies have reported the aberrations that occur with the wearing of spherical, toric or multifocal contact lenses in normal eyes [404, 408, 409]. The simplest approach to attempt to reduce aberrations induced by contact lens wear is to include an aspheric surface that is designed to reduce overall aberrations based on the population average, or for the average human eye, particularly spherical aberration [410-413]. While reducing high order aberrations is believed to improve overall visual quality for the wearer, the amount of change in high order aberrations that is clinically detectable differs between patients [414]. As wavefront measures of high order aberrations are limited to monochromatic light [415] and high order aberrations may vary due to blinking, tear film changes, varying pupil size and contact lens decentration, ensuring that lenses remain highly wettable and retain a stable tear film over their front surface may well have a greater visual impact than correcting high order aberrations [416].

The addition of corneal topography to laser vision correction means that a laser profile can be added to the patient's unique corneal shape, with the option of reducing high order aberrations during the surgical procedure. An extension of this

concept has made its way into contact lens design for highly aberrated eyes, with the front surface of the lens being manufactured to specifically reduce the measured aberrations that occur with the lens in situ [417-419]. The future for this concept will likely result in an improvement in custom-made lenses for corneal irregularities such as keratoconus [402, 420], particularly in scleral lenses or mini-scleral designs, where the lens is more stable and aberration control becomes easier to achieve [421, 422].

8.2 Accommodative contact lenses for presbyopia

It is estimated that presbyopia affects 1.8 billion people globally [423] and, as the world's population ages, this figure will rise substantially. Although a number of approaches have been considered to treat the crystalline lens in presbyopia, for example, chemical softening, optical strategies remain the mainstay of management and some novel options for contact lens management have been proposed.

There are two fundamental problems that must be solved in designing an accommodative contact lenses. The first challenge is to be able to continually track the user's gaze or monitor the viewing distance, while the second is to actively control the focal length of the optical element [424, 425]. The optimal accommodating contact lenses should be able to transition between near and distance focus based on the patient's gaze and should be capable of producing at least +2.00 additional diopters of power for near vision [425].

8.2.1 Mechanically accommodating lenses for presbyopia

Two methods of using the gaze position as a mechanical control of the optics of the lens have been proposed. In the first example, the accommodative contact lens utilises contact with the eyelids to provide additional dioptric power. In the normal state, the contact lens provides a single dioptric power for distance vision. When eyelid pressure is applied, the contact lens is squeezed and lifted from the surface of the eye and, as a result, the shape of the lens and the tear film underneath causes a change in dioptric power [426]. In the second example, the contact lens uses fluid flow within the bulk of the material to change optical power [427]. When the eye moves downwards, the lower eyelid presses against the lens, which causes liquid at

the bottom of the lens to flow into the centre. This fluid movement changes the optical power of the lens from distance to near focus [427, 428].

8.2.2 Electronic accommodative or ‘tuneable’ contact lenses

The most ambitious method for an automatically accommodating contact lens proposes to embed microelectronics on a contact lens to control accommodation. In this type of system, the gaze is monitored using a capacitive sensor that determines the gaze direction of the cornea based on changes in capacitance [429]. These changes are detected in real-time, which is then used to control the optical element [429]. The gaze information from both eyes can also be sent to an external device for more refined processing and control [430]. A schematic of a proposed electronic presbyopic contact lens is shown in Figure 3. Similar to other smart contact lens designs, the optical components must also be supported by a power source [431, 432] and an antenna [433, 434] to function.

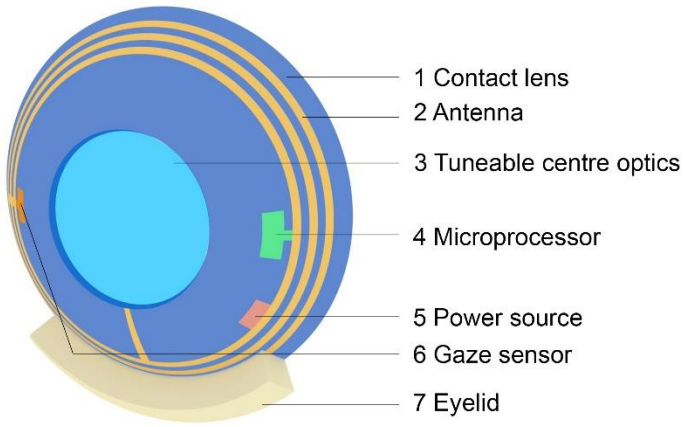

Figure 3: Schematic design of an electronic presbyopic contact lens [425]. The sensor monitors (6) the gaze and sends the information to a microprocessor (4), which controls the tuneable centre optics (3). The optics can be tuned using a responsive polymer [435] or liquid crystals [424, 425, 436]. The entire system is supported by a power source (5) and an antenna (2).

There are several ways that the optical elements can be controlled to induce changes in optical power; although many of these suggestions are patent filings alone and their functionality for correction of presbyopia is yet to be determined in clinical studies. A number of patents and patent applications describe the use of electroactive materials or elements (also referred to as accommodation actuators) that can change shape or be used to change shape, and thus refractive power, in response to a signal [435, 437]. In addition to the electroactive elements or materials, the contact lens system incorporates a view or gaze detection mechanism, a controller/actuator (such as a chip or an integrated circuit), an embedded battery and an external power source [437-441].

With respect to the electroactive elements or materials, they may be localised to the optic zone or embedded in the anterior or posterior segment of the contact lens [435]. In another example, fluids in a reservoir inside the lens can be circulated from the periphery of the lens to the centre using an electro-mechanical pump on the lens, which causes a change in shape and refractive power [428].

Another approach proposes the use of liquid crystals, which are best known for their applications in liquid crystal displays such as television or computer screens. Liquid crystals naturally form long rods that generally point in the same direction [442]. The positioning of these rods can be reoriented by a relatively low voltage, reverting to the original alignment when the electric potential is removed [442]. The changes in orientation of these rods consequently result in changes in the material's refractive index, which can be exploited to increase or decrease optical power [424, 425, 436] and to be configured with the aid of a controller to function as a pinhole, increasing the depth of focus of light. The overall design of a liquid crystal contact lens consists of the liquid crystal component sandwiched between two layers of electrodes [146, 425, 443, 444].

It is evident from the innovative technologies described that management of presbyopia using accommodating contact lenses is of substantial interest and that the industry may witness some significant developments in presbyopia management in the not too distant future.

8.3 Myopia control

The announcement in November 2019 of the FDA approval for the use of MiSight® 1 day (CooperVision, Pleasanton, CA, USA) for slowing myopia progression in children was an important milestone in myopia control, by demonstrating the feasibility of successfully slowing myopia progression and by acknowledging the need to reduce the risk of the eye becoming highly myopic [445]. In addition to MiSight® 1 day, there are other contact lenses that are now available in various markets to slow myopia that are backed by varying degrees of clinical evidence [446, 447]. The reader should also refer to the CLEAR reports on medical use of contact lenses [143], orthokeratology [448] and contact lens optics [449] for further information of myopia control by contact lenses.

Over the past two decades, a number of clinical studies have demonstrated that contact lenses are able to slow myopia progression in children [450]. The lens designs that have been assessed incorporate either concentric rings of plus power, peripheral optical zone(s) with add power and lens designs that incorporate non-monotonic variations in power, varying in both myopic and hyperopic directions. However, in spite of these significant advances, contact lens fittings for myopia control are limited to only about 2-5% of the total contact lens fittings, with single vision spectacles remaining the most popular myopia management modality [451, 452].

One of the reasons for low uptake of soft contact lenses for myopia management relate to perceptions on efficacy, with soft lenses ranking behind orthokeratology and pharmaceutical options in terms of perceived efficacy by ECPs worldwide [451, 452]. Despite this, the myopia control field is growing and research considering innovative and improved approaches to slow myopia is of great interest. Many of these approaches are related to innovations that appear in patent articles and not in the scientific literature and, therefore, may be in planning or pre-clinical development stages. There is interest in considering novel contact lens designs as well as optimisation of lens designs and considerations of subgroups such as astigmats. Some of the innovations around lens designs include: lens design with asymmetric radial power profile that increases from the centre to the margin of the optical zone of

the contact lens [453], non co-axial lenslets [454], a lens with varying peripheral power and an opaque mask beginning at a radial distances from the centre [455] and a star shaped or elliptical optical zone to increase peripheral defocus area [456]. It is not known if any of these designs are being clinically evaluated.

Astigmatism is common and varies with age and ethnicity [457]. The clinical evidence for myopia control is limited to astigmatism commonly <1D and therefore it is not clear if these previously mentioned designs can be effectively used for higher amounts of astigmatism. While studies have been undertaken to investigate this concept [458], more studies are required. A centre distance toric multifocal contact lens with free form stabilisation is under consideration for myopia control in children [459]. Additionally, improvements in terms of refining lens designs (optimised defocus incorporated soft contact lenses) and multifocal orthokeratology lenses wherein the back surface design of the lens is designed to create a multifocal shape on the cornea with alternating zones of flattening and steepening appear to be in various stages of clinical testing.

Combination strategies are successful if they provide additive or synergistic effects compared to single strategies and, increasingly, myopia management strategies are considering combination strategies to improve efficacy. Most commonly, these approaches have involved using orthokeratology or soft contact lenses in combination with pharmaceutical approaches. Recent studies found that combining atropine and orthokeratology contact lenses was more effective in slowing axial elongation than orthokeratology alone [460-463]. The effect of combining 0.01% atropine and soft bifocal contact lenses is also under consideration [464]. However, at this stage, it is not clear if the combination strategy improves efficacy via a synergistic mechanism or if the two treatment strategies act via different pathways. It has been suggested that sequential treatment with atropine based therapy during the period of rapid progression, followed by contact lens wear during the teenage years is an option [465].

A further novel concept reports an electronic contact lens comprising multiple light sources coupled to optics which project multiple images anterior to the retina (in myopic defocus) to decrease progression [466].

8.4 Sports enhancement

Contact lenses are commonly advocated for athletes due to their increased field of view, in sports where spectacles may be easily displaced and for sports where vision correction methods are prohibited as they may cause injury to other players.

Enhancement of visual performance using contact lenses has primarily centred on studies using the now discontinued Nike MaxSight amber or grey/green tinted contact lenses from Bausch + Lomb (Rochester, NY, USA) [467]. Subjectively, subjects showed a preference for the tinted lenses in comparison to clear ones in bright light conditions [468-470]. The lenses also allowed for participants to switch gaze between objects in bright and dark lighting conditions faster and visually recover more rapidly when moving from dark to bright light [469]. The recent introduction of photochromic lenses from Johnson & Johnson Vision (Jacksonville, FL, USA) may fill the gap left by the discontinuation of the MaxSight lenses, but to date no data on their use in athletes has been published. However, their value in reducing light scatter and improvements in other vision aspects have been presented [471-473]. Given the interest within the sports arena to even marginally improve any aspect of performance that provides a benefit to athletes, further development of tinted lenses for sports remains an area worthy of pursuit.

8.5 Low vision enhancements

Patients with low vision may be visually assisted with the use of a ‘contact lens telescope’ [474]. The principles behind this system are that of a Galilean telescope, which comprises a high negative eyepiece lens and a positive objective lens placed at a set distance in front of the eyepiece lens. The separation of the two lenses will affect the magnifying power of the telescope. Applying the same theory to contact lenses, the high-powered negative eyepiece is the contact lens (for example a -20DS) and the eye is refracted at the spectacle plane. The neutralising lens will be approximately +16DS at a back vertex distance of 12mm. The +16DS lens would be placed at the spectacle plane, as an optical lens glazed into a spectacle frame and will act as the positive objective lens in this Galilean telescope set up [474, 475]. In

this example, the nominal magnification is only around 20%, but this may be enough to give the patient a useful functional increase in vision [476]. This concept could be further adapted with a switchable contact lens telescope system that switches between normal and magnified vision using polarisation [477].

8.6 Augmented vision

Recent advances in augmented reality technologies have provided novel approaches to digital enhancement of visual function, especially to improve the mobility and independence of patients with low vision. These advances include head-mounted devices utilising video see-through displays, in which a magnified or contrast-enhanced view of the world, captured by real-time outward facing video is projected on a micro-display in front of the eyes [478, 479].

Approaches to vision augmentation have included selective edge enhancement to highlight object boundaries and distance enhancements, which displays pixel brightness based on the distance of points in the visual field [480, 481]. Several studies have proposed see-through head-mounted displays with varying levels of success [482-484]. Researchers at Google were among the first to commercialise such products with Google Glass, a non-medical augmented reality device worn as spectacles. Google Glass is controlled by vocal commands similar to the functionality of a hands-free smartphone, as well as a touchpad on the side of the device. The most up to date iteration is outfitted with an 8 megapixel 80° field of view camera and a liquid crystal on silicon, field-sequential colour system, light emitting diode (LED) illuminated display. Amazon and Facebook are reported to be developing their own head-mounted augmented vision devices, in the form of consumer-friendly smart glasses [485].

Alongside these avenues, Mojo Vision (Saragota, CA, USA) has proposed a similar technology in the form of contact lenses. Although the product has yet to reach the market, the company’s plans have been released into the public arena. While many uses of this new technology have been described, including scrolling information and text to access personal correspondence, translating languages or aiding with public speaking, this lens will first be used to help those with severely impaired vision by

providing enhanced image overlays, drawing crisp lines around objects in the user's view [486]. In one prototype demonstration of the display capabilities, users reported real-time edge detection, which even highlighted the facial features of others in the room enough to detect facial expressions in low light [487].

The functionality and wearability of augmented vision contact lenses require the development of micro-components of the product to assist with motion sensors, image sensors, wireless power systems and radios, and a high-resolution microdisplay [487]. The proposed Mojo hexagonal display, which will lie directly in front of the pupil in the contact lens, is measured at 0.41 mm and contains approximately 100,000 LEDs in the array. Resting directly on the cornea, the contact lens and centrally positioned display will be out of the focal plane of the eye and therefore the opaque micro hexagon will not be imaged on the retina, making it invisible to the viewer. The micro optic on the display of future augmented vision contact lenses will project light on the retina. As the eye moves, so will the contact lens and display, maintaining the visual augmentation across the fovea and near periphery [488]. In particular, it is the focus of light onto the fovea which will likely limit visual field requirements, allowing the display to require less light and power to transmit images [485].

Potential limitations to augmented vision contact lenses include the use of monochrome displays in the early devices; the highest resolution achieved by researchers used a green LED array on a complementary metal-oxide-semiconductor backplane. Additionally, augmented vision contact lenses are likely not as usable in bright outdoor light conditions, since the contrast is dependent on the background in which the augmentation is displayed. As ambient light increases, so does the brightness needed from the display [488].

As medical devices, future augmented vision contact lenses will require approval from the FDA, and Mojo lenses have been allocated 'breakthrough device' status [487]. An added zoom feature has also been proposed by the company as an aid for those with low vision [487].

9 Contact Lens Packaging

Microbial keratitis is the most serious complication of contact lens wear, yet its incidence and associated risks have not changed over decades [372, 489, 490]. Many elements of poor compliance have been linked to microbial keratitis, including hand hygiene [490-492], and storage case hygiene and replacement [372, 491, 493-495]. For these reasons, the contact lens storage case and primary blister-pack packaging, often overlooked, are important elements of contact lens wearing success.

Soft contact lenses are packaged as sterile medical devices, but once opened and handled become contaminated and a microbial load can be easily transferred from the fingers to the lens and into the eye [496]. Thus, efforts have been made to minimise the amount of handling (and therefore contamination of the contact lens during the application process) by design of the case and/or application devices.

Almost two decades ago, two patents described methods to insert the lens directly from the packaging solution without touching the finger; in one case while also controlling the eyelid position such that lid contamination of the lens with microbes did not occur during the insertion process. [497, 498]. In a more recent patent, the inventors describe a disposable lens package that contains a film that adheres to the surface of the finger which is then used to pick up the contact lens for placement on the eye [499].

One approach to minimise contamination has been commercialised by Menicon Company Limited (Nagoya, Japan) in their “flat pack” technology [500]. In this package, which is approximately 1-mm thick, the lens is compressed in a small amount of solution (~0.2ml) between two layers of foil, that when separated, allows the lens to “pop up” into a hemispherical shape, with the outer lens surface presenting. The lens can easily be manipulated onto a clean finger and applied to the eye with high confidence that the inner surface that comes into contact with the cornea has not been contaminated. Simulated tests of bacterial adherence using 3-5µm PMMA beads or bacterial adherence of *S. aureus* to lenses removed from the flat pack compared to lenses removed from more conventional blister packages

found contamination was reduced on the flat pack lenses [501]. This has particular relevance for single use lenses, as contaminated fingers are likely to be the main route of transferring bacteria to the eye using this wearing modality.

10 Storage Cases

Contact lens storage cases have been implicated in microbial keratitis involving bacteria, fungi and *Acanthamoeba* [372, 493, 494, 502-505]. A population attributable risk model of microbial keratitis predicts that disease load in daily wear reusable lenses could be reduced by almost two thirds by merely attending to storage case hygiene and storage case replacement [494]. Thus, efforts to minimise the negative impact of the contact lens case should remain a priority.

10.1 Increasing case replacement frequency

A new storage case can become contaminated by single isolated bacterial colonies after as few as 7 days of use, with microcolonies seen at 14 days and mature biofilms and heavy contamination by 30 days [506]. Upwards of 80% of cases can be contaminated after two weeks of use [507]. Methods to remind wearers to replace their cases have been attempted by building reminder systems into the case itself [508-510], and while some have been marketed, uptake has been minimal. There are also patents in the area of controlled obsolescence [511], but these have not been commercialised. However, until daily disposability becomes the only option, methods to encourage case replacement should be pursued.

10.2 Reducing case contamination levels

Biofilms within cases have been linked to contact lens-related corneal disease [512]. One strategy to control microbial adhesion and biofilm formation is to use silver in the lens case. The first silver-impregnated contact lens case (called Microblock or Proguard, CIBA Vision Inc., Atlanta, GA, USA) was approved by the FDA in 2005. Ionic silver is mixed into the plastic during the moulding step, ensuring an even distribution of silver throughout [513]. When used in conjunction with a multipurpose disinfecting solution, silver ions slowly leached from the Microblock case material to prevent bacterial growth. A comparison of the Microblock silver-containing case to

non-silver cases in an *in vitro* study showed that the number of recovered colonies from the silver-impregnated case inoculated with Gram-positive and Gram-negative bacterial strains was significantly lower than that recovered from conventional cases [513]. Another *in vitro* study compared the efficacy of Microblock silver cases to i-clean (Sauflon Pharmaceuticals Ltd., London, UK) and Nano-case (Marietta Vision) silver lenses, and to control non-silver cases for *P. aeruginosa, S. aureus, S. marcescens, S. maltophilia, Delftia acidovorans, C. albicans* and *F. solanii* [514]. Significant antimicrobial activity for most bacteria was found for the Microblock case but only after incubation with the bacteria for 24 hours; there was usually no significant activity if incubated for 6 or 10 hours. The i-clean case only had significant antimicrobial activity for *S. aureus* usually after 24 hours incubation. No silver containing lens case was active against *F. solanii* and Microblock was the only case active against *C. albicans* but even that showed a low but significant level of activity [514]. Another study using a barrel-shaped silver case (Sauflon) was able to show activity after only 6 hours incubation using a variety of Gram-positive and Gram-negative bacteria [515]. Further investigation of silver lens cases showed that preconditioning the lens case with multipurpose disinfecting solution increased the antimicrobial activity for the Microblock case but not i-clean [516]. Two studies have shown that incorporating a wipe step in lens case hygiene improves the removal of bacteria from silver lens cases [516, 517]

However, clinical studies examining contamination with MicroBlock and conventional cases found that more than 70% of the storage cases used for a month were contaminated, whether silver-containing or not [518]. Although the silver-impregnated cases were colonised by reduced levels of Gram-negative bacteria, this did not result in a significant reduction in adverse events over the course of the study. Another study using a barrel-shaped silver lens case (Sauflon) found that when this was used in conjunction with SiHy lenses there was a significant reduction in the numbers of microbes (mostly bacteria) from silver cases compared to non-silver barrel-shaped cases, but if hydrogel lenses were used there was an increase in the number of microbes from silver barrel-shaped cases [519]. Thus, while *in vitro* data has generally shown reduced contamination, the reduction may take greater than 10 hours with some cases and clinical trials have struggled to show significant clinical benefits when silver cases are used.

Selenium has also been studied as a potential additive to contact lens cases. Organoselenium completely inhibited biofilm formation by several organisms and the inhibitory properties were retained against *S. aureus* even after 8 weeks soaking in phosphate buffered saline [520]. Organoselenium kills bacteria by the catalytic generation of superoxide radicals in the solution and does not have to elute from the case (like silver), leaving the concentration constant over the life of the case.

Passive surface modifications that hinder microbial adhesion may also help reduce the risk of microbial keratitis. Surface modified silica nanoparticles, chemically grafted with UV crosslinkable acrylates and PEG groups were coated onto polypropylene cases to form an anti-fouling coating [521, 522]. The result was an approximate 10-fold reduction in the adhesive forces of 9 bacterial strains, including *Pseudomonas*, *staphylococci* and *Serratia*.

10.3 Sensing of contact lens and case contamination

Bacterial detection is not only an issue for the contact lens field, with areas such as dental hygiene and wound care also concerned with detecting and characterising microbial load. In these fields, technology is currently under development to detect bacterial contamination. The development of a peptide-graphene nanosensor to allow ‘on tooth’ monitoring of bacterial detection in saliva has been described [523]. These compact sensors are around 50 µm thick and can be externally powered, highlighting the potential for integration within a contact lens. Such technology would allow the contact lens to be monitored for microbial contamination, prompting lens removal and disinfection/disposal, if a high bacterial load was detected.

Contact lens case contamination is commonplace [507, 518, 524]. To address this issue, a small real-time sensing device embedded within a contact lens case which undergoes a colour change to signal the presence of abnormally high levels of bacteria has been described (Figure 4) [525]. The sensor was embedded into a contact lens case and contained tetrazolium dye, which changed colour from yellow to blue when the bacterial level reached over a million counts in 1ml of solution. This

type of technology readily allows the contact lens user to see microbial case contamination which would otherwise not be apparent, prompting case replacement.

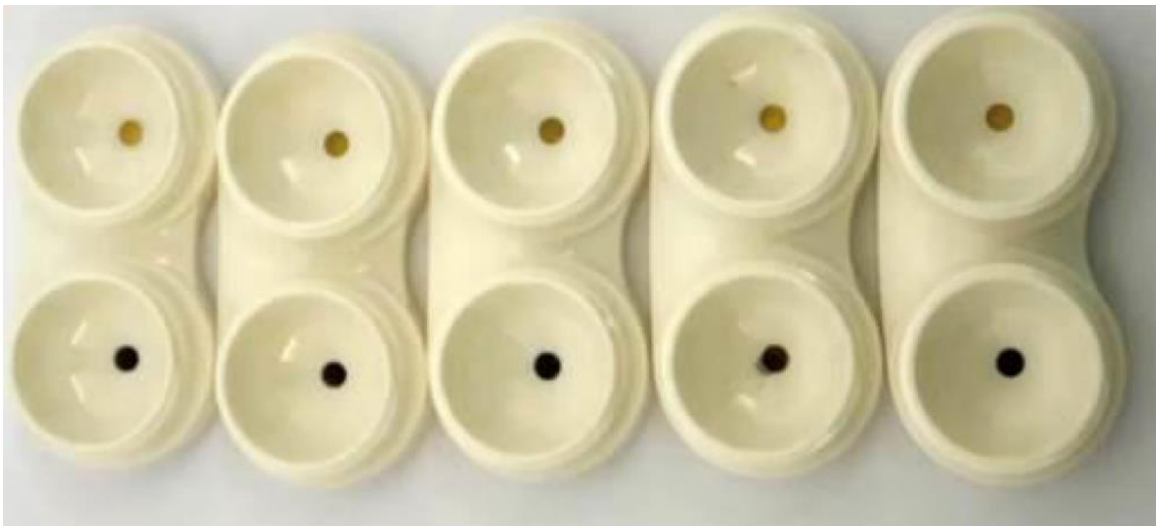

Figure 4. Microbiosensor in a contact lens case with the bottom blue colour indicating microbial contamination [525].

The presence of a biofilm within a contact lens case has also been shown to increase the risk of both microbial keratitis and infiltrative keratitis [496]. As biofilms are typically not visible to the naked eye, a method to identify the presence of the biofilm is needed. To address this issue, a colourimetric biosensor has been developed to detect biofilms on the surface of a contact lens case [526, 527]. Gold nanoparticles are immobilised on the case surface to form the biosensor, where biofilm formation results in an increase in refractive index and an associated visible colour change from blue to purple, which is visible to the user, prompting lens case disposal.

Given the well-known links between case contamination and microbial keratitis, methods to instruct the wearer to replace a contaminated case or lenses prior to clinical complications occurring would seem worthy technologies to pursue.

11 Conclusion

This review demonstrates the incredible diversity of new technologies under development that will shape the future for contact lenses. The rapid growth in novel

biomaterials and, in particular, the development of powered contact lenses through advancements in nanotechnology will enable the commercialisation of lenses that can both detect and treat ocular and, in some cases, systemic disease. Novel optical designs will help manage common ocular conditions such as myopia and presbyopia, in addition to providing enhanced vision for patients with low vision and corneal conditions such as keratoconus. Improvements in biosensing and antibacterial surfaces will produce safer contact lens cases and materials, reducing the numbers of patients who develop sight threatening microbial keratitis and infiltrative responses.

Contact lenses have been around for over 100 years and their future remains bright, with many exciting developments under consideration.

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[1] Hagan S, Martin E, Enriquez-de-Salamanca A. Tear fluid biomarkers in ocular and systemic disease: Potential use for predictive, preventive and personalised medicine. EPMA J 2016;7:15. https://doi.org/10.1186/s13167-016-0065-3.

[2] Kallo G, Emri M, Varga Z, Ujhelyi B, Tozser J, Csutak A, et al. Changes in the chemical barrier composition of tears in Alzheimer's disease reveal potential tear diagnostic biomarkers. PLoS One 2016;11(6):e0158000. https://doi.org/10.1371/journal.pone.0158000.

[3] Evans V, Vockler C, Friedlander M, Walsh B, Willcox MD. Lacryglobin in human tears, a potential marker for cancer. Clin Exp Ophthalmol 2001;29(3):161-3. https://doi.org/10.1046/j.1442-9071.2001.00408.x.

[4] de Freitas Campos C, Cole N, Van Dyk D, Walsh BJ, Diakos P, Almeida D, et al. Proteomic analysis of dog tears for potential cancer markers. Res Vet Sci 2008;85(2):349-52. https://doi.org/10.1016/j.rvsc.2007.11.006.

[5] You J, Willcox MD, Madigan MC, Wasinger V, Schiller B, Walsh BJ, et al. Tear fluid protein biomarkers. Adv Clin Chem 2013;62:151-96. https://doi.org/10.1016/b978-0-12-800096-0.00004-4.

[6] Mrugacz M, Kaczmarski M, Bakunowicz-Lazarczyk A, Zelazowska B, Wysocka J, Minarowska A. IL-8 and IFN-gamma in tear fluid of patients with cystic fibrosis. J Interferon Cytokine Res 2006;26(2):71-5. https://doi.org/10.1089/jir.2006.26.71.

[7] Mrugacz M, Zelazowska B, Bakunowicz-Lazarczyk A, Kaczmarski M, Wysocka J. Elevated tear fluid levels of MIP-1alpha in patients with cystic fibrosis. J Interferon Cytokine Res 2007;27(6):491-5. https://doi.org/10.1089/jir.2007.0149.

[8] Mrugacz M. CCL4/MIP-1beta levels in tear fluid and serum of patients with cystic fibrosis. J Interferon Cytokine Res 2010;30(7):509-12. https://doi.org/10.1089/jir.2009.0102.

[9] Aihara M, Kubota N, Kadowaki T. Study of the correlation between tear glucose concentrations and blood glucose concentrations. Diabetes 2018;67(Supplement 1):944-P. https://doi.org/10.2337/db18-944-P.

[10] Zhao Z, Liu J, Shi B, He S, Yao X, Willcox MD. Advanced glycation end product (age) modified proteins in tears of diabetic patients. Mol Vis 2010;16:1576-84, https://www.ncbi.nlm.nih.gov/pubmed/20806041.

[11] Liu J, Shi B, He S, Yao X, Willcox MD, Zhao Z. Changes to tear cytokines of type 2 diabetic patients with or without retinopathy. Mol Vis 2010;16:2931-8, https://www.ncbi.nlm.nih.gov/pubmed/21203348.

[12] Coyle PK, Sibony P, Johnson C. Oligoclonal IgG in tears. Neurology 1987;37(5):853-6. https://doi.org/10.1212/wnl.37.5.853.

[13] Devos D, Forzy G, de Seze J, Caillez S, Louchart P, Gallois P, et al. Silver stained isoelectrophoresis of tears and cerebrospinal fluid in multiple sclerosis. J Neurol 2001;248(8):672-5. https://doi.org/10.1007/pl00007833.

[14] Salvisberg C, Tajouri N, Hainard A, Burkhard PR, Lalive PH, Turck N. Exploring the human tear fluid: Discovery of new biomarkers in multiple sclerosis. Proteomics Clin Appl 2014;8(3-4):185-94. https://doi.org/10.1002/prca.201300053.

[15] Comoglu SS, Guven H, Acar M, Ozturk G, Kocer B. Tear levels of tumor necrosis factor-alpha in patients with Parkinson's disease. Neurosci Lett 2013;553:63-7. https://doi.org/10.1016/j.neulet.2013.08.019.
[16] Hamm-Alvarez SF, Janga SR, Edman MC, Feigenbaum D, Freire D, Mack WJ, et al. Levels of oligomeric alpha-synuclein in reflex tears distinguish Parkinson's disease patients from healthy controls. Biomark Med 2019;13(17):1447-57. https://doi.org/10.2217/bmm-2019-0315.
[17] Huang D, Luo Q, Yang H, Mao Y. Changes of lacrimal gland and tear inflammatory cytokines in thyroid-associated ophthalmopathy. Invest Ophthalmol Vis Sci 2014;55(8):4935-43. https://doi.org/10.1167/iovs.13-13704.
[18] Cai K, Wei R. Interleukin-7 expression in tears and orbital tissues of patients with graves' ophthalmopathy. Endocrine 2013;44(1):140-4. https://doi.org/10.1007/s12020-012-9840-7.
[19] Tseng RC, Chen CC, Hsu SM, Chuang HS. Contact-lens biosensors. Sensors (Basel) 2018;18(8):2651. https://doi.org/10.3390/s18082651.
[20] Kim YS. Functionalized eyewear device for detecting biomarker in tears. *Google Patents.* US10830776B2. USA: University of Central Florida Research Foundation Inc; 2019.
[21] Pugh RB, Toner A, Humphreys SR, Otts DB, Neeley WC. Blink detection system for electronic ophthalmic lens. *Google Patents.* US9498124B2. USA: Johnson and Johnson Vision Care Inc; 2014.
[22] Chen R, Kalinli O. Interface using eye tracking contact lenses. US9244285B2. USA: Sony Interactive Entertainment Inc; 2014.
[23] Shtukater A. Smart contact lens. *Google Patents.* US10845620B2. USA; 2015.
[24] Pugh RB. Ophthalmic lens with retinal vascularization monitoring system. *Google Patents.* US10159461B2. USA: Johnson & Johnson Vision Inc.; 2018.
[25] Badugu R, Jeng BH, Reece EA, Lakowicz JR. Contact lens to measure individual ion concentrations in tears and applications to dry eye disease. Anal Biochem 2018;542:84-94. https://doi.org/10.1016/j.ab.2017.11.014.
[26] Yetisen AK, Jiang N, Castaneda Gonzalez CM, Erenoglu ZI, Dong J, Dong X, et al. Scleral lens sensor for ocular electrolyte analysis. Adv Mater 2020;32(6):e1906762. https://doi.org/10.1002/adma.201906762.
[27] Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the international diabetes federation diabetes atlas, 9(th) edition. Diabetes research and clinical practice 2019;157:107843. https://doi.org/10.1016/j.diabres.2019.107843.
[28] Heinemann L. Finger pricking and pain: A never ending story. Journal of diabetes science and technology 2008;2(5):919-21. https://doi.org/10.1177/193229680800200526.
[29] Liao Y-T, Yao H, Lingley A, Parviz B, Otis BP. A 3-µw cmos glucose sensor for wireless contact-lens tear glucose monitoring. Ieee J Solid-St Circ 2012;47(1):335-44. https://doi.org/10.1109/jssc.2011.2170633.
[30] Otis B, Liao Y, Amirparviz B, Yao H. Wireless powered contact lens with biosensor. *Google Patents.* US8608310B2. USA: University of Washington Center for Commercialization; 2012.

[31] Elsherif M, Hassan MU, Yetisen AK, Butt H. Wearable contact lens biosensors for continuous glucose monitoring using smartphones. ACS nano 2018;12(6):5452-62. https://doi.org/10.1021/acsnano.8b00829.
[32] Cummins BM, Garza JT, Cote GL. Optimization of a Concanavalin A-based glucose sensor using fluorescence anisotropy. Anal Chem 2013;85(11):5397-404. https://doi.org/10.1021/ac303689j.
[33] Lamrani M. Glucose sensing contact lens. *Google Patents.* US10478104B2. USA: Menicon Co Ltd; 2019.
[34] Senior M. Novartis signs up for Google smart lens. Nature biotechnology 2014;32(9):856. https://doi.org/10.1038/nbt0914-856.
[35] Park S, Boo H, Chung TD. Electrochemical non-enzymatic glucose sensors. Analytica chimica acta 2006;556(1):46-57. https://doi.org/10.1016/j.aca.2005.05.080.
[36] Liu M, Liu R, Chen W. Graphene wrapped Cu2O nanocubes: Non-enzymatic electrochemical sensors for the detection of glucose and hydrogen peroxide with enhanced stability. Biosensors & bioelectronics 2013;45:206-12. https://doi.org/10.1016/j.bios.2013.02.010.
[37] Feng D, Wang F, Chen Z. Electrochemical glucose sensor based on one-step construction of gold nanoparticle–chitosan composite film. Sensor Actuat B-Chem 2009;138(2):539-44. https://doi.org/10.1016/j.snb.2009.02.048.
[38] Park J, Kim J, Kim SY, Cheong WH, Jang J, Park YG, et al. Soft, smart contact lenses with integrations of wireless circuits, glucose sensors, and displays. Science advances 2018;4(1):eaap9841. https://doi.org/10.1126/sciadv.aap9841.
[39] Shende P, Sahu P, Gaud R. A technology roadmap of smart biosensors from conventional glucose monitoring systems. Therapeutic delivery 2017;8(6):411-23. https://doi.org/10.4155/tde-2017-0012.
[40] Yang Y, Rim YS, Yang j. High performance chemical and bio sensors using metal oxide semiconductors. *US 20180059051 A1.* 2019.
[41] Sei KH, Young CS, Beom HM, Keon JL, Dohee K, K SJ. Smart contact lenses and smart glasses. *Google Patents.* US10399291B2. USA: Phi Biomed Co Ltd; 2016.
[42] Miyashita M, Ito N, Ikeda S, Murayama T, Oguma K, Kimura J. Development of urine glucose meter based on micro-planer amperometric biosensor and its clinical application for self-monitoring of urine glucose. Biosensors & bioelectronics 2009;24(5):1336-40. https://doi.org/10.1016/j.bios.2008.07.072.
[43] Koudelka M, Gernet S, De Rooij NF. Planar amperometric enzyme-based glucose microelectrode. Sensor Actuator 1989;18(2):157-65. https://doi.org/10.1016/0250-6874(89)87015-5.
[44] Clark LC, Jr., Lyons C. Electrode systems for continuous monitoring in cardiovascular surgery. Annals of the New York Academy of Sciences 1962;102(1):29-45. https://doi.org/10.1111/j.1749-6632.1962.tb13623.x.
[45] Kajisa T, Sakata T. Glucose-responsive hydrogel electrode for biocompatible glucose transistor. Science and technology of advanced materials 2017;18(1):26-33. https://doi.org/10.1080/14686996.2016.1257344.
[46] Yao H, Liao Y, Lingley AR, Afanasiev A, Lähdesmäki I, Otis BP, et al. A contact lens with integrated telecommunication circuit and sensors for wireless and continuous tear glucose monitoring. Journal of Micromechanics and Microengineering 2012;22(7):075007. https://doi.org/10.1088/0960-1317/22/7/075007.

[47] Alexeev VL, Das S, Finegold DN, Asher SA. Photonic crystal glucose-sensing material for noninvasive monitoring of glucose in tear fluid. Clin Chem 2004;50(12):2353-60. https://doi.org/10.1373/clinchem.2004.039701.
[48] Sun X, Zhai W, Fossey JS, James TD. Boronic acids for fluorescence imaging of carbohydrates. Chemical communications 2016;52(17):3456-69. https://doi.org/10.1039/c5cc08633g.
[49] March W, Lazzaro D, Rastogi S. Fluorescent measurement in the non-invasive contact lens glucose sensor. Diabetes technology & therapeutics 2006;8(3):312-7. https://doi.org/10.1089/dia.2006.8.312.
[50] Aslan K, Lakowicz JR, Geddes CD. Tunable plasmonic glucose sensing based on the dissociation of con a-aggregated dextran-coated gold colloids. Analytica chimica acta 2004;517(1-2):139-44. https://doi.org/10.1016/j.aca.2004.04.060.
[51] Villena Gonzales W, Mobashsher AT, Abbosh A. The progress of glucose monitoring-a review of invasive to minimally and non-invasive techniques, devices and sensors. Sensors (Basel) 2019;19(4):800. https://doi.org/10.3390/s19040800.
[52] Zhu H, Li L, Zhou W, Shao Z, Chen X. Advances in non-enzymatic glucose sensors based on metal oxides. Journal of materials chemistry B 2016;4(46):7333-49. https://doi.org/10.1039/c6tb02037b.
[53] Guo S, Wu K, Li C, Wang H, Sun Z, Xi D, et al. Integrated contact lens sensor system based on multifunctional ultrathin mos2 transistors. Matter 2020. https://doi.org/10.1016/j.matt.2020.12.002.
[54] Zhang J, Hodge W, Hutnick C, Wang X. Noninvasive diagnostic devices for diabetes through measuring tear glucose. Journal of diabetes science and technology 2011;5(1):166-72. https://doi.org/10.1177/193229681100500123.
[55] Badugu R, Lakowicz JR, Geddes CD. A glucose-sensing contact lens: From bench top to patient. Curr Opin Biotechnol 2005;16(1):100-7. https://doi.org/10.1016/j.copbio.2004.12.007.
[56] Vaddiraju S, Burgess DJ, Tomazos I, Jain FC, Papadimitrakopoulos F. Technologies for continuous glucose monitoring: Current problems and future promises. Journal of diabetes science and technology 2010;4(6):1540-62. https://doi.org/10.1177/193229681000400632.
[57] McQueen RB, Ellis SL, Campbell JD, Nair KV, Sullivan PW. Cost-effectiveness of continuous glucose monitoring and intensive insulin therapy for type 1 diabetes. Cost Eff Resour Alloc 2011;9:13. https://doi.org/10.1186/1478-7547-9-13.
[58] Diabetes C, Complications Trial Research G, Nathan DM, Genuth S, Lachin J, Cleary P, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The New England journal of medicine 1993;329(14):977-86. https://doi.org/10.1056/NEJM199309303291401.
[59] Comstock J. Alphabet's verily shelves glucose-sensing contact lens project with novartis; 2018. Available from: https://www.mobihealthnews.com/content/alphabets-verily-shelves-glucose-sensing-contact-lens-project-novartis. [Accessed 26 July 2020 2019].
[60] March WF, Mowery-McKee MF. Ocular analyte sensor. *Google Patents.* US6980842B2. USA: Eyesense AG; 2002.

[61] Geddes CD, Badugu R, Lakowiccz JR. Quaternary nitrogen heterocyclic compounds for detecting aqueous monosaccharides in physiological fluids. *Google Patents.* US8569502B2. USA: Geddes Chris Dr; 2012.
[62] Morris CA, Carney FP, Lane JD. Kits for assays of rapid screening of diabetes. *Google Patents.* US7429462B2. USA: Novartis AG; 2007.
[63] Zhang J, Hodge WG. Contact lens integrated with a biosensor for the detection of glucose and other components in tears. *Google Patents.* US8385998B2. USA; 2009.
[64] Ibey BL, Yadavalli VK, Rounds RM, Beier HT, Cote GL, Pishko MV. Method for glucose monitoring using fluorescence quenching. *Google Patents.* US8088595B2. USA: Texas A&M University System Penn State Research Foundation; 2010.
[65] Besling WFA. Flexible eye insert and glucose measuring system. *Google Patents.* US9737245B2. USA: NXP BV; 2012.
[66] Yildirim CA. A contact lens design sensing tear glucose level. *Google Patents.* WO2017116350A1. 2017.
[67] Liu Z. Contact lenses having two-electrode electrochemical sensors. *Google Patents.* US20140194713A1. USA: Verily Life Sciences LLC; 2014.
[68] Gandhi H, Gao H, Baig M, Chen R. Functional contact lens and related systems and methods. *Google Patents.* US20170042480A1. USA: Medella Health Inc; 2015.
[69] Zhou L, Beuerman RW. The power of tears: How tear proteomics research could revolutionize the clinic. Expert Rev Proteomics 2017;14(3):189-91. https://doi.org/10.1080/14789450.2017.1285703.
[70] Zhou L, Zhao SZ, Koh SK, Chen L, Vaz C, Tanavde V, et al. In-depth analysis of the human tear proteome. J Proteomics 2012;75(13):3877-85. https://doi.org/10.1016/j.jprot.2012.04.053.
[71] Molloy MP, Bolis S, Herbert BR, Ou K, Tyler MI, van Dyk DD, et al. Establishment of the human reflex tear two-dimensional polyacrylamide gel electrophoresis reference map: New proteins of potential diagnostic value. Electrophoresis 1997;18(15):2811-5. https://doi.org/10.1002/elps.1150181516.
[72] Goedegebuure PS, Watson MA, Viehl CT, Fleming TP. Mammaglobin-based strategies for treatment of breast cancer. Curr Cancer Drug Targets 2004;4(6):531-42. https://doi.org/10.2174/1568009043332862.
[73] Bohm D, Keller K, Pieter J, Boehm N, Wolters D, Siggelkow W, et al. Comparison of tear protein levels in breast cancer patients and healthy controls using a de novo proteomic approach. Oncol Rep 2012;28(2):429-38. https://doi.org/10.3892/or.2012.1849.
[74] Lebrecht A, Boehm D, Schmidt M, Koelbl H, Grus FH. Surface-enhanced laser desorption/ionisation time-of-flight mass spectrometry to detect breast cancer markers in tears and serum. Cancer Genomics Proteomics 2009;6(2):75-83, https://www.ncbi.nlm.nih.gov/pubmed/19451091.
[75] Lebrecht A, Boehm D, Schmidt M, Koelbl H, Schwirz RL, Grus FH. Diagnosis of breast cancer by tear proteomic pattern. Cancer Genomics Proteomics 2009;6(3):177-82, https://www.ncbi.nlm.nih.gov/pubmed/19487546.
[76] Herman G. Glucose-monitoring contact lens would feature transparent sensor. Oregon State University; 2016.

[77] Sit AJ. Continuous monitoring of intraocular pressure: Rationale and progress toward a clinical device. J Glaucoma 2009;18(4):272-9. https://doi.org/10.1097/IJG.0b013e3181862490.
[78] Matlach J, Bender S, Konig J, Binder H, Pfeiffer N, Hoffmann EM. Investigation of intraocular pressure fluctuation as a risk factor of glaucoma progression. Clin Ophthalmol 2019;13:9-16. https://doi.org/10.2147/OPTH.S186526.
[79] Asrani S, Zeimer R, Wilensky J, Gieser D, Vitale S, Lindenmuth K. Large diurnal fluctuations in intraocular pressure are an independent risk factor in patients with glaucoma. J Glaucoma 2000;9(2):134-42. https://doi.org/10.1097/00061198-200004000-00002.
[80] Gillmann K, Bravetti GE, Niegowski LJ, Mansouri K. Using sensors to estimate intraocular pressure: A review of intraocular pressure telemetry in clinical practice. Expert Review of Ophthalmology 2019;14(6):263-76. https://doi.org/10.1080/17469899.2019.1681264.
[81] Leonardi M, Leuenberger P, Bertrand D, Bertsch A, Renaud P. First steps toward noninvasive intraocular pressure monitoring with a sensing contact lens. Invest Ophthalmol Vis Sci 2004;45(9):3113-7. https://doi.org/10.1167/iovs.04-0015.
[82] Mansouri K, Medeiros FA, Tafreshi A, Weinreb RN. Continuous 24-hour monitoring of intraocular pressure patterns with a contact lens sensor: Safety, tolerability, and reproducibility in patients with glaucoma. Arch Ophthalmol 2012;130(12):1534-9. https://doi.org/10.1001/archophthalmol.2012.2280.
[83] Leonardi M, Pitchon EM, Bertsch A, Renaud P, Mermoud A. Wireless contact lens sensor for intraocular pressure monitoring: Assessment on enucleated pig eyes. Acta Ophthalmol 2009;87(4):433-7. https://doi.org/10.1111/j.1755-3768.2008.01404.x.
[84] De Smedt S, Mermoud A, Schnyder C. 24-hour intraocular pressure fluctuation monitoring using an ocular telemetry sensor: Tolerability and functionality in healthy subjects. J Glaucoma 2012;21(8):539-44. https://doi.org/10.1097/IJG.0b013e31821dac43.
[85] Lorenz K, Korb C, Herzog N, Vetter JM, Elflein H, Keilani MM, et al. Tolerability of 24-hour intraocular pressure monitoring of a pressure-sensitive contact lens. J Glaucoma 2013;22(4):311-6. https://doi.org/10.1097/IJG.0b013e318241b874.
[86] Hollo G, Kothy P, Vargha P. Evaluation of continuous 24-hour intraocular pressure monitoring for assessment of prostaglandin-induced pressure reduction in glaucoma. J Glaucoma 2014;23(1):e6-12. https://doi.org/10.1097/IJG.0b013e31829e5635.
[87] Marando CM, Mansouri K, Kahook MY, Seibold LK. Tolerability and functionality of a wireless 24-hour ocular telemetry sensor in african american glaucoma patients. J Glaucoma 2019;28(2):119-24. https://doi.org/10.1097/IJG.0000000000001141.
[88] Morales-Fernandez L, Garcia-Bella J, Martinez-de-la-Casa JM, Sanchez-Jean R, Saenz-Frances F, Arriola-Villalobos P, et al. Changes in corneal biomechanical properties after 24 hours of continuous intraocular pressure monitoring using a contact lens sensor. Can J Ophthalmol 2018;53(3):236-41. https://doi.org/10.1016/j.jcjo.2017.10.028.

[89] Tojo N, Hayashi A. Influence of ocular dimensional change on 24-hour intraocular pressure measurement with contact lens sensor. J Glaucoma 2019;28(9):808-10. https://doi.org/10.1097/IJG.0000000000001318.
[90] Mottet B, Aptel F, Romanet JP, Hubanova R, Pepin JL, Chiquet C. 24-hour intraocular pressure rhythm in young healthy subjects evaluated with continuous monitoring using a contact lens sensor. JAMA Ophthalmol 2013;131(12):1507-16. https://doi.org/10.1001/jamaophthalmol.2013.5297.
[91] Agnifili L, Mastropasqua R, Frezzotti P, Fasanella V, Motolese I, Pedrotti E, et al. Circadian intraocular pressure patterns in healthy subjects, primary open angle and normal tension glaucoma patients with a contact lens sensor. Acta Ophthalmol 2015;93(1):e14-21. https://doi.org/10.1111/aos.12408.
[92] Cutolo CA, De Moraes CG, Liebmann JM, Mansouri K, Traverso CE, Ritch R, et al. The effect of therapeutic IOP-lowering interventions on the 24-hour ocular dimensional profile recorded with a sensing contact lens. J Glaucoma 2019;28(3):252-7. https://doi.org/10.1097/IJG.0000000000001185.
[93] Dunbar GE, Shen BY, Aref AA. The Sensimed Triggerfish contact lens sensor: Efficacy, safety, and patient perspectives. Clin Ophthalmol 2017;11:875-82. https://doi.org/10.2147/OPTH.S109708.
[94] Chen GZ, Chan IS, Leung LK, Lam DC. Soft wearable contact lens sensor for continuous intraocular pressure monitoring. Med Eng Phys 2014;36(9):1134-9. https://doi.org/10.1016/j.medengphy.2014.06.005.
[95] Pang Y, Li Y, Wang X, Qi C, Yang Y, Ren T-L. A contact lens promising for non-invasive continuous intraocular pressure monitoring. RSC Advances 2019;9(9):5076-82. https://doi.org/10.1039/c8ra10257k.
[96] Sanchez I, Laukhin V, Moya A, Martin R, Ussa F, Laukhina E, et al. Prototype of a nanostructured sensing contact lens for noninvasive intraocular pressure monitoring. Invest Ophthalmol Vis Sci 2011;52(11):8310-5. https://doi.org/10.1167/iovs.10-7064.
[97] Zhang Y, Chen Y, Man T, Huang D, Li X, Zhu H, et al. High resolution non-invasive intraocular pressure monitoring by use of graphene woven fabrics on contact lens. Microsyst Nanoeng 2019;5:39. https://doi.org/10.1038/s41378-019-0078-x.
[98] Puers R. Capacitive sensors: When and how to use them. Sensors and Actuators A: Physical 1993;37-38:93-105. https://doi.org/10.1016/0924-4247(93)80019-d.
[99] Kim J, Kim M, Lee MS, Kim K, Ji S, Kim YT, et al. Wearable smart sensor systems integrated on soft contact lenses for wireless ocular diagnostics. Nature communications 2017;8:14997. https://doi.org/10.1038/ncomms14997.
[100] Huang Y-C, Yeh G-T, Yang T-S, Chiou J-C. A contact lens sensor system with a micro-capacitor for wireless intraocular pressure monitoring. 2013 IEEE SENSORS 2013:1-4.
[101] Kouhani M, Wu J, Tavakoli A, Weber AJ, Li W. Wireless, passive strain sensor in a doughnut-shaped contact lens for continuous non-invasive self-monitoring of intraocular pressure. Lab Chip 2020;20(2):332-42. https://doi.org/10.1039/c9lc00735k.
[102] Elsheikh A, Clamp J. Device for monitoring intraocular pressure. *Google Patents.* US9247877B2. USA: Contact Lens Precision Laboratories Ltd University of Dundee; 2015.
[103] Steer R. Feeling the pressure. *The Ophthalmologist.* Texere Publishing Limited; 2017.

[104] Elsheikh A. Clinical study success for novel contact lens device to improve glaucoma treatment. University Press Release 2017;https://news.liverpool.ac.uk/2017/10/19/clinical-study-success-for-novel-contact-lens-device-aimed-at-improving-glaucoma-treatment/, https://news.liverpool.ac.uk/2017/10/19/clinical-study-success-for-novel-contact-lens-device-aimed-at-improving-glaucoma-treatment/.
[105] Campigotto A, Leahy S, Zhao G, Campbell RJ, Lai Y. Non-invasive intraocular pressure monitoring with contact lens. Br J Ophthalmol 2020;104(9):1324-8. https://doi.org/10.1136/bjophthalmol-2018-313714.
[106] An H, Chen L, Liu X, Zhao B, Zhang H, Wu Z. Microfluidic contact lenses for unpowered, continuous and non-invasive intraocular pressure monitoring. Sensors and Actuators A: Physical 2019;295:177-87. https://doi.org/10.1016/j.sna.2019.04.050.
[107] AlQattan B, Yetisen AK, Butt H. Direct laser writing of nanophotonic structures on contact lenses. ACS nano 2018;12(6):5130-40. https://doi.org/10.1021/acsnano.8b00222.
[108] Wasilewicz R, Varidel T, Simon-Zoula S, Schlund M, Cerboni S, Mansouri K. First-in-human continuous 24-hour measurement of intraocular pressure and ocular pulsation using a novel contact lens sensor. Br J Ophthalmol 2020;104(11):1519-23. https://doi.org/10.1136/bjophthalmol-2019-315276.
[109] Wolffsohn JS, Arita R, Chalmers R, Djalilian A, Dogru M, Dumbleton K, et al. TFOS DEWS ii diagnostic methodology report. Ocul Surf 2017;15(3):539-74. https://doi.org/10.1016/j.jtos.2017.05.001.
[110] Downie LE, Bandlitz S, Bergmanson JPG, Craig JP, Dutta D, Maldonado-Codina C, et al. CLEAR - anatomy and physiology of the anterior eye. Contact Lens and Anterior Eye 2021;44(2):In press.
[111] Potvin R, Makari S, Rapuano CJ. Tear film osmolarity and dry eye disease: A review of the literature. Clin Ophthalmol 2015;9:2039-47. https://doi.org/10.2147/OPTH.S95242.
[112] Lemp MA, Bron AJ, Baudouin C, Benitez Del Castillo JM, Geffen D, Tauber J, et al. Tear osmolarity in the diagnosis and management of dry eye disease. Am J Ophthalmol 2011;151(5):792-8 e1. https://doi.org/10.1016/j.ajo.2010.10.032.
[113] Chiou JC. The development of smart contact lens system: Taking dry eye syndrome diagnosis as an example. Future Tech Expo 2019 2019;https://www.futuretech.org.tw/futuretech/index.php?action=product_detail&prod_no=P0008700001856&web_lang=en-us, https://www.futuretech.org.tw/futuretech/index.php?action=product_detail&prod_no=P0008700001856&web_lang=en-us.
[114] Tsangarides CP, Yetisen AK, da Cruz Vasconcellos F, Montelongo Y, Qasim MM, Wilkinson TD, et al. Computational modelling and characterisation of nanoparticle-based tuneable photonic crystal sensors. RSC Adv 2014;4(21):10454-61. https://doi.org/10.1039/c3ra47984f.
[115] Yetisen AK, Montelongo Y, da Cruz Vasconcellos F, Martinez-Hurtado JL, Neupane S, Butt H, et al. Reusable, robust, and accurate laser-generated photonic nanosensor. Nano Lett 2014;14(6):3587-93. https://doi.org/10.1021/nl5012504.
[116] Yetisen AK, Butt H, Volpatti LR, Pavlichenko I, Humar M, Kwok SJ, et al. Photonic hydrogel sensors. Biotechnol Adv 2016;34(3):250-71. https://doi.org/10.1016/j.biotechadv.2015.10.005.

[117] Hu Y, Jiang X, Zhang L, Fan J, Wu W. Construction of near-infrared photonic crystal glucose-sensing materials for ratiometric sensing of glucose in tears. Biosensors & bioelectronics 2013;48:94-9. https://doi.org/10.1016/j.bios.2013.03.082.
[118] Roy NS, Wei Y, Kuklinski E, Asbell PA. The growing need for validated biomarkers and endpoints for dry eye clinical research. Invest Ophthalmol Vis Sci 2017;58(6):BIO1-BIO19. https://doi.org/10.1167/iovs.17-21709.
[119] Munje RD, Muthukumar S, Jagannath B, Prasad S. A new paradigm in sweat based wearable diagnostics biosensors using room temperature ionic liquids (RTILs). Sci Rep 2017;7(1):1950. https://doi.org/10.1038/s41598-017-02133-0.
[120] Borderie VM, Gineys R, Goldschmidt P, Batellier L, Laroche L, Chaumeil C. Association of anti-herpes simplex virus IgG in tears and serum with clinical presentation in patients with presumed herpetic simplex keratitis. Cornea 2012;31(11):1251-6. https://doi.org/10.1097/ICO.0b013e31823f771f.
[121] Grus FH, Dick B, Augustin AJ, Pfeiffer N. Analysis of the antibody repertoire in tears of dry-eye patients. Ophthalmologica 2001;215(6):430-4. https://doi.org/10.1159/000050903.
[122] Kwon J, Surenkhuu B, Raju I, Atassi N, Mun J, Chen YF, et al. Pathological consequences of anti-citrullinated protein antibodies in tear fluid and therapeutic potential of pooled human immune globulin-eye drops in dry eye disease. Ocul Surf 2020;18(1):80-97. https://doi.org/10.1016/j.jtos.2019.10.004.
[123] Zandbelt M, te Boome L, Klasen I, van de Putte L, van den Hoogen F. Tear fluid measurement of anti-SS-a and anti-SS-b antibody in anti-SS-a and anti-SS-b seronegative Sjogren's syndrome patients. Clin Exp Rheumatol 2009;27(3):536, https://www.ncbi.nlm.nih.gov/pubmed/19604453.
[124] Choi E, Choi Y, Nejad YHP, Shin K, Park J. Label-free specific detection of immunoglobulin g antibody using nanoporous hydrogel photonic crystals. Sensor Actuat B-Chem 2013;180:107-13. https://doi.org/10.1016/j.snb.2012.03.053.
[125] Craig JP, Willcox MD, Argueso P, Maissa C, Stahl U, Tomlinson A, et al. The TFOS international workshop on contact lens discomfort: Report of the contact lens interactions with the tear film subcommittee. Invest Ophthalmol Vis Sci 2013;54(11):TFOS123-56. https://doi.org/10.1167/iovs.13-13235.
[126] Ballard Z, Bazargan S, Jung D, Sathianathan S, Clemens A, Shir D, et al. Contact lens-based lysozyme detection in tear using a mobile sensor. Lab Chip 2020;20(8):1493-502. https://doi.org/10.1039/c9lc01039d.
[127] von Thun Und Hohenstein-Blaul N, Funke S, Grus FH. Tears as a source of biomarkers for ocular and systemic diseases. Exp Eye Res 2013;117:126-37. https://doi.org/10.1016/j.exer.2013.07.015.
[128] Morgan P, Murphy PJ, Gifford K, Gifford P, Golebiowski B, Johnson L, et al. CLEAR - effect of contact lens materials and designs on the anatomy and physiology of the eye. Contact Lens and Anterior Eye 2021;44(2):In press.
[129] Tsubota K. Tear dynamics and dry eye. Prog Retin Eye Res 1998;17(4):565-96. https://doi.org/10.1016/s1350-9462(98)00004-4.
[130] Su Y, Liang Q, Su G, Wang N, Baudouin C, Labbe A. Spontaneous eye blink patterns in dry eye: Clinical correlations. Invest Ophthalmol Vis Sci 2018;59(12):5149-56. https://doi.org/10.1167/iovs.18-24690.

[131] Jansen ME, Begley CG, Himebaugh NH, Port NL. Effect of contact lens wear and a near task on tear film break-up. Optom Vis Sci 2010;87(5):350-7. https://doi.org/10.1097/OPX.0b013e3181d951df.
[132] Gisler C, Ridi A, Hennebert J, Weinreb RN, Mansouri K. Automated detection and quantification of circadian eye blinks using a contact lens sensor. Transl Vis Sci Technol 2015;4(1):4. https://doi.org/10.1167/tvst.4.1.4.
[133] Wang Y, Zhao Q, Du X. Structurally coloured contact lens sensor for point-of-care ophthalmic health monitoring. Journal of materials chemistry B 2020;8(16):3519-26. https://doi.org/10.1039/c9tb02389e.
[134] Braun RJ, King-Smith PE, Begley CG, Li L, Gewecke NR. Dynamics and function of the tear film in relation to the blink cycle. Prog Retin Eye Res 2015;45:132-64. https://doi.org/10.1016/j.preteyeres.2014.11.001.
[135] Li W, Graham AD, Selvin S, Lin MC. Ocular surface cooling corresponds to tear film thinning and breakup. Optom Vis Sci 2015;92(9):e248-56. https://doi.org/10.1097/OPX.0000000000000672.
[136] Su TY, Chang SW, Yang CJ, Chiang HK. Direct observation and validation of fluorescein tear film break-up patterns by using a dual thermal-fluorescent imaging system. Biomed Opt Express 2014;5(8):2614-9. https://doi.org/10.1364/BOE.5.002614.
[137] Tan LL, Sanjay S, Morgan PB. Static and dynamic measurement of ocular surface temperature in dry eyes. J Ophthalmol 2016;2016:7285132. https://doi.org/10.1155/2016/7285132.
[138] Moreddu R, Elsherif M, Butt H, Vigolo D, Yetisen AK. Contact lenses for continuous corneal temperature monitoring. RSC Advances 2019;9(20):11433-42. https://doi.org/10.1039/c9ra00601j.
[139] Lai HJ. System for measuring and analyzing ocular temperature, receiving analyzer and methods for using the same. *Google Patents.* US9642533B2. USA: Ubiquity Biomedical Corp; 2017.
[140] Pugh RB, Toner A, Humphreys SR, Otts DB, Neeley WC. Ophthalmic lens with retinal vascularization monitoring system. *Google Patents.* US10159461B2. USA: Johnson & Johnson Vision Inc.; 2018.
[141] Murphy PJ, Lau JS, Sim MM, Woods RL. How red is a white eye? Clinical grading of normal conjunctival hyperaemia. Eye (Lond) 2007;21(5):633-8. https://doi.org/10.1038/sj.eye.6702295.
[142] Ho H, Amirparviz B. Contact lens with integrated pulse oximeter. In: Office UP, ed. *Google Patents.* US8971978B2. USA: Verily Life Sciences LLC; 2012:25.
[143] Jacobs DS, Carrasquillo KG, Cottrell PD, Fernández-Velázquez FJ, Gil-Cazorla R, Jalbert I, et al. CLEAR - medical use of contact lenses. Contact Lens and Anterior Eye 2021;44(2):In press.
[144] Kusama S, Sato K, Yoshida S, Nishizawa M. Self‐moisturizing smart contact lens employing electroosmosis. Advanced Materials Technologies 2019;5(1):1900889. https://doi.org/10.1002/admt.201900889.
[145] Lee S, Jo I, Kang S, Jang B, Moon J, Park JB, et al. Smart contact lenses with graphene coating for electromagnetic interference shielding and dehydration protection. ACS nano 2017;11(6):5318-24. https://doi.org/10.1021/acsnano.7b00370.
[146] Kaur S, Kim YJ, Milton H, Mistry D, Syed IM, Bailey J, et al. Graphene electrodes for adaptive liquid crystal contact lenses. Optics express 2016;24(8):8782-7. https://doi.org/10.1364/OE.24.008782.

[147] Moser T, Celma C, Lebert A, Charrault E, Brooke R, Murphy PJ, et al. Hydrophilic organic electrodes on flexible hydrogels. ACS Appl Mater Interfaces 2016;8(1):974-82. https://doi.org/10.1021/acsami.5b10831.
[148] Liu CH, Chang YC, Norris TB, Zhong Z. Graphene photodetectors with ultra-broadband and high responsivity at room temperature. Nat Nanotechnol 2014;9(4):273-8. https://doi.org/10.1038/nnano.2014.31.
[149] Huang JF, Zhong J, Chen GP, Lin ZT, Deng Y, Liu YL, et al. A hydrogel-based hybrid theranostic contact lens for fungal keratitis. ACS nano 2016;10(7):6464-73. https://doi.org/10.1021/acsnano.6b00601.
[150] Alex A, Edwards A, Hays JD, Kerkstra M, Shih A, de Paiva CS, et al. Factors predicting the ocular surface response to desiccating environmental stress. Invest Ophthalmol Vis Sci 2013;54(5):3325-32. https://doi.org/10.1167/iovs.12-11322.
[151] Friedman NJ, Butron K, Robledo N, Loudin J, Baba SN, Chayet A. A nonrandomized, open-label study to evaluate the effect of nasal stimulation on tear production in subjects with dry eye disease. Clin Ophthalmol 2016;10:795-804. https://doi.org/10.2147/OPTH.S101716.
[152] Gumus K, Schuetzle KL, Pflugfelder SC. Randomized controlled crossover trial comparing the impact of sham or intranasal tear neurostimulation on conjunctival goblet cell degranulation. Am J Ophthalmol 2017;177:159-68. https://doi.org/10.1016/j.ajo.2017.03.002.
[153] Loudin JD, Franke M, HAMILTON DN, Doraiswamy A, Ackermann DM. Contact lens for increasing tear production. *Google Patents.* AU2020250288A1. Australia: Oculeve Inc; 2017.
[154] Dogru M, Kojima T, Simsek C, Tsubota K. Potential role of oxidative stress in ocular surface inflammation and dry eye disease. Invest Ophthalmol Vis Sci 2018;59(14):DES163-DES8. https://doi.org/10.1167/iovs.17-23402.
[155] Seen S, Tong L. Dry eye disease and oxidative stress. Acta Ophthalmol 2018;96(4):e412-e20. https://doi.org/10.1111/aos.13526.
[156] Stoddard AR, Koetje LR, Mitchell AK, Schotanus MP, Ubels JL. Bioavailability of antioxidants applied to stratified human corneal epithelial cells. J Ocul Pharmacol Ther 2013;29(7):681-7. https://doi.org/10.1089/jop.2013.0014.
[157] Brzheskiy VV, Efimova EL, Vorontsova TN, Alekseev VN, Gusarevich OG, Shaidurova KN, et al. Results of a multicenter, randomized, double-masked, placebo-controlled clinical study of the efficacy and safety of visomitin eye drops in patients with dry eye syndrome. Adv Ther 2015;32(12):1263-79. https://doi.org/10.1007/s12325-015-0273-6.
[158] Janagam DR, Wu L, Lowe TL. Nanoparticles for drug delivery to the anterior segment of the eye. Adv Drug Deliv Rev 2017;122:31-64. https://doi.org/10.1016/j.addr.2017.04.001.
[159] Choi SW, Cha BG, Kim J. Therapeutic contact lens for scavenging excessive reactive oxygen species on the ocular surface. ACS nano 2020;14(2):2483-96. https://doi.org/10.1021/acsnano.9b10145.
[160] Walkey C, Das S, Seal S, Erlichman J, Heckman K, Ghibelli L, et al. Catalytic properties and biomedical applications of cerium oxide nanoparticles. Environ Sci Nano 2015;2(1):33-53. https://doi.org/10.1039/C4EN00138A.
[161] Bian F, Pelegrino FS, Henriksson JT, Pflugfelder SC, Volpe EA, Li DQ, et al. Differential effects of dexamethasone and doxycycline on inflammation and MMP production in murine alkali-burned corneas associated with dry eye. Ocul Surf 2016;14(2):242-54. https://doi.org/10.1016/j.jtos.2015.11.006.

[162] Lopez C, Park S, Edwards S, Vong S, Hou S, Lee M, et al. Matrix metalloproteinase-deactivating contact lens for corneal melting. ACS Biomater Sci Eng 2019;5(3):1195-9. https://doi.org/10.1021/acsbiomaterials.8b01404.
[163] Jamerson EC, Elhusseiny AM, ElSheikh RH, Eleiwa TK, El Sayed YM. Role of matrix metalloproteinase 9 in ocular surface disorders. Eye Contact Lens 2020;46 Suppl 2:S57-S63. https://doi.org/10.1097/ICL.0000000000000668.
[164] Lanza NL, Valenzuela F, Perez VL, Galor A. The matrix metalloproteinase 9 point-of-care test in dry eye. Ocul Surf 2016;14(2):189-95. https://doi.org/10.1016/j.jtos.2015.10.004.
[165] Dohlman TH, Ciralsky JB, Lai EC. Tear film assessments for the diagnosis of dry eye. Curr Opin Allergy Clin Immunol 2016;16(5):487-91. https://doi.org/10.1097/ACI.0000000000000307.
[166] Barnett M, Courey C, Fadel D, Lee K, Michaud L, Montani G, et al. CLEAR - scleral lenses. Contact Lens and Anterior Eye 2021;44(2):In press.
[167] Bains KK, Fukuoka H, Hammond GM, Sotozono C, Quantock AJ. Recovering vision in corneal epithelial stem cell deficient eyes. Cont Lens Anterior Eye 2019;42(4):350-8. https://doi.org/10.1016/j.clae.2019.04.006.
[168] Bobba S. Contact lens delivery of stem cells for restoring the ocular surface. Biomaterials and regenerative medicine in ophthalmology Woodhead Publishing 2016.
[169] Levis HJ, Kureshi AK, Massie I, Morgan L, Vernon AJ, Daniels JT. Tissue engineering the cornea: The evolution of RAFT. J Funct Biomater 2015;6(1):50-65. https://doi.org/10.3390/jfb6010050.
[170] Pellegrini G, Traverso CE, Franzi AT, Zingirian M, Cancedda R, De Luca M. Long-term restoration of damaged corneal surfaces with autologous cultivated corneal epithelium. Lancet 1997;349(9057):990-3. https://doi.org/10.1016/S0140-6736(96)11188-0.
[171] Deshpande P, Notara M, Bullett N, Daniels JT, Haddow DB, MacNeil S. Development of a surface-modified contact lens for the transfer of cultured limbal epithelial cells to the cornea for ocular surface diseases. Tissue Eng Part A 2009;15(10):2889-902. https://doi.org/10.1089/ten.TEA.2008.0528.
[172] Brown KD, Low S, Mariappan I, Abberton KM, Short R, Zhang H, et al. Plasma polymer-coated contact lenses for the culture and transfer of corneal epithelial cells in the treatment of limbal stem cell deficiency. Tissue Eng Part A 2014;20(3-4):646-55. https://doi.org/10.1089/ten.TEA.2013.0089.
[173] Di Girolamo N, Bosch M, Zamora K, Coroneo MT, Wakefield D, Watson SL. A contact lens-based technique for expansion and transplantation of autologous epithelial progenitors for ocular surface reconstruction. Transplantation 2009;87(10):1571-8. https://doi.org/10.1097/TP.0b013e3181a4bbf2.
[174] Vasquez Quintero A, Perez-Merino P, De Smet H. Artificial iris performance for smart contact lens vision correction applications. Sci Rep 2020;10(1):14641. https://doi.org/10.1038/s41598-020-71376-1.
[175] Raducanu BC, Zaliasl S, Stanzione S, van Liempd C, Quintero AV, De Smet H, et al. An artificial iris ASIC with high voltage liquid crystal driver, 10-nA light range detector and 40-nA blink detector for LCD flicker removal. IEEE Solid-State Circuits Letters 2020;3:506-9. https://doi.org/10.1109/lssc.2020.3032232.
[176] Vásquez Quintero A, Verplancke R, De Smet H, Vanfleteren J. Stretchable electronic platform for soft and smart contact lens applications. Advanced

Materials Technologies 2017;2(8):1700073. https://doi.org/10.1002/admt.201700073.

[177] Vásquez Quintero A, Arai R, Yamazaki Y, Sato T, De Smet H. Near‐field communication powered hydrogel‐based smart contact lens. Advanced Materials Technologies 2020;5(12). https://doi.org/10.1002/admt.202000702.

[178] Birol G, Wang S, Budzynski E, Wangsa-Wirawan ND, Linsenmeier RA. Oxygen distribution and consumption in the macaque retina. Am J Physiol Heart Circ Physiol 2007;293(3):H1696-704. https://doi.org/10.1152/ajpheart.00221.2007.

[179] Arden GB, Jyothi S, Hogg CH, Lee YF, Sivaprasad S. Regression of early diabetic macular oedema is associated with prevention of dark adaptation. Eye (Lond) 2011;25(12):1546-54. https://doi.org/10.1038/eye.2011.264.

[180] Sahni JN, Czanner G, Gutu T, Taylor SA, Bennett KM, Wuerger SM, et al. Safety and acceptability of an organic light-emitting diode sleep mask as a potential therapy for retinal disease. Eye (Lond) 2017;31(1):97-106. https://doi.org/10.1038/eye.2016.259.

[181] Cook CA, Martinez-Camarillo JC, Yang Q, Scianmarello NE, Humayun MS, Tai Y. Phototherapeutic contact lens for diabetic retinopathy. *IEEE Micro Electro Mechanical Systems* Belfast; 2018:62-5_CHAUTEST.

[182] Sivaprasad S, Vasconcelos JC, Prevost AT, Holmes H, Hykin P, George S, et al. Clinical efficacy and safety of a light mask for prevention of dark adaptation in treating and preventing progression of early diabetic macular oedema at 24 months (CLEOPATRA): A multicentre, phase 3, randomised controlled trial. Lancet Diabetes Endocrinol 2018;6(5):382-91. https://doi.org/10.1016/S2213-8587(18)30036-6.

[183] Zeltzer HI. Method of improving color discrimination. *Google Patents.* US3586423A. USA; 1970.

[184] Hovis JK, Sirkka D. Color discrimination of deutan and protan observers through tinted soft contact lenses. International Contact Lens Clinic 1990;17(11-12):287-95. https://doi.org/10.1016/0892-8967(90)90075-q.

[185] Harris DA, Lane G, Green E. Color discrimination. In: Office USP, ed. *Google Patents.* US6089712A. USA: ChromaGen Vision LLC; 2000:6.

[186] Swarbrick HA, Nguyen P, Nguyen T, Pham P. The ChromaGen contact lens system: Colour vision test results and subjective responses. Ophthalmic Physiol Opt 2001;21(3):182-96. https://doi.org/10.1046/j.1475-1313.2001.00583.x.

[187] Karepov S, Ellenbogen T. Metasurface-based contact lenses for color vision deficiency. Opt Lett 2020;45(6):1379-82. https://doi.org/10.1364/OL.384970.

[188] Urtti A. Challenges and obstacles of ocular pharmacokinetics and drug delivery. Adv Drug Deliv Rev 2006;58(11):1131-5. https://doi.org/10.1016/j.addr.2006.07.027.

[189] Zhang X, Cao X, Qi P. Therapeutic contact lenses for ophthalmic drug delivery: Major challenges. J Biomater Sci Polym Ed 2020;31(4):549-60. https://doi.org/10.1080/09205063.2020.1712175.

[190] Alvarez-Lorenzo C, Anguiano-Igea S, Varela-Garcia A, Vivero-Lopez M, Concheiro A. Bioinspired hydrogels for drug-eluting contact lenses. Acta Biomater 2019;84:49-62. https://doi.org/10.1016/j.actbio.2018.11.020.

[191] Muntz A, Subbaraman LN, Sorbara L, Jones L. Tear exchange and contact lenses: A review. J Optom 2015;8(1):2-11. https://doi.org/10.1016/j.optom.2014.12.001.
[192] Li C-C, Chauhan A. Modeling ophthalmic drug delivery by soaked contact lenses. Industrial & Engineering Chemistry Research 2006;45(10):3718-34. https://doi.org/10.1021/ie0507934.
[193] Davis SA, Sleath B, Carpenter DM, Blalock SJ, Muir KW, Budenz DL. Drop instillation and glaucoma. Curr Opin Ophthalmol 2018;29(2):171-7. https://doi.org/10.1097/ICU.0000000000000451.
[194] Sklubalova Z, Zatloukal Z. Study of eye drops dispensing and dose variability by using plastic dropper tips. Drug development and industrial pharmacy 2006;32(2):197-205. https://doi.org/10.1080/03639040500466130.
[195] Winfield AJ, Jessiman D, Williams A, Esakowitz L. A study of the causes of non-compliance by patients prescribed eyedrops. Br J Ophthalmol 1990;74(8):477-80. https://doi.org/10.1136/bjo.74.8.477.
[196] Walsh K, Jones L. The use of preservatives in dry eye drops. Clin Ophthalmol 2019;13:1409-25. https://doi.org/10.2147/OPTH.S211611.
[197] Epstein SP, Ahdoot M, Marcus E, Asbell PA. Comparative toxicity of preservatives on immortalized corneal and conjunctival epithelial cells. J Ocul Pharmacol Ther 2009;25(2):113-9. https://doi.org/10.1089/jop.2008.0098.
[198] Maulvi FA, Soni TG, Shah DO. A review on therapeutic contact lenses for ocular drug delivery. Drug Deliv 2016;23(8):3017-26. https://doi.org/10.3109/10717544.2016.1138342.
[199] Minami T, Ishida W, Kishimoto T, Nakajima I, Hino S, Arai R, et al. In vitro and in vivo performance of epinastine hydrochloride-releasing contact lenses. PLoS One 2019;14(1):e0210362. https://doi.org/10.1371/journal.pone.0210362.
[200] Zaki M, Pardo J, Carracedo G. A review of international medical device regulations: Contact lenses and lens care solutions. Cont Lens Anterior Eye 2019;42(2):136-46. https://doi.org/10.1016/j.clae.2018.11.001.
[201] Maulvi FA, Choksi HH, Desai AR, Patel AS, Ranch KM, Vyas BA, et al. pH triggered controlled drug delivery from contact lenses: Addressing the challenges of drug leaching during sterilization and storage. Colloids Surf B Biointerfaces 2017;157:72-82. https://doi.org/10.1016/j.colsurfb.2017.05.064.
[202] Baenninger PB. Survey on bandage contact lens practice in the united kingdom. Journal of Clinical & Experimental Ophthalmology 2014;05(01):2. https://doi.org/10.4172/2155-9570.1000325.
[203] Miller DD, Hasan SA, Simmons NL, Stewart MW. Recurrent corneal erosion: A comprehensive review. Clin Ophthalmol 2019;13:325-35. https://doi.org/10.2147/OPTH.S157430.
[204] Karlgard CCS, Jones LW, Moresoli C. Survey of bandage lens use in North America, october-december 2002. Eye Contact Lens 2004;30(1):25, http://www.scopus.com/inward/record.url?eid=2-s2.0-1842590463&partnerID=40&md5=227a5288a703adf59bda5bbd3b4c5981.
[205] Soluri A, Hui A, Jones L. Delivery of ketotifen fumarate by commercial contact lens materials. Optom Vis Sci 2012;89(8):1140-9. https://doi.org/10.1097/OPX.0b013e3182639dc8.
[206] Karlgard CC, Wong NS, Jones LW, Moresoli C. In vitro uptake and release studies of ocular pharmaceutical agents by silicon-containing and p-HEMA

hydrogel contact lens materials. Int J Pharm 2003;257(1-2):141-51. https://doi.org/10.1016/s0378-5173(03)00124-8.
[207] Hui A, Boone A, Jones L. Uptake and release of ciprofloxacin-HCl from conventional and silicone hydrogel contact lens materials. Eye Contact Lens 2008;34(5):266-71. https://doi.org/10.1097/ICL.0b013e3181812ba2.
[208] Karlgard CC, Jones LW, Moresoli C. Ciprofloxacin interaction with silicon-based and conventional hydrogel contact lenses. Eye Contact Lens 2003;29(2):83-9. https://doi.org/10.1097/01.ICL.0000061756.66151.1C.
[209] Karlgard C, Jones L, Moresoli C. Uptake and release of ciloxan from silicone-hydrogel and conventional hydrogel contact lens materials. Invest Ophthalmol Vis Sci 2001;42(4):s592.
[210] Bajgrowicz M, Phan CM, Subbaraman LN, Jones L. Release of ciprofloxacin and moxifloxacin from daily disposable contact lenses from an in vitro eye model. Invest Ophthalmol Vis Sci 2015;56(4):2234-42. https://doi.org/10.1167/iovs.15-16379.
[211] Dixon P, Chauhan A. Effect of the surface layer on drug release from delefilcon-A (Dailies Total1((r))) contact lenses. Int J Pharm 2017;529(1-2):89-101. https://doi.org/10.1016/j.ijpharm.2017.06.036.
[212] Tian X, Iwatsu M, Sado K, Kanai A. Studies on the uptake and release of fluoroquinolones by disposable contact lenses. CLAO J 2001;27(4):216-20, https://www.ncbi.nlm.nih.gov/pubmed/11725985.
[213] Tian X, Iwatsu M, Kanai A. Disposable 1-day Acuvue® contact lenses for the delivery of lomefloxacin to rabbits' eyes. CLAO Journal 2001;27(4):212-5, http://www.scopus.com/inward/record.url?eid=2-s2.0-0034766352&partnerID=40&md5=d847d19f5aaa992c0147ed853e11b235.
[214] Phan CM, Subbaraman LN, Jones L. In vitro uptake and release of natamycin from conventional and silicone hydrogel contact lens materials. Eye Contact Lens 2013;39(2):162-8. https://doi.org/10.1097/ICL.0b013e31827a7a07.
[215] Boone A, Hui A, Jones L. Uptake and release of dexamethasone phosphate from silicone hydrogel and group i, ii, and iv hydrogel contact lenses. Eye Contact Lens 2009;35(5):260-7. https://doi.org/10.1097/ICL.0b013e3181b26c49.
[216] Hui A, Bajgrowicz-Cieslak M, Phan CM, Jones L. In vitro release of two anti-muscarinic drugs from soft contact lenses. Clin Ophthalmol 2017;11:1657-65. https://doi.org/10.2147/OPTH.S141404.
[217] Jaishankar D, Buhrman JS, Valyi-Nagy T, Gemeinhart RA, Shukla D. Extended release of an anti-heparan sulfate peptide from a contact lens suppresses corneal Herpes simplex virus-1 infection. Invest Ophthalmol Vis Sci 2016;57(1):169-80. https://doi.org/10.1167/iovs.15-18365.
[218] Sharma M, Bhowmick R, Gappa-Fahlenkamp H. Drug-loaded nanoparticles embedded in a biomembrane provide a dual-release mechanism for drug delivery to the eye. J Ocul Pharmacol Ther 2016;32(9):565-73. https://doi.org/10.1089/jop.2016.0050.
[219] Peng CC, Burke MT, Chauhan A. Transport of topical anesthetics in vitamin E loaded silicone hydrogel contact lenses. Langmuir 2012;28(2):1478-87. https://doi.org/10.1021/la203606z.
[220] Gulsen D, Chauhan A. Ophthalmic drug delivery through contact lenses. Invest Ophthalmol Vis Sci 2004;45(7):2342-7. https://doi.org/10.1167/iovs.03-0959.

[221] Gulsen D, Li CC, Chauhan A. Dispersion of DMPC liposomes in contact lenses for ophthalmic drug delivery. Current eye research 2005;30(12):1071-80. https://doi.org/10.1080/02713680500346633.
[222] Dominguez-Godinez CO, Martin-Gil A, Carracedo G, Guzman-Aranguez A, González-Méijome JM, Pintor J. In vitro and in vivo delivery of the secretagogue diadenosine tetraphosphate from conventional and silicone hydrogel soft contact lenses. Journal of Optometry 2013;6(4):205-11. https://doi.org/10.1016/j.optom.2013.07.004.
[223] Dominguez-Godinez C, Carracedo G, Pintor J. Diquafosol delivery from silicone hydrogel contact lenses: Improved effect on tear secretion. J Ocul Pharmacol Ther 2018;34(1-2):170-6. https://doi.org/10.1089/jop.2016.0193.
[224] Dixon P, Fentzke RC, Bhattacharya A, Konar A, Hazra S, Chauhan A. In vitro drug release and in vivo safety of vitamin E and cysteamine loaded contact lenses. Int J Pharm 2018;544(2):380-91. https://doi.org/10.1016/j.ijpharm.2017.11.059.
[225] Horne RR, Rich JT, Bradley MW, Pitt WG. Latanoprost uptake and release from commercial contact lenses. J Biomater Sci Polym Ed 2020;31(1):1-19. https://doi.org/10.1080/09205063.2019.1669126.
[226] Horne RR, Judd KE, Pitt WG. Rapid loading and prolonged release of latanoprost from a silicone hydrogel contact lens. Journal of Drug Delivery Science and Technology 2017;41:410-8. https://doi.org/10.1016/j.jddst.2017.08.011.
[227] Mohammadi S, Jones L, Gorbet M. Extended latanoprost release from commercial contact lenses: In vitro studies using corneal models. PLoS One 2014;9(9):e106653. https://doi.org/10.1371/journal.pone.0106653.
[228] Hui A. Contact lenses for ophthalmic drug delivery. Clinical & experimental optometry 2017;100(5):494-512. https://doi.org/10.1111/cxo.12592.
[229] Phan CM, Bajgrowicz-Cieslak M, Subbaraman LN, Jones L. Release of moxifloxacin from contact lenses using an in vitro eye model: Impact of artificial tear fluid composition and mechanical rubbing. Transl Vis Sci Technol 2016;5(6):3. https://doi.org/10.1167/tvst.5.6.3.
[230] Zarbin MA, Montemagno C, Leary JF, Ritch R. Nanotechnology in ophthalmology. Can J Ophthalmol 2010;45(5):457-76. https://doi.org/10.3129/i10-090.
[231] Kang-Mieler JJ, Rudeen KM, Liu W, Mieler WF. Advances in ocular drug delivery systems. Eye (Lond) 2020;34(8):1371-9. https://doi.org/10.1038/s41433-020-0809-0.
[232] Khan I, Saeed K, Khan I. Nanoparticles: Properties, applications and toxicities. Arab J Chem 2019;12(7):908-31.
[233] Husseini GA, Pitt WG. Micelles and nanoparticles for ultrasonic drug and gene delivery. Adv Drug Deliv Rev 2008;60(10):1137-52. https://doi.org/10.1016/j.addr.2008.03.008.
[234] Mc Carthy DJ, Malhotra M, O'Mahony AM, Cryan JF, O'Driscoll CM. Nanoparticles and the blood-brain barrier: Advancing from in-vitro models towards therapeutic significance. Pharm Res 2015;32(4):1161-85. https://doi.org/10.1007/s11095-014-1545-6.
[235] Honda M, Asai T, Oku N, Araki Y, Tanaka M, Ebihara N. Liposomes and nanotechnology in drug development: Focus on ocular targets. International journal of nanomedicine 2013;8:495-503. https://doi.org/10.2147/IJN.S30725.

[236] Panzarini E, Inguscio V, Tenuzzo BA, Carata E, Dini L. Nanomaterials and autophagy: New insights in cancer treatment. Cancers 2013;5(1):296-319. https://doi.org/10.3390/cancers5010296.
[237] Balamurugan K, Chintamani P. Lipid nano particulate drug delivery: An overview of the emerging trend. The Pharma Innovation Journal 2018;7(7):779-89.
[238] Jung HJ, Abou-Jaoude M, Carbia BE, Plummer C, Chauhan A. Glaucoma therapy by extended release of timolol from nanoparticle loaded silicone-hydrogel contact lenses. Journal of controlled release : official journal of the Controlled Release Society 2013;165(1):82-9. https://doi.org/10.1016/j.jconrel.2012.10.010.
[239] Kharaghani D, Dutta D, Gitigard P, Tamada Y, Katagiri A, Phan D-N, et al. Development of antibacterial contact lenses containing metallic nanoparticles. Polym Test 2019;79:106034.
[240] Mourad R, Helaly F, Darwesh O, El-Sawy S. Antimicrobial and physicomechanical natures of silver nanoparticles incorporated into silicone-hydrogel films. Cont Lens Anterior Eye 2019;42(3):325-33.
[241] Maulvi FA, Lakdawala DH, Shaikh AA, Desai AR, Choksi HH, Vaidya RJ, et al. In vitro and in vivo evaluation of novel implantation technology in hydrogel contact lenses for controlled drug delivery. Journal of controlled release : official journal of the Controlled Release Society 2016;226:47-56. https://doi.org/10.1016/j.jconrel.2016.02.012.
[242] Maulvi FA, Mangukiya MA, Patel PA, Vaidya RJ, Koli AR, Ranch KM, et al. Extended release of ketotifen from silica shell nanoparticle-laden hydrogel contact lenses: In vitro and in vivo evaluation. J Mater Sci Mater Med 2016;27(6):113. https://doi.org/10.1007/s10856-016-5724-3.
[243] Mun J, Mok Jw, Jeong S, Cho S, Joo C-K, Hahn SK. Drug-eluting contact lens containing cyclosporine-loaded cholesterol-hyaluronate micelles for dry eye syndrome. RSC Advances 2019;9(29):16578-85. https://doi.org/10.1039/c9ra02858g.
[244] Ealias AM, Saravanakumar M. A review on the classification, characterisation, synthesis of nanoparticles and their application. *IOP Conf Ser Mater Sci Eng.* 263. 2017:032019.
[245] Carvalho IM, Marques CS, Oliveira RS, Coelho PB, Costa PC, Ferreira DC. Sustained drug release by contact lenses for glaucoma treatment-a review. Journal of controlled release : official journal of the Controlled Release Society 2015;202:76-82. https://doi.org/10.1016/j.jconrel.2015.01.023.
[246] Choi SW, Kim J. Therapeutic contact lenses with polymeric vehicles for ocular drug delivery: A review. Materials (Basel) 2018;11(7):1125. https://doi.org/10.3390/ma11071125.
[247] Singh RB, Ichhpujani P, Thakur S, Jindal S. Promising therapeutic drug delivery systems for glaucoma: A comprehensive review. Therapeutic advances in ophthalmology 2020;12:2515841420905740. https://doi.org/10.1177/2515841420905740.
[248] Maulvi FA, Soni TG, Shah DO. Extended release of timolol from ethyl cellulose microparticles laden hydrogel contact lenses. Open Pharm Sci J 2015;2(1).
[249] Garhwal R, Shady SF, Ellis EJ, Ellis JY, Leahy CD, McCarthy SP, et al. Sustained ocular delivery of ciprofloxacin using nanospheres and

conventional contact lens materials. Invest Ophthalmol Vis Sci 2012;53(3):1341-52.
[250] Kapoor Y, Thomas JC, Tan G, John VT, Chauhan A. Surfactant-laden soft contact lenses for extended delivery of ophthalmic drugs. Biomaterials 2009;30(5):867-78. https://doi.org/10.1016/j.biomaterials.2008.10.032.
[251] Nasr FH, Khoee S, Dehghan MM, Chaleshtori SS, Shafiee A. Preparation and evaluation of contact lenses embedded with polycaprolactone-based nanoparticles for ocular drug delivery. Biomacromolecules 2016;17(2):485-95. https://doi.org/10.1021/acs.biomac.5b01387.
[252] Phan CM, Subbaraman L, Liu S, Gu F, Jones L. In vitro uptake and release of natamycin Dex-b-PLA nanoparticles from model contact lens materials. J Biomater Sci Polym Ed 2014;25(1):18-31. https://doi.org/10.1080/09205063.2013.830914.
[253] ElShaer A, Mustafa S, Kasar M, Thapa S, Ghatora B, Alany RG. Nanoparticle-laden contact lens for controlled ocular delivery of Prednisolone: Formulation optimization using statistical experimental design. Pharmaceutics 2016;8(2):14. https://doi.org/10.3390/pharmaceutics8020014.
[254] Mehta P, Al-Kinani AA, Haj-Ahmad R, Arshad MS, Chang MW, Alany RG, et al. Electrically atomised formulations of timolol maleate for direct and on-demand ocular lens coatings. European journal of pharmaceutics and biopharmaceutics : official journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik eV 2017;119:170-84. https://doi.org/10.1016/j.ejpb.2017.06.016.
[255] Bin Sahadan MY, Tong WY, Tan WN, Leong CR, Bin Misri MN, Chan M, et al. Phomopsidione nanoparticles coated contact lenses reduce microbial keratitis causing pathogens. Exp Eye Res 2019;178:10-4. https://doi.org/10.1016/j.exer.2018.09.011.
[256] Jung HJ, Chauhan A. Temperature sensitive contact lenses for triggered ophthalmic drug delivery. Biomaterials 2012;33(7):2289-300. https://doi.org/10.1016/j.biomaterials.2011.10.076.
[257] Hu X, Tan H, Chen P, Wang X, Pang J. Polymer micelles laden hydrogel contact lenses for ophthalmic drug delivery. Journal of nanoscience and nanotechnology 2016;16(6):5480-8. https://doi.org/10.1166/jnn.2016.11733.
[258] Paradiso P, Colaco R, Mata JLG, Krastev R, Saramago B, Serro AP. Drug release from liposome coated hydrogels for soft contact lenses: The blinking and temperature effect. J Biomed Mater Res B Appl Biomater 2017;105(7):1799-807. https://doi.org/10.1002/jbm.b.33715.
[259] Danion A, Brochu H, Martin Y, Vermette P. Fabrication and characterization of contact lenses bearing surface-immobilized layers of intact liposomes. J Biomed Mater Res A 2007;82(1):41-51. https://doi.org/10.1002/jbm.a.31147.
[260] Venkatesh N, Bhowmik H, Kuila A. Metallic nanoparticle: A review. Biomed J Sci Tech Res 2018;4(2):3765-75.
[261] Huang YW, Cambre M, Lee HJ. The toxicity of nanoparticles depends on multiple molecular and physicochemical mechanisms. International journal of molecular sciences 2017;18(12):2702. https://doi.org/10.3390/ijms18122702.
[262] Malik MA, Wani MY, Hashim MA. Microemulsion method: A novel route to synthesize organic and inorganic nanomaterials: 1st nano update. Arab J Chem 2012;5(4):397-417.

[263] Ganguli AK, Ganguly A, Vaidya S. Microemulsion-based synthesis of nanocrystalline materials. Chemical Society reviews 2010;39(2):474-85. https://doi.org/10.1039/b814613f.
[264] McClements DJ. Nanoemulsions versus microemulsions: Terminology, differences, and similarities. Soft matter 2012;8(6):1719-29.
[265] Agrawal OP, Agrawal S. An overview of new drug delivery system: Microemulsion. Asian J Pharm Sci Tech 2012;2:5-12.
[266] Rane AV, Kanny K, Abitha V, Thomas S. Methods for synthesis of nanoparticles and fabrication of nanocomposites. Synthesis of inorganic nanomaterials. Woodhead Publishing; 2018, p. 121-39.
[267] Maulvi FA, Desai AR, Choksi HH, Patil RJ, Ranch KM, Vyas BA, et al. Effect of surfactant chain length on drug release kinetics from microemulsion-laden contact lenses. Int J Pharm 2017;524(1-2):193-204. https://doi.org/10.1016/j.ijpharm.2017.03.083.
[268] Lee SH, Kim HJ, Kim DH, Chang WS, Vales TP, Kim JW, et al. Thermo-sensitive nanogel-laden bicontinuous microemulsion drug-eluting contact lenses. J Biomed Mater Res B Appl Biomater 2019;107(4):1159-69. https://doi.org/10.1002/jbm.b.34209.
[269] Li CC, Abrahamson M, Kapoor Y, Chauhan A. Timolol transport from microemulsions trapped in HEMA gels. Journal of colloid and interface science 2007;315(1):297-306. https://doi.org/10.1016/j.jcis.2007.06.054.
[270] Xu W, Jiao W, Li S, Tao X, Mu G. Bimatoprost loaded microemulsion laden contact lens to treat glaucoma. J Drug Deliv Sci Technol 2019;54:101330.
[271] Torres-Luna C, Hu N, Koolivand A, Fan X, Zhu Y, Domszy R, et al. Effect of a cationic surfactant on microemulsion globules and drug release from hydrogel contact lenses. Pharmaceutics 2019;11(6):262. https://doi.org/10.3390/pharmaceutics11060262.
[272] Li Y, Huang C, Yang X, Zhang X. Ofloxacin laden microemulsion contact lens to treat conjunctivitis. J Biomater Sci Polym Ed 2020;31(12):1566-79. https://doi.org/10.1080/09205063.2020.1764165.
[273] Wei N, Dang H, Huang C, Sheng Y. Timolol loaded microemulsion laden silicone contact lens to manage glaucoma: In vitro and in vivo studies. J Dispers Sci Technol 2020:1-9.
[274] Kapoor Y, Chauhan A. Ophthalmic delivery of cyclosporine a from Brij-97 microemulsion and surfactant-laden p-HEMA hydrogels. Int J Pharm 2008;361(1-2):222-9. https://doi.org/10.1016/j.ijpharm.2008.05.028.
[275] Sekar P, Chauhan A. Effect of vitamin-e integration on delivery of prostaglandin analogs from therapeutic lenses. Journal of colloid and interface science 2019;539:457-67. https://doi.org/10.1016/j.jcis.2018.12.036.
[276] Ubani-Ukoma UG, D; Schultz, G; Silva, BO; Chauhan, A. Evaluating the potential of drug eluting contact lenses for treatment of bacterial keratitis using an ex vivo corneal model Int J Pharm 2019;565:499-508.
[277] Kim J, Peng CC, Chauhan A. Extended release of dexamethasone from silicone-hydrogel contact lenses containing vitamin E. Journal of controlled release : official journal of the Controlled Release Society 2010;148(1):110-6. https://doi.org/10.1016/j.jconrel.2010.07.119.
[278] Peng CC, Burke MT, Carbia BE, Plummer C, Chauhan A. Extended drug delivery by contact lenses for glaucoma therapy. Journal of controlled release : official journal of the Controlled Release Society 2012;162(1):152-8. https://doi.org/10.1016/j.jconrel.2012.06.017.

[279] Paradiso P, Serro AP, Saramago B, Colaco R, Chauhan A. Controlled release of antibiotics from vitamin e-loaded silicone-hydrogel contact lenses. J Pharm Sci 2016;105(3):1164-72. https://doi.org/10.1016/S0022-3549(15)00193-8.
[280] Rad MS, Mohajeri SA. Simultaneously load and extended release of betamethasone and ciprofloxacin from vitamin e-loaded silicone-based soft contact lenses. Current eye research 2016;41(9):1185-91. https://doi.org/10.3109/02713683.2015.1107591.
[281] Lee D, Cho S, Park HS, Kwon I. Ocular drug delivery through pHEMA-hydrogel contact lenses co-loaded with lipophilic vitamins. Sci Rep 2016;6:34194. https://doi.org/10.1038/srep34194.
[282] Dixon PG, T; Mondal, K; Konar, A; Chauhan, A; Hazra, S. Controlled delivery of pirfenidone through vitamin E-loaded contact lens ameliorates corneal inflammation. Drug Deliv Transl Res 2018;8(5):1114-26.
[283] Alvarez-Lorenzo C, Concheiro A. Molecularly imprinted polymers for drug delivery. J Chromatogr B Analyt Technol Biomed Life Sci 2004;804(1):231-45. https://doi.org/10.1016/j.jchromb.2003.12.032.
[284] Hiratani H, Alvarez-Lorenzo C. The nature of backbone monomers determines the performance of imprinted soft contact lenses as timolol drug delivery systems. Biomaterials 2004;25(6):1105-13. https://doi.org/10.1016/s0142-9612(03)00622-7.
[285] Alvarez-Lorenzo C, Hiratani H, Gomez-Amoza JL, Martinez-Pacheco R, Souto C, Concheiro A. Soft contact lenses capable of sustained delivery of timolol. J Pharm Sci 2002;91(10):2182-92. https://doi.org/10.1002/jps.10209.
[286] Hiratani H, Fujiwara A, Tamiya Y, Mizutani Y, Alvarez-Lorenzo C. Ocular release of timolol from molecularly imprinted soft contact lenses. Biomaterials 2005;26(11):1293-8. https://doi.org/10.1016/j.biomaterials.2004.04.030.
[287] Ali M, Horikawa S, Venkatesh S, Saha J, Hong JW, Byrne ME. Zero-order therapeutic release from imprinted hydrogel contact lenses within in vitro physiological ocular tear flow. Journal of controlled release : official journal of the Controlled Release Society 2007;124(3):154-62. https://doi.org/10.1016/j.jconrel.2007.09.006.
[288] Gonzalez-Chomon C, Silva M, Concheiro A, Alvarez-Lorenzo C. Biomimetic contact lenses eluting olopatadine for allergic conjunctivitis. Acta Biomater 2016;41:302-11. https://doi.org/10.1016/j.actbio.2016.05.032.
[289] Alvarez-Lorenzo C, Yañez F, Barreiro-Iglesias R, Concheiro A. Imprinted soft contact lenses as norfloxacin delivery systems. Journal of controlled release : official journal of the Controlled Release Society 2006;113(3):236-44, http://www.scopus.com/inward/record.url?eid=2-s2.0-33745480945&partnerID=40&md5=0cad1bc682cda87134ca18989f7be59c http://ac.els-cdn.com/S0168365906002008/1-s2.0-S0168365906002008-main.pdf?_tid=b63a59d2-839a-11e6-9f08-00000aacb361&acdnat=1474861298_dcea73fb17a5a5acb513db3f8a8f89b4.
[290] Hui A, Sheardown H, Jones L. Acetic and acrylic acid molecular imprinted model silicone hydrogel materials for ciprofloxacin-HCl delivery. Materials (Basel) 2012;5(1):85-107. https://doi.org/10.3390/ma5010085.
[291] Hui A, Willcox M, Jones L. In vitro and in vivo evaluation of novel ciprofloxacin-releasing silicone hydrogel contact lenses. Invest Ophthalmol Vis Sci 2014;55(8):4896-904. https://doi.org/10.1167/iovs.14-14855.

[292] Malakooti N, Alexander C, Alvarez-Lorenzo C. Imprinted contact lenses for sustained release of polymyxin b and related antimicrobial peptides. J Pharm Sci 2015;104(10):3386-94. https://doi.org/10.1002/jps.24537.
[293] Andrade-Vivero P, Fernandez-Gabriel E, Alvarez-Lorenzo C, Concheiro A. Improving the loading and release of nsaids from pHEMA hydrogels by copolymerization with functionalized monomers. J Pharm Sci 2007;96(4):802-13. https://doi.org/10.1002/jps.20761.
[294] Malaekeh-Nikouei B, Ghaeni FA, Motamedshariaty VS, Mohajeri SA. Controlled release of prednisolone acetate from molecularly imprinted hydrogel contact lenses. J Appl Pol Sci 2012;126(1):387-94, http://www.scopus.com/inward/record.url?eid=2-s2.0-84863843416&partnerID=40&md5=d3c8ecf1193a9d88786beb997cfd3ba0.
[295] Tieppo A, Pate KM, Byrne ME. In vitro controlled release of an anti-inflammatory from daily disposable therapeutic contact lenses under physiological ocular tear flow. European journal of pharmaceutics and biopharmaceutics : official journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik eV 2012;81(1):170-7. https://doi.org/10.1016/j.ejpb.2012.01.015.
[296] Malaekeh-Nikouei B, Vahabzadeh SA, Mohajeri SA. Preparation of a molecularly imprinted soft contact lens as a new ocular drug delivery system for dorzolamide. Curr Drug Deliv 2013;10(3):279-85. https://doi.org/10.2174/1567201811310030004.
[297] Yan F, Liu Y, Han S, Zhao Q, Liu N. Bimatoprost imprinted silicone contact lens to treat glaucoma. AAPS PharmSciTech 2020;21(2):63. https://doi.org/10.1208/s12249-020-1622-6.
[298] Ali M, Byrne ME. Controlled release of high molecular weight hyaluronic acid from molecularly imprinted hydrogel contact lenses. Pharm Res 2009;26(3):714-26. https://doi.org/10.1007/s11095-008-9818-6.
[299] White CJ, McBride MK, Pate KM, Tieppo A, Byrne ME. Extended release of high molecular weight hydroxypropyl methylcellulose from molecularly imprinted, extended wear silicone hydrogel contact lenses. Biomaterials 2011;32(24):5698-705. https://doi.org/10.1016/j.biomaterials.2011.04.044.
[300] Hiratani H, Mizutani Y, Alvarez-Lorenzo C. Controlling drug release from imprinted hydrogels by modifying the characteristics of the imprinted cavities. Macromol Biosci 2005;5(8):728-33. https://doi.org/10.1002/mabi.200500065.
[301] Tieppo A, White CJ, Paine AC, Voyles ML, McBride MK, Byrne ME. Sustained in vivo release from imprinted therapeutic contact lenses. Journal of controlled release : official journal of the Controlled Release Society 2012;157(3):391-7. https://doi.org/10.1016/j.jconrel.2011.09.087.
[302] Behl G, Iqbal J, O'Reilly NJ, McLoughlin P, Fitzhenry L. Synthesis and characterization of poly(2-hydroxyethylmethacrylate) contact lenses containing chitosan nanoparticles as an ocular delivery system for dexamethasone sodium phosphate. Pharm Res 2016;33(7):1638-48. https://doi.org/10.1007/s11095-016-1903-7.
[303] Lee D, Lee N, Kwon I. Efficient loading of ophthalmic drugs with poor loadability into contact lenses using functional comonomers. Biomaterials science 2018;6(10):2639-46. https://doi.org/10.1039/c8bm00586a.
[304] Kakisu K, Matsunaga T, Kobayakawa S, Sato T, Tochikubo T. Development and efficacy of a drug-releasing soft contact lens. Invest Ophthalmol Vis Sci 2013;54(4):2551-61. https://doi.org/10.1167/iovs.12-10614.

[305] Kim G, Kim HJ, Noh H. Influence of solution pH on drug release from ionic hydrogel lens. Macromol Res 2019;27(2):191-7.
[306] Kanemoto M, Sato T, Aoyama A, Matsunaga T, Uno K, Toshida H, et al. The interaction and compatibility between a soft contact lens and an ophthalmic drug. Eye Contact Lens 2006;32(4):192-6. https://doi.org/10.1097/01.icl.0000191593.87142.dd.
[307] Kamberi M, Tsutsumi K, Kotegawa T, Kawano K, Nakamura K, Niki Y, et al. Influences of urinary pH on ciprofloxacin pharmacokinetics in humans and antimicrobial activity in vitro versus those of sparfloxacin. Antimicrobial agents and chemotherapy 1999;43(3):525-9. https://doi.org/10.1128/AAC.43.3.525.
[308] Tranoudis I, Efron N. Water properties of soft contact lens materials. Cont Lens Anterior Eye 2004;27(4):193-208. https://doi.org/10.1016/j.clae.2004.08.003.
[309] Luensmann D, Jones L. Protein deposition on contact lenses: The past, the present, and the future. Cont Lens Anterior Eye 2012;35(2):53-64. https://doi.org/10.1016/j.clae.2011.12.005.
[310] Xu JL, X; Sun, F. Cyclodextrin-containing hydrogels for contact lenses as a platform for drug incorporation and release. Acta Biomaterialia 2010;6(2):486-93.
[311] Phan CM, Subbaraman LN, Jones L. In vitro drug release of natamycin from beta-cyclodextrin and 2-hydroxypropyl-beta-cyclodextrin-functionalized contact lens materials. J Biomater Sci Polym Ed 2014;25(17):1907-19. https://doi.org/10.1080/09205063.2014.958016.
[312] Ciolino JB, Hoare TR, Iwata NG, Behlau I, Dohlman CH, Langer R, et al. A drug-eluting contact lens. Invest Ophthalmol Vis Sci 2009;50(7):3346-52. https://doi.org/10.1167/iovs.08-2826.
[313] Ciolino JB, Stefanescu CF, Ross AE, Salvador-Culla B, Cortez P, Ford EM, et al. In vivo performance of a drug-eluting contact lens to treat glaucoma for a month. Biomaterials 2014;35(1):432-9. https://doi.org/10.1016/j.biomaterials.2013.09.032.
[314] Ciolino JB, Ross AE, Tulsan R, Watts AC, Wang RF, Zurakowski D, et al. Latanoprost-eluting contact lenses in glaucomatous monkeys. Ophthalmology 2016;123(10):2085-92. https://doi.org/10.1016/j.ophtha.2016.06.038.
[315] Ross AE, Bengani LC, Tulsan R, Maidana DE, Salvador-Culla B, Kobashi H, et al. Topical sustained drug delivery to the retina with a drug-eluting contact lens. Biomaterials 2019;217:119285. https://doi.org/10.1016/j.biomaterials.2019.119285.
[316] Maulvi FA, Singhania SS, Desai AR, Shukla MR, Tannk AS, Ranch KM, et al. Contact lenses with dual drug delivery for the treatment of bacterial conjunctivitis. Int J Pharm 2018;548(1):139-50. https://doi.org/10.1016/j.ijpharm.2018.06.059.
[317] Maulvi FA, Shaikh AA, Lakdawala DH, Desai AR, Pandya MM, Singhania SS, et al. Design and optimization of a novel implantation technology in contact lenses for the treatment of dry eye syndrome: In vitro and in vivo evaluation. Acta Biomater 2017;53:211-21. https://doi.org/10.1016/j.actbio.2017.01.063.
[318] Koffler BH, McDonald M, Nelinson DS, Group LACS. Improved signs, symptoms, and quality of life associated with dry eye syndrome: Hydroxypropyl cellulose ophthalmic insert patient registry. Eye Contact Lens 2010;36(3):170-6. https://doi.org/10.1097/ICL.0b013e3181db352f.

[319] McDonald M, D'Aversa G, Perry HD, Wittpenn JR, Donnenfeld ED, Nelinson DS. Hydroxypropyl cellulose ophthalmic inserts (lacrisert) reduce the signs and symptoms of dry eye syndrome and improve patient quality of life. Trans Am Ophthalmol Soc 2009;107:214-21, https://www.ncbi.nlm.nih.gov/pubmed/20126497.
[320] Luchs JI, Nelinson DS, Macy JI, Group LACS. Efficacy of hydroxypropyl cellulose ophthalmic inserts (LACRISERT) in subsets of patients with dry eye syndrome: Findings from a patient registry. Cornea 2010;29(12):1417-27. https://doi.org/10.1097/ICO.0b013e3181e3f05b.
[321] McDonald M, D'Aversa G, Perry HD, Wittpenn JR, Nelinson DS. Correlating patient-reported response to hydroxypropyl cellulose ophthalmic insert (LACRISERT(r)) therapy with clinical outcomes: Tools for predicting response. Current eye research 2010;35(10):880-7. https://doi.org/10.3109/02713683.2010.495811.
[322] Pitt WG, Jack DR, Zhao Y, Nelson JL, Pruitt JD. Loading and release of a phospholipid from contact lenses. Optom Vis Sci 2011;88(4):502-6. https://doi.org/10.1097/OPX.0b013e31820e9ff8.
[323] de Paiva CS, Pflugfelder SC, Ng SM, Akpek EK. Topical cyclosporine A therapy for dry eye syndrome. Cochrane Database Syst Rev 2019;9:CD010051. https://doi.org/10.1002/14651858.CD010051.pub2.
[324] Peng CC, Chauhan A. Extended cyclosporine delivery by silicone-hydrogel contact lenses. Journal of controlled release : official journal of the Controlled Release Society 2011;154(3):267-74. https://doi.org/10.1016/j.jconrel.2011.06.028.
[325] Choi JH, Li Y, Jin R, Shrestha T, Choi JS, Lee WJ, et al. The efficiency of cyclosporine a-eluting contact lenses for the treatment of dry eye. Current eye research 2019;44(5):486-96. https://doi.org/10.1080/02713683.2018.1563702.
[326] Jones L, Downie LE, Korb D, Benitez-Del-Castillo JM, Dana R, Deng SX, et al. TFOS DEWS ii management and therapy report. Ocul Surf 2017;15(3):575-628. https://doi.org/10.1016/j.jtos.2017.05.006.
[327] Peng CC, Kim J, Chauhan A. Extended delivery of hydrophilic drugs from silicone-hydrogel contact lenses containing vitamin E diffusion barriers. Biomaterials 2010;31(14):4032-47. https://doi.org/10.1016/j.biomaterials.2010.01.113.
[328] Macoul KL, Pavan-Langston D. Pilocarpine ocusert system for sustained control of ocular hypertension. Arch Ophthalmol 1975;93(8):587-90. https://doi.org/10.1001/archopht.1975.01010020571003.
[329] Brandt JD, Sall K, DuBiner H, Benza R, Alster Y, Walker G, et al. Six-month intraocular pressure reduction with a topical bimatoprost ocular insert: Results of a phase ii randomized controlled study. Ophthalmology 2016;123(8):1685-94. https://doi.org/10.1016/j.ophtha.2016.04.026.
[330] Peng CC, Ben-Shlomo A, Mackay EO, Plummer CE, Chauhan A. Drug delivery by contact lens in spontaneously glaucomatous dogs. Current eye research 2012;37(3):204-11. https://doi.org/10.3109/02713683.2011.630154.
[331] Taniguchi EV, Kalout P, Pasquale LR, Kohane DS, Ciolino JB. Clinicians' perspectives on the use of drug-eluting contact lenses for the treatment of glaucoma. Therapeutic delivery 2014;5(10):1077-83. https://doi.org/10.4155/tde.14.76.
[332] Xu J, Xue Y, Hu G, Lin T, Gou J, Yin T, et al. A comprehensive review on contact lens for ophthalmic drug delivery. Journal of controlled release :

official journal of the Controlled Release Society 2018;281:97-118. https://doi.org/10.1016/j.jconrel.2018.05.020.
[333] Busin M, Spitznas M. Sustained gentamicin release by presoaked medicated bandage contact lenses. Ophthalmology 1988;95(6):796-8. https://doi.org/10.1016/s0161-6420(88)33106-4.
[334] Kalayci D, Basci N, Kortunay S, Hasiripi H, Bozkurt A. Penetration of topical ciprofloxacin by presoaked medicated soft contact lenses. CLAO J 1999;25(3):182-4, https://www.ncbi.nlm.nih.gov/pubmed/10444056.
[335] Kennedy SM, Deshpande P, Gallagher AG, Horsburgh MJ, Allison HE, Kaye SB, et al. Antimicrobial activity of poly-epsilon-lysine peptide hydrogels against Pseudomonas aeruginosa. Invest Ophthalmol Vis Sci 2020;61(10):18. https://doi.org/10.1167/iovs.61.10.18.
[336] Gallagher AG, McLean K, Stewart RMK, Wellings DA, Allison HE, Williams RL. Development of a poly-epsilon-lysine contact lens as a drug delivery device for the treatment of fungal keratitis. Invest Ophthalmol Vis Sci 2017;58(11):4499-505. https://doi.org/10.1167/iovs.17-22301.
[337] Gallagher AG, Alorabi JA, Wellings DA, Lace R, Horsburgh MJ, Williams RL. A novel peptide hydrogel for an antimicrobial bandage contact lens. Adv Healthc Mater 2016;5(16):2013-8. https://doi.org/10.1002/adhm.201600258.
[338] Lace R, Doherty KG, Dutta D, Willcox MDP, Williams RL. Poly-ε-lysine or Mel4 antimicrobial surface modification on a novel peptide hydrogel bandage contact lens. Adv Mater Interfaces 2020;7:2001232.
[339] Bielory L, Friedlaender MH. Allergic conjunctivitis. Immunol Allergy Clin North Am 2008;28(1):43-58, vi. https://doi.org/10.1016/j.iac.2007.12.005.
[340] Abelson MB, McLaughlin JT, Gomes PJ. Antihistamines in ocular allergy: Are they all created equal? Curr Allergy Asthma Rep 2011;11(3):205-11. https://doi.org/10.1007/s11882-011-0188-5.
[341] Gomes PJ. Trends in prevalence and treatment of ocular allergy. Curr Opin Allergy Clin Immunol 2014;14(5):451-6. https://doi.org/10.1097/ACI.0000000000000100.
[342] Pitt AD, Smith AF, Lindsell L, Voon LW, Rose PW, Bron AJ. Economic and quality-of-life impact of seasonal allergic conjunctivitis in oxfordshire. Ophthalmic Epidemiol 2004;11(1):17-33. https://doi.org/10.1076/opep.11.1.17.26437.
[343] Lemp MA. Contact lenses and allergy. Curr Opin Allergy Clin Immunol 2008;8(5):457-60. https://doi.org/10.1097/ACI.0b013e32830e6adc.
[344] Najmi H, Mobarki Y, Mania K, Altowairqi B, Basehi M, Mahfouz MS, et al. The correlation between keratoconus and eye rubbing: A review. Int J Ophthalmol 2019;12(11):1775-81. https://doi.org/10.18240/ijo.2019.11.17.
[345] Ackerman S, Smith LM, Gomes PJ. Ocular itch associated with allergic conjunctivitis: Latest evidence and clinical management. Ther Adv Chronic Dis 2016;7(1):52-67. https://doi.org/10.1177/2040622315612745.
[346] Wolffsohn JS, Emberlin JC. Role of contact lenses in relieving ocular allergy. Cont Lens Anterior Eye 2011;34(4):169-72. https://doi.org/10.1016/j.clae.2011.03.004.
[347] Xue Y, Zhang W, Lei Y, Dang M. Novel polyvinyl pyrrolidone-loaded olopatadine HCl-laden doughnut contact lens to treat allergic conjunctivitis. J Pharm Sci 2020;109(5):1714-24. https://doi.org/10.1016/j.xphs.2020.01.022.
[348] Vistakon. Safety study of a contact lens with ketotifen in healthy, normal volunteers (a). *ClinicalTrials.gov.* NIH-US National Library of Medicine; 2007.

[349] Vistakon. Safety study of a contact lens with ketotifen in healthy, normal volunteers (b). *ClinicalTrials.gov.* NIH- US National Library of Medicine; 2009.
[350] Vistakon. Evaluation of efficacy and safety of an anti-allergy drug with a contact lens in allergic conjunctivitis (a). *ClinicalTrials.gov.* NIH - US National Library of Medicine; 2007.
[351] Vistakon. Evaluation of efficacy and safety of an anti-allergy drug with a contact lens in the treatment of allergic conjunctivitis (b). *ClinicalTrials.gov.* NIH-US National Library of Medicine; 2007.
[352] Raja RR, Mahadevan S, Alli A, Molock F, Pall B. Methods and ophthalmic devices used in the treatment of ocular allergies. *Google Patents.* US10045975B2. USA: Johnson and Johnson Vision Care Inc; 2017.
[353] Pall B, Gomes P, Yi F, Torkildsen G. Management of ocular allergy itch with an antihistamine-releasing contact lens. Cornea 2019;38(6):713-7. https://doi.org/10.1097/ICO.0000000000001911.
[354] Linsley CS, Wu BM. Recent advances in light-responsive on-demand drug-delivery systems. Therapeutic delivery 2017;8(2):89-107. https://doi.org/10.4155/tde-2016-0060.
[355] Li C, Wang J, Wang Y, Gao H, Wei G, Huang Y, et al. Recent progress in drug delivery. Acta pharmaceutica Sinica B 2019;9(6):1145-62. https://doi.org/10.1016/j.apsb.2019.08.003.
[356] Li L, Scheiger JM, Levkin PA. Design and applications of photoresponsive hydrogels. Adv Mater 2019;31(26):e1807333. https://doi.org/10.1002/adma.201807333.
[357] Geng S, Wang Y, Wang L, Kouyama T, Gotoh T, Wada S, et al. A light-responsive self-assembly formed by a cationic azobenzene derivative and SDS as a drug delivery system. Sci Rep 2017;7(1):39202. https://doi.org/10.1038/srep39202.
[358] Behar-Cohen F, Baillet G, de Ayguavives T, Garcia PO, Krutmann J, Pena-Garcia P, et al. Ultraviolet damage to the eye revisited: Eye-sun protection factor (e-spf(r)), a new ultraviolet protection label for eyewear. Clin Ophthalmol 2014;8:87-104. https://doi.org/10.2147/OPTH.S46189.
[359] Söderberg P, Talebizadeh N, Yu Z, Galichanin K. Does infrared or ultraviolet light damage the lens? Eye 2016;30(2):241-6.
[360] Kim J, Him H, Lee S, Kim D. Thermo-responsive hydrogel contact lens for controlled drug delivery and manufacturing method thereof. *Google Patents.* KR102009571B1. Korea; 2017.
[361] Kim Y-J, Matsunaga YT. Thermo-responsive polymers and their application as smart biomaterials. Journal of materials chemistry B 2017;5(23):4307-21.
[362] Kopecek J. Hydrogels from soft contact lenses and implants to self-assembled nanomaterials. Journal of polymer science Part A, Polymer chemistry 2009;47(22):5929-46. https://doi.org/10.1002/pola.23607.
[363] Matsumoto K, Sakikawa N, Miyata T. Thermo-responsive gels that absorb moisture and ooze water. Nature communications 2018;9(1):1-7.
[364] Villa C, Martello F, Erratico S, Tocchio A, Belicchi M, Lenardi C, et al. P(NIPAAM-co-HEMA) thermoresponsive hydrogels: An alternative approach for muscle cell sheet engineering. Journal of tissue engineering and regenerative medicine 2017;11(1):187-96. https://doi.org/10.1002/term.1898.
[365] Liu YY, Lu J, Shao YH. Preparation and characterization of poly(n-isopropylacrylamide)-modified poly(2-hydroxyethyl acrylate) hydrogels by

interpenetrating polymer networks for sustained drug release. Macromol Biosci 2006;6(6):452-8. https://doi.org/10.1002/mabi.200600007.
[366] Ashraf S, Park H-K, Park H, Lee S-H. Snapshot of phase transition in thermoresponsive hydrogel pnipam: Role in drug delivery and tissue engineering. Macromol Res 2016;24(4):297-304.
[367] Fu R, Klinngam W, Heur M, Edman MC, Hamm-Alvarez SF. Tear proteases and protease inhibitors: Potential biomarkers and disease drivers in ocular surface disease. Eye Contact Lens 2020;46 Suppl 2:S70-S83. https://doi.org/10.1097/ICL.0000000000000641.
[368] Ahlen M, Tummala GK, Mihranyan A. Nanoparticle-loaded hydrogels as a pathway for enzyme-triggered drug release in ophthalmic applications. Int J Pharm 2018;536(1):73-81. https://doi.org/10.1016/j.ijpharm.2017.11.053.
[369] Kim HJ, Zhang K, Moore L, Ho D. Diamond nanogel-embedded contact lenses mediate lysozyme-dependent therapeutic release. ACS nano 2014;8(3):2998-3005. https://doi.org/10.1021/nn5002968.
[370] Willcox MD. Microbial adhesion to silicone hydrogel lenses: A review. Eye Contact Lens 2013;39(1):61-6. https://doi.org/10.1097/ICL.0b013e318275e284.
[371] Stapleton F, Keay L, Jalbert I, Cole N. The epidemiology of contact lens related infiltrates. Optom Vis Sci 2007;84(4):257-72. https://doi.org/10.1097/OPX.0b013e3180485d5f.
[372] Stapleton F, Keay L, Edwards K, Naduvilath T, Dart JK, Brian G, et al. The incidence of contact lens-related microbial keratitis in australia. Ophthalmology 2008;115(10):1655-62. https://doi.org/10.1016/j.ophtha.2008.04.002.
[373] Schein OD, McNally JJ, Katz J, Chalmers RL, Tielsch JM, Alfonso E, et al. The incidence of microbial keratitis among wearers of a 30-day silicone hydrogel extended-wear contact lens. Ophthalmology 2005;112(12):2172-9. https://doi.org/10.1016/j.ophtha.2005.09.014.
[374] Willcox M, Keir N, Maseedupally V, Masoudi S, McDermott A, Mobeen R, et al. CLEAR - contact lens wettability, cleaning, disinfection and interaction with tears. Contact Lens and Anterior Eye 2021;44(2):In press.
[375] Willcox MDP, Hume EBH, Vijay AK, Petcavich R. Ability of silver-impregnated contact lenses to control microbial growth and colonisation. Journal of Optometry 2010;3(3):143-8. https://doi.org/10.1016/s1888-4296(10)70020-0.
[376] Kharaghani D, Dutta D, Gitigard P, Tamada Y, Katagiri A, Phan D-N, et al. Development of antibacterial contact lenses containing metallic nanoparticles. Polymer Testing 2019;79:106034. https://doi.org/10.1016/j.polymertesting.2019.106034.
[377] Nissen S, Furkert FH. [antimicrobial efficacy of a silver layer on hydrogel lenses] citation]. Der Ophthalmologe : Zeitschrift der Deutschen Ophthalmologischen Gesellschaft 2000;97(9):640-3. https://doi.org/10.1007/s003470070054.
[378] Mourad R, Helaly F, Darwesh O, Sawy SE. Antimicrobial and physicomechanical natures of silver nanoparticles incorporated into silicone-hydrogel films. Cont Lens Anterior Eye 2019;42(3):325-33. https://doi.org/10.1016/j.clae.2019.02.007.
[379] Willcox MD, Hume EB, Aliwarga Y, Kumar N, Cole N. A novel cationic-peptide coating for the prevention of microbial colonization on contact lenses. Journal

of applied microbiology 2008;105(6):1817-25. https://doi.org/10.1111/j.1365-2672.2008.03942.x.
[380] Dutta D, Vijay AK, Kumar N, Willcox MD. Melimine-coated antimicrobial contact lenses reduce microbial keratitis in an animal model. Invest Ophthalmol Vis Sci 2016;57(13):5616-24. https://doi.org/10.1167/iovs.16-19882.
[381] Dutta D, Ozkan J, Willcox MD. Biocompatibility of antimicrobial melimine lenses: Rabbit and human studies. Optom Vis Sci 2014;91(5):570-81. https://doi.org/10.1097/OPX.0000000000000232.
[382] Dutta D, Kamphuis B, Ozcelik B, Thissen H, Pinarbasi R, Kumar N, et al. Development of silicone hydrogel antimicrobial contact lenses with Mel4 peptide coating. Optom Vis Sci 2018;95(10):937-46. https://doi.org/10.1097/OPX.0000000000001282.
[383] Dutta D, Cole N, Kumar N, Willcox MD. Broad spectrum antimicrobial activity of melimine covalently bound to contact lenses. Invest Ophthalmol Vis Sci 2013;54(1):175-82. https://doi.org/10.1167/iovs.12-10989.
[384] Dutta D, Zhao T, Cheah KB, Holmlund L, Willcox MDP. Activity of a melimine derived peptide Mel4 against Stenotrophomonas, Delftia, Elizabethkingia, Burkholderia and biocompatibility as a contact lens coating. Cont Lens Anterior Eye 2017;40(3):175-83. https://doi.org/10.1016/j.clae.2017.01.002.
[385] Ren D, Sims JJ, Wood TK. Inhibition of biofilm formation and swarming of Bacillus subtilis by (5Z)-4-bromo-5-(bromomethylene)-3-butyl-2(5H)-furanone. Letters in applied microbiology 2002;34(4):293-9. https://doi.org/10.1046/j.1472-765x.2002.01087.x.
[386] Jones MB, Jani R, Ren D, Wood TK, Blaser MJ. Inhibition of Bacillus anthracis growth and virulence-gene expression by inhibitors of quorum-sensing. J Infect Dis 2005;191(11):1881-8. https://doi.org/10.1086/429696.
[387] George M, Pierce G, Gabriel M, Morris C, Ahearn D. Effects of quorum sensing molecules of Pseudomonas aeruginosa on organism growth, elastase b production, and primary adhesion to hydrogel contact lenses. Eye Contact Lens 2005;31(2):54-61. https://doi.org/10.1097/01.icl.0000146324.28865.e8.
[388] Hentzer M, Wu H, Andersen JB, Riedel K, Rasmussen TB, Bagge N, et al. Attenuation of Pseudomonas aeruginosa virulence by quorum sensing inhibitors. The EMBO journal 2003;22(15):3803-15. https://doi.org/10.1093/emboj/cdg366.
[389] Read R, Kumar N, Willcox M, Griesser H, Muir B, Thissen H, et al. Antimicrobial coatings. 2003.
[390] Zhu H, Kumar A, Ozkan J, Bandara R, Ding A, Perera I, et al. Fimbrolide-coated antimicrobial lenses: Their in vitro and in vivo effects. Optom Vis Sci 2008;85(5):292-300. https://doi.org/10.1097/OPX.0b013e31816bea0f.
[391] Taylor RL, Willcox MD, Williams TJ, Verran J. Modulation of bacterial adhesion to hydrogel contact lenses by albumin. Optom Vis Sci 1998;75(1):23-9. https://doi.org/10.1097/00006324-199801000-00021.
[392] Thissen H, Gengenbach T, du Toit R, Sweeney DF, Kingshott P, Griesser HJ, et al. Clinical observations of biofouling on PEO coated silicone hydrogel contact lenses. Biomaterials 2010;31(21):5510-9. https://doi.org/10.1016/j.biomaterials.2010.03.040.
[393] Svenson S. Theranostics: Are we there yet? Mol Pharm 2013;10(3):848-56. https://doi.org/10.1021/mp300644n.

[394] Jeelani S, Reddy RC, Maheswaran T, Asokan GS, Dany A, Anand B. Theranostics: A treasured tailor for tomorrow. J Pharm Bioallied Sci 2014;6(Suppl 1):S6-8. https://doi.org/10.4103/0975-7406.137249.
[395] Mansouri K, Weinreb R. Continuous 24-hour intraocular pressure monitoring for glaucoma--time for a paradigm change. Swiss Med Wkly 2012;142(1314):w13545. https://doi.org/10.4414/smw.2012.13545.
[396] Ascaso FJ, Huerva V. Noninvasive continuous monitoring of tear glucose using glucose-sensing contact lenses. Optom Vis Sci 2016;93(4):426-34. https://doi.org/10.1097/OPX.0000000000000698.
[397] Badugu R, Reece EA, Lakowicz JR. Glucose-sensitive silicone hydrogel contact lens toward tear glucose monitoring. J Biomed Opt 2018;23(5):1-9. https://doi.org/10.1117/1.JBO.23.5.057005.
[398] Farandos NM, Yetisen AK, Monteiro MJ, Lowe CR, Yun SH. Contact lens sensors in ocular diagnostics. Adv Healthc Mater 2015;4(6):792-810. https://doi.org/10.1002/adhm.201400504.
[399] Keum DH, Kim SK, Koo J, Lee GH, Jeon C, Mok JW, et al. Wireless smart contact lens for diabetic diagnosis and therapy. Science advances 2020;6(17):eaba3252. https://doi.org/10.1126/sciadv.aba3252.
[400] Prescott JH, Lipka S, Baldwin S, Sheppard NF, Jr., Maloney JM, Coppeta J, et al. Chronic, programmed polypeptide delivery from an implanted, multireservoir microchip device. Nature biotechnology 2006;24(4):437-8. https://doi.org/10.1038/nbt1199.
[401] Jinabhai A, O'Donnell C, Tromans C, Radhakrishnan H. Optical quality and visual performance with customised soft contact lenses for keratoconus. Ophthalmic Physiol Opt 2014;34(5):528-39. https://doi.org/10.1111/opo.12133.
[402] Jinabhai AN. Customised aberration-controlling corrections for keratoconic patients using contact lenses. Clinical & experimental optometry 2020;103(1):31-43. https://doi.org/10.1111/cxo.12937.
[403] Shokrollahzadeh F, Hashemi H, Jafarzadehpur E, Mirzajani A, Khabazkhoob M, Yekta A, et al. Corneal aberration changes after rigid gas permeable contact lens wear in keratokonic patients. J Curr Ophthalmol 2016;28(4):194-8. https://doi.org/10.1016/j.joco.2016.08.002.
[404] Yang B, Liang B, Liu L, Liao M, Li Q, Dai Y, et al. Contrast sensitivity function after correcting residual wavefront aberrations during RGP lens wear. Optom Vis Sci 2014;91(10):1271-7. https://doi.org/10.1097/OPX.0000000000000253.
[405] Charman WN. Wavefront technology: Past, present and future. Cont Lens Anterior Eye 2005;28(2):75-92. https://doi.org/10.1016/j.clae.2005.02.003.
[406] Carones F, Vigo L, Scandola E. Wavefront-guided treatment of abnormal eyes using the LADARVision platform. J Refract Surg 2003;19(6):S703-8, https://www.ncbi.nlm.nih.gov/pubmed/14640439.
[407] Myrowitz EH, Chuck RS. A comparison of wavefront-optimized and wavefront-guided ablations. Curr Opin Ophthalmol 2009;20(4):247-50. https://doi.org/10.1097/icu.0b013e32832a2336.
[408] Bakaraju RC, Ehrmann K, Ho A, Papas E. Inherent ocular spherical aberration and multifocal contact lens optical performance. Optom Vis Sci 2010;87(12):1009-22. https://doi.org/10.1097/OPX.0b013e3181fbad60.
[409] Lopes-Ferreira D, Fernandes P, Queiros A, Gonzalez-Meijome JM. Combined effect of ocular and multifocal contact lens induced aberrations on visual

performance: Center-distance versus center-near design. Eye Contact Lens 2018;44 Suppl 1:S131-S7. https://doi.org/10.1097/ICL.0000000000000355.
[410] Dietze HH, Cox MJ. On- and off-eye spherical aberration of soft contact lenses and consequent changes of effective lens power. Optom Vis Sci 2003;80(2):126-34. https://doi.org/10.1097/00006324-200302000-00008.
[411] Dietze HH, Cox MJ. Correcting ocular spherical aberration with soft contact lenses. J Opt Soc Am A Opt Image Sci Vis 2004;21(4):473-85. https://doi.org/10.1364/josaa.21.000473.
[412] Efron S, Efron N, Morgan PB. Optical and visual performance of aspheric soft contact lenses. Optom Vis Sci 2008;85(3):201-10. https://doi.org/10.1097/OPX.0b013e318165100a.
[413] Lindskoog Pettersson A, Martensson L, Salkic J, Unsbo P, Brautaset R. Spherical aberration in relation to visual performance in contact lens wear. Cont Lens Anterior Eye 2011;34(1):12-6; quiz 50-1. https://doi.org/10.1016/j.clae.2010.08.008.
[414] Legras R, Chateau N, Charman WN. Assessment of just-noticeable differences for refractive errors and spherical aberration using visual simulation. Optom Vis Sci 2004;81(9):718-28. https://doi.org/10.1097/01.opx.0000144751.11213.cd.
[415] Lu F, Mao X, Qu J, Xu D, He JC. Monochromatic wavefront aberrations in the human eye with contact lenses. Optom Vis Sci 2003;80(2):135-41. https://doi.org/10.1097/00006324-200302000-00009.
[416] Rae SM, Price HC. The effect of soft contact lens wear and time from blink on wavefront aberration measurement variation. Clinical & experimental optometry 2009;92(3):274-82. https://doi.org/10.1111/j.1444-0938.2009.00377.x.
[417] Marsack JD, Ravikumar A, Nguyen C, Ticak A, Koenig DE, Elswick JD, et al. Wavefront-guided scleral lens correction in keratoconus. Optom Vis Sci 2014;91(10):1221-30. https://doi.org/10.1097/OPX.0000000000000275.
[418] Sabesan R, Johns L, Tomashevskaya O, Jacobs DS, Rosenthal P, Yoon G. Wavefront-guided scleral lens prosthetic device for keratoconus. Optom Vis Sci 2013;90(4):314-23. https://doi.org/10.1097/OPX.0b013e318288d19c.
[419] Thibos LN, Cheng X, Bradley A. Design principles and limitations of wave-front guided contact lenses. Eye Contact Lens 2003;29(1 Suppl):S167-70; discussion S90-1, S92-4. https://doi.org/10.1097/00140068-200301001-00046.
[420] Hastings GD, Applegate RA, Nguyen LC, Kauffman MJ, Hemmati RT, Marsack JD. Comparison of wavefront-guided and best conventional scleral lenses after habituation in eyes with corneal ectasia. Optom Vis Sci 2019;96(4):238-47. https://doi.org/10.1097/OPX.0000000000001365.
[421] Kumar M, Shetty R, Dutta D, Rao HL, Jayadev C, Atchison DA. Effects of a semi-scleral contact lens on refraction and higher order aberrations. Cont Lens Anterior Eye 2019;42(6):670-4. https://doi.org/10.1016/j.clae.2019.06.002.
[422] Vincent SJ, Fadel D. Optical considerations for scleral contact lenses: A review. Cont Lens Anterior Eye 2019;42(6):598-613. https://doi.org/10.1016/j.clae.2019.04.012.
[423] Fricke TR, Tahhan N, Resnikoff S, Papas E, Burnett A, Ho SM, et al. Global prevalence of presbyopia and vision impairment from uncorrected presbyopia:

Systematic review, meta-analysis, and modelling. Ophthalmology 2018;125(10):1492-9. https://doi.org/10.1016/j.ophtha.2018.04.013.
[424] Papas EB. Contact lens technology to 2020 and beyond: A review of recent patent literature. Clinical & experimental optometry 2017;100(5):529-36. https://doi.org/10.1111/cxo.12596.
[425] Bailey J, Morgan PB, Gleeson HF, Jones JC. Switchable liquid crystal contact lenses for the correction of presbyopia. Crystals 2018;8(1):29.
[426] Win-Hall DM. Accommodating or focusable contact lens. *Google Patents.* US7866815B2. USA; 2009.
[427] Waite SB, Gupta A, Schnell U, Roulet J-C, Saint-Ghislain M, Troller S. Fluidic module for accommodating soft contact lens. *Google Patents.* US20170131571A1. USA: Onefocus Vision Inc; 2017.
[428] Egan W, Nibauer L. Fluid filled adjustable contact lenses. *Google Patents.* US9500884B2. USA: Adiens Beacon Inc.; 2011.
[429] Biederman WJ, Yeager DJ, Otis B, Pletcher N. Capacitive gaze tracking for auto-accommodation in a contact lens. *Google Patents.* US9442310B2. USA: Google LLC Verily Life Sciences LLC; 2016.
[430] Sako Y, Hayashi K, Nakamura T, Onuma T, Kon T, Tange A, et al. Pair of contact lenses, contact lens and storage medium. *Google Patents.* US10495904B2. USA: Sony Corp; 2018.
[431] Flitsch FA, Otts DB, Pugh RB, Riall JD, Toner A. Biocompatibility of biomedical energization elements. *Google Patents.* US20180159091A1. USA: Johnson and Johnson Vision Care Inc.; 2018.
[432] Markus DT, Hayes MC. Piezoelectric energy harvesting contact lens. *Google Patents.* US10025118B1. USA; 2018.
[433] Pugh RB, Otts DB. Ophthalmic lens media insert. *Google Patents.* US7931832B2. USA: Johnson and Johnson Vision Care Inc; 2009.
[434] Honoré F, Otis B, Nelson A. Reader communication with contact lens sensors and display device. *Google Patents.* US9128305B2. USA: Google LLC Verily Life Sciences LLC; 2013.
[435] Guillon M, Maissa CA. Multifocal contact lenses manufactured from a responsive polymer gel. *Google Patents.* US8167427B2. USA: Optometric Technology Group Ltd; 2012.
[436] Etzkorn J, Linhardt JG, Otis B. Eye-mountable device to provide automatic accommodation and method of making same. *Google Patents.* US9690118B2. USA: Google LLC Verily Life Sciences LLC; 2015.
[437] Blum R, Kokonaski W. Electro-active contact lens system. *Google Patents.* EP1947501B1. Europe: E Vision LLC; 2004.
[438] Lindhardt JG, Liu Z, Kennedy SB. Flexible conductor for use within a contact lens. *Google Patents.* US10670887B2. USA: Verily Life Sciences LLC; 2017.
[439] Burkert T, Nolan JC, Lawrenson MJ, Anderson L. Controlling a lens for adjustable vision correction. *Google Patents.* US10416478B2. USA: Telefonaktiebolaget LM Ericsson AB; 2015.
[440] Jones JC, Gleeson HF, Morgan PB. A control system for a switchable lens. *Google Patents.* US20200026099A1. USA: Dynamic Vision Systems Ltd; 2017.
[441] Lin YR, Hung CC, Chiu HY, Chang BH, Li BR, Cheng SJ, et al. Noninvasive glucose monitoring with a contact lens and smartphone. Sensors (Basel) 2018;18(10). https://doi.org/10.3390/s18103208.

[442] Ye M, Sato S. Optical properties of liquid crystal lens of any size. Japanese Journal of Applied Physics 2002;41(Part 2, No. 5B):L571-L3. https://doi.org/10.1143/jjap.41.L571.
[443] De Smet J, Avci A, Beernaert R, Cuypers D, De Smet H. Design and wrinkling behavior of a contact lens with an integrated liquid crystal light modulator. J Display Tech 2012;8(5):299-305.
[444] Milton HE, Gleeson HF, Morgan PB, Goodby JW, Cowling S, Clamp JH. Switchable liquid crystal contact lenses: Dynamic vision for the ageing eye. *Emerging Liquid Crystal Technologies IX.* 9004. International Society for Optics and Photonics; 2014:90040H.
[445] Chamberlain P, Peixoto-de-Matos SC, Logan NS, Ngo C, Jones D, Young G. A 3-year randomized clinical trial of misight lenses for myopia control. Optom Vis Sci 2019;96(8):556-67. https://doi.org/10.1097/OPX.0000000000001410.
[446] Sankaridurg P, Bakaraju RC, Naduvilath T, Chen X, Weng R, Tilia D, et al. Myopia control with novel central and peripheral plus contact lenses and extended depth of focus contact lenses: 2 year results from a randomised clinical trial. Ophthalmic Physiol Opt 2019;39(4):294-307. https://doi.org/10.1111/opo.12621.
[447] Walline JJ, Walker MK, Mutti DO, Jones-Jordan LA, Sinnott LT, Giannoni AG, et al. Effect of high add power, medium add power, or single-vision contact lenses on myopia progression in children: The blink randomized clinical trial. JAMA 2020;324(6):571-80. https://doi.org/10.1001/jama.2020.10834.
[448] Vincent SJ, Cho P, Chan KY, Fadel D, Ghorbani-Mojarrad N, González-Meijome JM, et al. CLEAR - orthokeratology. Contact Lens and Anterior Eye 2021;44(2):In press.
[449] Richdale K, Cox I, Kollbaum P, Bullimore MA, Bakaraju RC, Gifford P, et al. CLEAR - contact lens optics. Contact Lens and Anterior Eye 2021;44(2):In press.
[450] Wildsoet CF, Chia A, Cho P, Guggenheim JA, Polling JR, Read S, et al. IMI - interventions myopia institute: Interventions for controlling myopia onset and progression report. Invest Ophthalmol Vis Sci 2019;60(3):M106-M31. https://doi.org/10.1167/iovs.18-25958.
[451] Wolffsohn JS, Calossi A, Cho P, Gifford K, Jones L, Jones D, et al. Global trends in myopia management attitudes and strategies in clinical practice - 2019 update. Cont Lens Anterior Eye 2020;43(1):9-17. https://doi.org/10.1016/j.clae.2019.11.002.
[452] Douglass A, Keller PR, He M, Downie LE. Knowledge, perspectives and clinical practices of Australian optometrists in relation to childhood myopia. Clinical & experimental optometry 2020;103(2):155-66. https://doi.org/10.1111/cxo.12936.
[453] Wei X, Brennan NA, Chehab KA, Roffman JH, Wooley B. Asymmetric lens design and method for preventing and/or slowing myopia progression. *Google Patents.* AU2017202382B2. Australia: Johnson and Johnson Vision Care Inc; 2017.
[454] Lau MC, Brennan N, K. C, X. C, M. C, B. D, et al. Ophthalmic lens comprising lenslets for preventing and/or slowing myopia progression. *Google Patents.* US20180275427A1. USA: Johnson and Johnson Vision Care Inc; 20018.
[455] Brennan NA, Chehab KA, Cheng X, Moody K, Roffman JH, Wei X. Mask lens design and method for preventing and/or slowing myopia progression. *Google Patents.* US10012848B2. USA: Johnson and Johnson Vision Care Inc; 2017.

[456] Wu IT. Lens with star shaped optical zone to increase defocus image area. *Google Patents.* US10558061B2. USA: Brighten Optix Corp; 2018.
[457] Read SA, Collins MJ, Carney LG. A review of astigmatism and its possible genesis. Clinical & experimental optometry 2007;90(1):5-19. https://doi.org/10.1111/j.1444-0938.2007.00112.x.
[458] Chen C, Cheung SW, Cho P. Myopia control using toric orthokeratology (TO-SEE study). Invest Ophthalmol Vis Sci 2013;54(10):6510-7. https://doi.org/10.1167/iovs.13-12527.
[459] University of Alabama at Birmingham. Customizing myopia control with multifocal toric contact lens. *ClinicalTrials.gov.* NIH-US National Library of Medicine; 2020.
[460] Tan Q, Ng AL, Cheng GP, Woo VC, Cho P. Combined atropine with orthokeratology for myopia control: Study design and preliminary results. Current eye research 2019;44(6):671-8. https://doi.org/10.1080/02713683.2019.1568501.
[461] Kinoshita N, Konno Y, Hamada N, Kanda Y, Shimmura-Tomita M, Kakehashi A. Additive effects of orthokeratology and atropine 0.01% ophthalmic solution in slowing axial elongation in children with myopia: First year results. Japanese journal of ophthalmology 2018;62(5):544-53. https://doi.org/10.1007/s10384-018-0608-3.
[462] Vincent SJ, Tan Q, Ng ALK, Cheng GPM, Woo VCP, Cho P. Higher order aberrations and axial elongation in combined 0.01% atropine with orthokeratology for myopia control. Ophthalmic Physiol Opt 2020;40(6):728-37. https://doi.org/10.1111/opo.12730.
[463] Tan Q, Ng AL, Choy BN, Cheng GP, Woo VC, Cho P. One-year results of 0.01% atropine with orthokeratology (AOK) study: A randomised clinical trial. Ophthalmic Physiol Opt 2020;40(5):557-66. https://doi.org/10.1111/opo.12722.
[464] Huang J, Mutti DO, Jones-Jordan LA, Walline JJ. Bifocal & atropine in myopia study: Baseline data and methods. Optom Vis Sci 2019;96(5):335-44. https://doi.org/10.1097/OPX.0000000000001378.
[465] Saw SM, Matsumura S, Hoang QV. Prevention and management of myopia and myopic pathology. Invest Ophthalmol Vis Sci 2019;60(2):488-99. https://doi.org/10.1167/iovs.18-25221.
[466] Kubota RW, B.; Fehr, J-N.; Noronha, G.; Haroud, K.; Sauvet, J.; Bernhard, H.; Oggefuss, C.; Gupta, A. Optical designs of electronic contact lens to decrease myopia progression. *Google Patents.* WO2020028177A1. 2018.
[467] Zimmerman AB, Lust KL, Bullimore MA. Visual acuity and contrast sensitivity testing for sports vision. Eye Contact Lens 2011;37(3):153-9. https://doi.org/10.1097/ICL.0b013e31820d12f4.
[468] Cervino A, Gonzalez-Meijome JM, Linhares JM, Hosking SL, Montes-Mico R. Effect of sport-tinted contact lenses for contrast enhancement on retinal straylight measurements. Ophthalmic Physiol Opt 2008;28(2):151-6. https://doi.org/10.1111/j.1475-1313.2008.00541.x.
[469] Erickson GB, Horn FC, Barney T, Pexton B, Baird RY. Visual performance with sport-tinted contact lenses in natural sunlight. Optom Vis Sci 2009;86(5):509-16. https://doi.org/10.1097/OPX.0b013e31819f9aa2.
[470] Horn FC, Erickson GB, Karben B, Moore B. Comparison of low-contrast visual acuity between eye black and maxsight tinted contact lenses. Eye Contact Lens 2011;37(3):147-52. https://doi.org/10.1097/ICL.0b013e31820c6e09.

[471] Buch JR, Toubouti Y, Cannon J. Randomized crossover trial evaluating the impact of senofilcon a photochromic lens on driving performance. Optom Vis Sci 2020;97(1):15-23. https://doi.org/10.1097/OPX.0000000000001466.
[472] Hammond BR, Jr., Buch J, Hacker L, Cannon J, Toubouti Y, Renzi-Hammond LM. The effects of light scatter when using a photochromic vs. Non-photochromic contact lens. J Optom 2020;13(4):227-34. https://doi.org/10.1016/j.optom.2020.03.006.
[473] Renzi-Hammond L, Buch JR, Cannon J, Hacker L, Toubouti Y, Hammond BR. A contra-lateral comparison of the visual effects of a photochromic vs. Non-photochromic contact lens. Cont Lens Anterior Eye 2020;43(3):250-5. https://doi.org/10.1016/j.clae.2019.10.138.
[474] Vincent SJ. The use of contact lens telescopic systems in low vision rehabilitation. Cont Lens Anterior Eye 2017;40(3):131-42. https://doi.org/10.1016/j.clae.2017.03.002.
[475] Arianpour A, Schuster GM, Tremblay EJ, Stamenov I, Groisman A, Legerton J, et al. Wearable telescopic contact lens. Appl Opt 2015;54(24):7195-204. https://doi.org/10.1364/AO.54.007195.
[476] Byer A. Magnification limitations of a contact lens telescope. Am J Optom Physiol Opt 1986;63(1):71-5. https://doi.org/10.1097/00006324-198601000-00011.
[477] Tremblay EJ, Stamenov I, Beer RD, Arianpour A, Ford JE. Switchable telescopic contact lens. Optics express 2013;21(13):15980-6. https://doi.org/10.1364/OE.21.015980.
[478] Moshtael H, Aslam T, Underwood I, Dhillon B. High tech aids low vision: A review of image processing for the visually impaired. Transl Vis Sci Technol 2015;4(4):6. https://doi.org/10.1167/tvst.4.4.6.
[479] Culham LE, Chabra A, Rubin GS. Clinical performance of electronic, head-mounted, low-vision devices. Ophthalmic Physiol Opt 2004;24(4):281-90. https://doi.org/10.1111/j.1475-1313.2004.00193.x.
[480] Hicks SL, Wilson I, Muhammed L, Worsfold J, Downes SM, Kennard C. A depth-based head-mounted visual display to aid navigation in partially sighted individuals. PLoS One 2013;8(7):e67695. https://doi.org/10.1371/journal.pone.0067695.
[481] Everingham MR, Thomas BT, Troscianko T. Head-mounted mobility aid for low vision using scene classification techniques. International Journal of Virtual Reality 1998;3(4):1-10. https://doi.org/10.20870/ijvr.1998.3.4.2629.
[482] Zhao Y, Hu M, Hashash S, Azenkot S. Understanding low vision people's visual perception on commercial augmented reality glasses. *Proceedings of the 2017 CHI Conference on Human Factors in Computing Systems.* Denver, Colorado, USA: Association for Computing Machinery; 2017:4170-81.
[483] Kinateder M, Gualtieri J, Dunn MJ, Jarosz W, Yang XD, Cooper EA. Using an augmented reality device as a distance-based vision aid-promise and limitations. Optom Vis Sci 2018;95(9):727-37. https://doi.org/10.1097/OPX.0000000000001232.
[484] Hwang AD, Peli E. An augmented-reality edge enhancement application for Google glass. Optom Vis Sci 2014;91(8):1021-30. https://doi.org/10.1097/OPX.0000000000000326.
[485] Sullivan M. The making of mojo, ar contact lenses that give your eyes superpowers. *Fast Company* 2020.

[486] Dorrier J. Mojo vision's augmented reality contact lenses kick off a race to ar on your eye *Singularity Hub.* 2020.
[487] Perry TS. Augmented reality in a contact lens: It's the real deal. *IEEE Spectrum* 2020.
[488] Martin P. Mojo vision nanoleds for invisible computing. *SPIE OPTO.* 11302. SPIE; 2020.
[489] Poggio EC, Glynn RJ, Schein OD, Seddon JM, Shannon MJ, Scardino VA, et al. The incidence of ulcerative keratitis among users of daily-wear and extended-wear soft contact lenses. The New England journal of medicine 1989;321(12):779-83. https://doi.org/10.1056/NEJM198909213211202.
[490] Stapleton F, Keay L, Edwards K, Holden B. The epidemiology of microbial keratitis with silicone hydrogel contact lenses. Eye Contact Lens 2013;39(1):79-85. https://doi.org/10.1097/ICL.0b013e3182713919.
[491] Lim CH, Carnt NA, Farook M, Lam J, Tan DT, Mehta JS, et al. Risk factors for contact lens-related microbial keratitis in Singapore. Eye (Lond) 2016;30(3):447-55. https://doi.org/10.1038/eye.2015.250.
[492] Stapleton F, Naduvilath T, Keay L, Radford C, Dart J, Edwards K, et al. Risk factors and causative organisms in microbial keratitis in daily disposable contact lens wear. PLoS One 2017;12(8):e0181343. https://doi.org/10.1371/journal.pone.0181343.
[493] Lam DS, Houang E, Fan DS, Lyon D, Seal D, Wong E, et al. Incidence and risk factors for microbial keratitis in Hong Kong: Comparison with Europe and North America. Eye (Lond) 2002;16(5):608-18. https://doi.org/10.1038/sj.eye.6700151.
[494] Stapleton F, Edwards K, Keay L, Naduvilath T, Dart JK, Brian G, et al. Risk factors for moderate and severe microbial keratitis in daily wear contact lens users. Ophthalmology 2012;119(8):1516-21. https://doi.org/10.1016/j.ophtha.2012.01.052.
[495] Wu YT, Willcox M, Zhu H, Stapleton F. Contact lens hygiene compliance and lens case contamination: A review. Cont Lens Anterior Eye 2015;38(5):307-16. https://doi.org/10.1016/j.clae.2015.04.007.
[496] Szczotka-Flynn LB, Pearlman E, Ghannoum M. Microbial contamination of contact lenses, lens care solutions, and their accessories: A literature review. Eye Contact Lens 2010;36(2):116-29. https://doi.org/10.1097/ICL.0b013e3181d20cae.
[497] Py D. Contact lens applicator and cartridge used in connection therewith. In: States U, ed. *Google Patents.* US6739636B2. USA: Medinstill Development LLC; 2002.
[498] Faxe T. Package with an applicator for a contact lens. In: States U, ed. *Google Patents.* US6401915B1. USA; 2002.
[499] Greenwood AJ, Smith GSJT. Contact lens packaging. In: USA, ed. *Google Patents.* US20190046353A1. USA: Johnson and Johnson Vision Care Inc.; 2019:25.
[500] Newman SD. Packaging for disposable soft contact lenses. *Google Patents.* US7086526B2. USA: Clearlab International Pte Ltd; 2006.
[501] Nomachi M, Sakanishi K, Ichijima H, Cavanagh HD. Evaluation of diminished microbial contamination in handling of a novel daily disposable flat pack contact lens. Eye Contact Lens 2013;39(3):234-8. https://doi.org/10.1097/ICL.0b013e31828c0abe.

[502] Chang DC, Grant GB, O'Donnell K, Wannemuehler KA, Noble-Wang J, Rao CY, et al. Multistate outbreak of fusarium keratitis associated with use of a contact lens solution. JAMA 2006;296(8):953-63. https://doi.org/10.1001/jama.296.8.953.
[503] Radford CF, Lehmann OJ, Dart JK. Acanthamoeba keratitis: Multicentre survey in england 1992-6. National acanthamoeba keratitis study group. Br J Ophthalmol 1998;82(12):1387-92. https://doi.org/10.1136/bjo.82.12.1387.
[504] Schein OD, Glynn RJ, Poggio EC, Seddon JM, Kenyon KR. The relative risk of ulcerative keratitis among users of daily-wear and extended-wear soft contact lenses. A case-control study. Microbial keratitis study group. The New England journal of medicine 1989;321(12):773-8. https://doi.org/10.1056/NEJM198909213211201.
[505] Stapleton F, Dart JK, Minassian D. Risk factors with contact lens related suppurative keratitis. CLAO J 1993;19(4):204-10, https://www.ncbi.nlm.nih.gov/pubmed/8261602.
[506] Lakkis C, Anastasopoulos F, Terry C, Borazjani R. Time course of the development of contact lens case and contact lens contamination. InvestOphthalmol Vis Sci 2009;50(13):6352 (abstract), https://iovs.arvojournals.org/article.aspx?articleid=2368710.
[507] Dantam J, McCanna DJ, Subbaraman LN, Papinski D, Lakkis C, Mirza A, et al. Microbial contamination of contact lens storage cases during daily wear use. Optom Vis Sci 2016;93(8):925-32. https://doi.org/10.1097/OPX.0000000000000886.
[508] Newman SD, Coon JC, McCallum KK, Christy BV, Cheong DC, Oliver JM, et al. Contact lens package and storage case, holder, and system and method of making and using. In: States U, ed. *Google Patents.* US8069979B2. USA: 1-800 Contacts Inc; 2010.
[509] O'Hara J, Peterson CL, Maraia ML, Fehr RG, Stone MW, VanHoozer Jr TH. Countdown timer contact lens case. *Google Patents.* US7628269B2. USA; 2007.
[510] Song B. Contact lnes case with data storing feature. In: States U, ed. *Google Patents.* US7661383B2. USA; 2007.
[511] Josephson JE, Myers R, Sheardown H. Limited use, self-destructive contact lens case. In: States U, ed. *Google Patents.* US20110180429A1. USA: Compliance Case Corp; 2011.
[512] Wiley L, Bridge DR, Wiley LA, Odom JV, Elliott T, Olson JC. Bacterial biofilm diversity in contact lens-related disease: Emerging role of Achromobacter, Stenotrophomonas, and Delftia. Invest Ophthalmol Vis Sci 2012;53(7):3896-905. https://doi.org/10.1167/iovs.11-8762.
[513] Amos CF, George MD. Clinical and laboratory testing of a silver-impregnated lens case. Cont Lens Anterior Eye 2006;29(5):247-55. https://doi.org/10.1016/j.clae.2006.09.007.
[514] Dantam J, Zhu H, Stapleton F. Biocidal efficacy of silver-impregnated contact lens storage cases in vitro. Invest Ophthalmol Vis Sci 2011;52(1):51-7. https://doi.org/10.1167/iovs.09-4809.
[515] Datta A, Willcox M, Stapleton F. In vitro antimicrobial efficacy of silver lens cases used with a multipurpose disinfecting solution. Transl Vis Sci Technol 2019;8(3):52. https://doi.org/10.1167/tvst.8.3.52.

[516] Vijay AK, Zhu H, Willcox M, Ketelson H, Stapleton F. Bacterial biofilm in silver-impregnated contact lens cases. Cont Lens Anterior Eye 2020;43(4):408-12. https://doi.org/10.1016/j.clae.2019.11.004.
[517] Wu YT, Zhu H, Willcox M, Stapleton F. Impact of cleaning regimens in silver-impregnated and hydrogen peroxide lens cases. Eye Contact Lens 2011;37(6):365-9. https://doi.org/10.1097/ICL.0b013e318233c901.
[518] Dantam J, Zhu H, Willcox M, Ozkan J, Naduvilath T, Thomas V, et al. In vivo assessment of antimicrobial efficacy of silver-impregnated contact lens storage cases. Invest Ophthalmol Vis Sci 2012;53(3):1641-8. https://doi.org/10.1167/iovs.11-8197.
[519] Datta A, Willcox MDP, Stapleton F. In vivo efficacy of silver-impregnated barrel contact lens storage cases. Cont Lens Anterior Eye 2020. https://doi.org/10.1016/j.clae.2020.08.001.
[520] Tran PL, Huynh E, Pham P, Lacky B, Jarvis C, Mosley T, et al. Organoselenium polymer inhibits biofilm formation in polypropylene contact lens case material. Eye Contact Lens 2017;43(2):110-5. https://doi.org/10.1097/ICL.0000000000000239.
[521] Qu W, Hooymans JM, Qiu J, de-Bont N, Gelling OJ, van der Mei HC, et al. Nonadhesive, silica nanoparticles-based brush-coated contact lens cases--compromising between ease of cleaning and microbial transmission to contact lenses. J Biomed Mater Res B Appl Biomater 2013;101(4):640-7. https://doi.org/10.1002/jbm.b.32866.
[522] Xiao A, Dhand C, Leung CM, Beuerman RW, Ramakrishna S, Lakshminarayanan R. Strategies to design antimicrobial contact lenses and contact lens cases. Journal of materials chemistry B 2018;6(15):2171-86. https://doi.org/10.1039/c7tb03136j.
[523] Mannoor MS, Tao H, Clayton JD, Sengupta A, Kaplan DL, Naik RR, et al. Graphene-based wireless bacteria detection on tooth enamel. Nature communications 2012;3:763. https://doi.org/10.1038/ncomms1767.
[524] Willcox MD, Carnt N, Diec J, Naduvilath T, Evans V, Stapleton F, et al. Contact lens case contamination during daily wear of silicone hydrogels. Optom Vis Sci 2010;87(7):456-64. https://doi.org/10.1097/OPX.0b013e3181e19eda.
[525] Govindji-Bhatt N, Dobson C. Contact lens case changes color to signal bacterial contamination. *Interscience Conference on Antimicrobial Agents and Chemotherapy.* San Diego; 2015.
[526] Verma MS, Chen PZ, Jones L, Gu FX. "Chemical nose" for the visual identification of emerging ocular pathogens using gold nanostars. Biosensors & bioelectronics 2014;61:386-90. https://doi.org/10.1016/j.bios.2014.05.045.
[527] LeBlanc SA, Verma MS, Jones LW, Gu F. Detecting bacteria colorimetrically on contact lens cases using immobilized gold nanoparticles. Invest Ophth Vis Sci 2015;56(7):e-Abstract 2268, <Go to ISI>://WOS:000362882205269.