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Innovative Development of Contact Lenses

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Abstract

Contact lenses have been a common means of vision correction for more than half a century. Recent developments have raised the possibility that the next few decades will see a considerable broadening of the range of applications for contact lenses, with associated expansions in the number and type of individuals who consider them a valuable option. The novel applications of contact lenses include treatment platforms for myopic progression, biosensors, and ocular drug delivery. Orthokeratology has shown the most consistent treatment for myopia control with the least side effects. Recent work has resulted in commercialization of a device to monitor intraocular pressure for up to 24 hours, and extensive efforts are underway to develop a contact lens sensor capable of continuous glucose tear film monitoring for the management of diabetes. Other studies on drug-eluting contact lenses have focused on increasing the release duration through molecular imprinting, use of vitamin E, and increased drug binding to polymers by sandwiching a poly (lactic-co-glycolic acid) layer in the lens. This review demonstrates the potential for contact lenses to provide novel opportunities for refractive management, diagnosis, and management of diseases.

Keywords

contact lens; biosensor; drug delivery

It is estimated that 39 million people in the United States and 15 million in Japan wear contact lenses, with the global market size continuing to increase.^{1,2} Currently, contact lenses are almost exclusively used to correct ametropia and provide clear vision. However, recent availability of new materials and new technologies has resulted in some innovative proposals for contact lenses. Contact lenses offer new ways to deliver topical ocular and systemic drugs, assist with ocular surface disease management, control advancement of myopia in young people, and could potentially be used as novel biosensors. Many potential applications of contact lenses have little to do with vision correction. The main reason for this is the position of contact lenses in the body.³ It is well known that contact lenses sit in the visual pathway, but they are also very close to a visible portion of the vascular system and are in continuous contact with the tear film. Given that contact lenses are

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reasonably noninvasive, easy to insert and remove, and have a well-developed technical base underlying both their manufacture and physiological behavior, it is easy to understand why many individuals, physicians, and industries have noticed their potential as platforms for technologies that require access to these systems. In this review, we highlight the potential future opportunities for novel contact lenses that extend far beyond their traditional uses.

MYOPIA CONTROL

The prevalence of myopia has been steadily rising, with 28% of the global population reported to have been affected in 2010, and the proportion is estimated to reach nearly 50% by 2050.⁴ Increasing levels of myopia increase the risk of vision impairment, and particularly, high levels of myopia are associated with the risk of serious and permanent visual disability through associated sight-threatening complications. To prevent blindness associated with high levels of myopia, efforts have been made to slow the progression of myopia, and several optical and pharmaceutical strategies have been shown to be useful to varying degrees. Recently, numerous multifocal soft contact lenses and extended depth of focus soft contact lenses were found to be effective in slowing myopia.^{5,6} In contrast to overnight orthokeratology, myopia control contact lenses are worn during the day, and the hypotheses proposed to explain their efficacy are generally based on the premise that the stimulus for eye growth is a defocused retinal image with hyperopic blur either centrally or peripherally.⁷ Although the individual power profiles of contact lenses vary, they generally incorporate “positive power” to reduce the hyperopic blur and/or impose myopic defocus, or in the case of the extended depth of focus lenses, have a power profile designed to optimize retinal image quality for points on or in front of the retina.⁸ The use of soft contact lenses as a platform for myopia control offers an exciting and effective avenue to manage myopia, but there is a need for further research on issues such as clarifying the mechanism underlying myopia control, improving the efficacy of lenses, and understanding myopic regression observed on discontinuation of contact lens use. More significantly, although contact lenses are generally safe and improve quality of life in older children, a major challenge for improved uptake and acceptance of contact lenses centers on the perceived risk of complications with lens wear.

Orthokeratology

In overnight orthokeratology, the patient wears reverse-geometry lenses overnight to temporarily flatten the cornea and provide clear vision during the day without glasses or contact lenses.⁵ Reductions in myopia (up to -6 D) are achieved by central corneal epithelial thinning and midperipheral epithelial and stromal thickening. Orthokeratology lenses slow axial length growth compared with single-vision gas-permeable contact lenses, single-vision soft contact lenses, and single-vision spectacles.⁷⁻¹⁶ The first randomized clinical trial of orthokeratology myopia control demonstrated significantly slower mean axial elongation in children wearing orthokeratology lenses (0.36 ± 0.24 mm) compared with children wearing single-vision spectacles (0.63 ± 0.26 mm).¹¹ The results were similar to those in other randomized clinical trials.⁹ Orthokeratology contact lenses correct central refractive errors but leave peripheral myopic blur, which may act as a putative cue to slow the progression of myopia.¹³ A recent meta-analysis showed that in the 7 eligible studies,

myopic progression was reduced by approximately 45% after 2 years.¹⁶ The latest study involving 14 participants concluded that a trend toward a reduction in the axial elongation rate in the order of 33% was found in the orthokeratology group after 7 years of lens wear.¹⁷ In summary, orthokeratology results in an approximately 40% reduction in the progression of myopia. It has the advantage of eliminating the need for daytime contact lens wear. Its disadvantages include high cost, risk of infection, discomfort, problems with insertion and removal, and reduced visual acuity compared with glasses or daily wear contact lenses as the day progresses. More than 100 cases of severe microbial keratitis related to orthokeratology have been reported since 2001.⁶ There are no good, controlled, long-term follow-up studies demonstrating sustained myopia control effects, and there are no washout data.

Multifocal Contact Lenses

Multifocal contact lenses are available in several different formats, and although principally designed for correction of presbyopia, simultaneous designs and aspheric designs were shown to be influential in slowing progression of myopia.¹⁸⁻²²

BIOSENSORS

Development of contact lens sensors presents a noninvasive alternative for detection and management of various diseases. Recent work²³⁻²⁷ has resulted in commercialization of a device to monitor intraocular pressure (IOP) for up to 24 hours in patients with glaucoma, and extensive efforts are underway to develop a contact lens sensor that is capable of continuously monitoring glucose levels in the tear film for management of diabetes.

IOP

In the 1970s, Greene and Gilman²⁸ proposed the use of contact lenses for continuous IOP monitoring. They embedded 2 strain gauges in a soft contact lens and measured the changes in the meridional angle of the corneoscleral junction to assess fluctuations in IOP. Given the necessity to custom-fit each contact lens, cost became an insurmountable barrier to the widespread use of these lenses.²⁹

The next attempt followed a few decades later. Ziemer Ophthalmic Systems (Port, Switzerland) introduced a rigid gas-permeable contact lens with a piezoresistive pressure sensor that was centered within the lens and seated flush to the posterior surface. Lead wires, extending from the anterior surface of the sensor, were attached to a base unit that continuously recorded the IOP.³⁰ Twa et al³¹ demonstrated that the measurements were comparable to those of dynamic contour tonometry in the seated position. However, some defects of this model design were noted. The sensor was placed directly in the visual axis, thus impeding vision. Patients also reported subjective discomfort with rigid gas-permeable lens wear. In addition, the central processing unit needed to be supported and carried with caution to prevent external vector forces that would influence the IOP readings.^{29,31}

In terms of feasibility and design, the Triggerfish developed by Sensimed (Lausanne, Switzerland) has pioneered the way for the future development of contact lens sensors. The device contains a circular antenna that is placed at the periphery of the contact lens and is attached to a small microchip containing the biosensor. The system receives

power wirelessly and transmits IOP readings to an eyepiece worn by the patient.³²⁻³⁴ The Triggerfish is a soft contact lens sensor that was tested by Leonardi et al.³⁵ The contact lens sensor provides a minimally invasive method for continuous recording of IOP-related ocular patterns over 24 hours.³⁶ Patients can wear the device for 24 hours with minimal restriction in their activities. The 24-hour IOP-related ocular pattern data are retrieved by connecting the recorder to a computer. The contact lens sensor produces an electric output in millivolts. When the output is trended over time, the resulting graph is termed the IOP-related pattern or profile. The output is hypothesized to measure a composite of IOP, anterior volume change, and ocular biomechanical properties.²³⁻²⁵ Thus far, the contact lens sensor has been used safely and effectively in healthy individuals and patients with glaucoma.^{23,25,26,33} It has also been used to determine the effect of IOP-lowering interventions during a 24-hour period, particularly the nocturnal period.²⁷ With further investigation, the Triggerfish contact lens sensor (Sensimed AG, Lausanne, Switzerland) may be a useful tool for eye care practitioners in preference to the conventional Goldmann applanation tonometer (Haag-Streit UK, Harlow, UK).

Vascular Monitoring

Vascular behavior is a well-known indicator for a range of conditions that can signal the health or ill health of an individual, as well as their physiological status under conditions of exercise or stress. In the conjunctiva and retina, the eye provides 2 opportunities to directly and noninvasively observe vascular activity, and both sites have received attention for biosensing applications. In 1 patent, electronics mounted on a contact lens emit light toward the conjunctival vessels and analyze the reflection to yield information such as the blood oxygenation level and pulse rate.³⁷ A personal pulse-oximeter device like this would have clear medical applications and presumably pose a challenge to existing exercise and fitness technologies that are typically based on mobile phones or bracelets and limited to pulse rate monitoring.

Glucose Sensing

A contact lens is the ideal platform for continuous monitoring of glucose concentrations in the tear film. Several research groups are currently working on the development of contact lenses with embedded biosensors for continuous and noninvasive monitoring of tear film glucose levels. Although numerous aspects require improvement, this contact lens technology is one step closer to helping subjects with diabetes manage their condition more effectively, and these contact lenses will be able to measure tear film glucose levels and communicate the information to an internet device.

One approach to glucose detection is the use of boronic acids, which are well known to bind to diol-containing species, such as carbohydrates, through reversible boronate formation.³⁸ This unique property of boronic acids has been exploited to fabricate glucose-detecting contact lens sensors.^{38,39} Alexeev et al³⁹ described a method for producing a colorimetric contact lens sensor that can diffract light in a narrow wavelength band in the visible spectrum. Changes in the glucose concentration cause this band to shift from red to blue. The patient can determine the glucose outcome by viewing the contact lens sensor color with a compact device containing a white light source, mirror, and color chart.³⁸

In a similar manner, boronic acid derivatives can be designed to detect glucose using fluorescence. Badugu et al³⁸ demonstrated a method for synthesizing several contact lens sensors containing boronic acid fluorophores (BAFs), which induce spectral changes in the presence of sugars through an excited-state charge-transfer mechanism. BAFs can be incorporated into disposable commercial contact lenses by simple incubation for 24 hours, followed by washing with water to remove excess dye. Although BAFs in solution were shown to respond well to submillimolar glucose concentrations, the response of BAFs was notably less sensitive after their incorporation into contact lenses.³⁸

Another approach to glucose detection using fluorescence is a competitive assay with concanavalin A (conA). At low glucose concentrations, conA is bound to a competing ligand and fluorescence is minimal. As the glucose concentration increases, glucose binds to conA and releases the competing ligand, which fluoresces in response to the glucose concentration.⁴⁰ Eyesense GmbH (Großostheim, Germany) was one of the first companies to attempt to commercialize a glucose-sensing contact lens sensor based on conA fluorescence. However, initial efforts were not successful, and the company eventually opted to direct its biosensor development efforts toward an implantable subconjunctival glucose-monitoring device.⁴¹

DRUG DELIVERY

As a means of drug delivery, eye drops have a number of disadvantages. For example, dosing is periodic and does not deliver drug concentrations that are consistent over time, sleep prevents instillation for long periods, and many individuals have trouble correctly applying the drops. These and other factors may prevent a drug from being efficacious, even if it has intrinsic therapeutic value. The idea of loading the drug into a contact lens for subsequent release to the eye is an appealing solution, and was, in fact, originally proposed by Wichterle and Lim⁴² almost 60 years ago. Attempts to control IOP by, for example, soaking contact lenses in pilocarpine goes back to the early 1970s.⁴³ In the intervening years, creation of a practically useful device has been driven by the understanding that, although it is reasonably easy to load a drug into hydrogel and silicone hydrogel materials, its reemergence is typically much too rapid for therapeutic use.⁴⁴ Researchers are investigating various systems to achieve controlled and continuous drug delivery from contact lenses, using techniques such as the soaking method, molecular imprinting, vitamin E use, and poly lactic-co-glycolic acid (PLGA) drug reservoirs. We provide below a detailed discussion of the different methodologies used to develop therapeutic contact lenses, highlighting their advantages and disadvantages.

Soaking Method

The most simple, cost-effective, and conventional way to load a drug into contact lenses is the soaking method, which involves soaking preformed contact lenses in the drug solution, followed by drug uptake and release into the tear film when the contact lens is placed on the cornea.⁴⁵⁻⁴⁸ Contact lenses have internal channels/cavities for receiving/accommodating drug molecules. The drug reservoir ability is strongly dependent on the water content, lens thickness, drug molecular weight, soaking time, and drug concentration in soaking

solution.⁴⁹ As an alternative, contact lenses can be inserted into the eyes, followed by application of eye drops. By this means, drugs can be absorbed into and released from the contact lenses.⁵⁰ Use of therapeutic contact lenses prepared by the soaking method to deliver ophthalmic medications such as timolol,⁵¹ pilocarpine,⁵² dexamethasone,⁵³ hyaluronic acid,⁵⁴ and brimonidine tartrate⁵⁵ has been explored by many researchers.

Commercially available contact lenses can absorb and release drugs, but the duration of release tends to be limited to several hours.⁴⁸ Recent research has focused on extending the duration of drug release by modification of the contact lens design.^{48,56} However, no contact lenses have yet had the ability to elute a drug for weeks at a time.

Molecular Imprinting

Molecular imprinting is commonly used to increase partitioning of a solute in biomaterials. The approach relies on the creation of cavities that exhibit a very high affinity for the desired solute, designated the template. These high-affinity cavities provide binding sites for the drug, thus increasing the overall partition coefficient. When a molecularly imprinted material loaded with the drug is soaked in a release medium, the unbound drug diffuses, thereby creating a driving force for the drug bound to the imprinted cavities to desorb and diffuse. The net effect of the drug binding to the high-affinity cavities is a decrease in the effective diffusivity of the drug, resulting in an increase in the release duration.^{49,57-62} Notably, it may be feasible to design cavities with a very strong affinity, and thus the overall transport is limited by the rate of drug desorption from the cavities. However, in most cases, the transport process is diffusion-controlled with attenuated effective diffusivity.

Use of Vitamin E

To improve drug-release duration, Peng et al⁶³ proposed an approach involving in situ creation of vitamin E as a transport barrier for drug molecules. Release of timolol was significantly extended by increasing vitamin E loading from 10% to 40% in contact lenses, while simultaneously reducing oxygen and ion permeability.⁶³ Nano-sized hydrophobic vitamin E aggregates as a diffusion barrier in silicone contact lenses and were used to extend the release duration to 7 days in charged anesthetic drugs such as lidocaine, bupivacaine, and tetracaine. The developed therapeutic contact lenses can be useful for postoperative pain and photorefractive keratectomy surgery.⁶⁴ Peng et al⁶⁵ incorporated vitamin E as a diffusion barrier in Acuvue TruEye contact lenses (Johnson & Johnson, New Brunswick, NJ). They found significant IOP reductions in beagle dogs, with only 20% of the drug dose compared with eye drops therapy.

Through its powerful antioxidant property, vitamin E protects the cornea from ultraviolet radiation and also prevents oxidation of many susceptible drugs.⁶⁶ Although vitamin E was identified as a promising biocompatible diffusion barrier that can retard the release of many hydrophilic drugs, researchers should consider its limitations, including reductions in ion permeability and oxygen permeability, increase in storage modules, that is, changes in mechanical properties, and protein adsorption due to its hydrophobic nature,⁶³ which may limit the use of vitamin E for the development of therapeutic contact lenses.

PLGA Drug Reservoirs

PLGA is one of the most extensively studied materials for drug delivery applications in the body because of its biocompatibility, bioerodability, and FDA approval for use in humans.⁶⁷ It has been studied not only for ocular applications but also for tissue scaffolds and drug delivery implants in other parts of the body.⁶⁷ The material has high strength and release characteristics that can be tailored by the relative composition of lactide to glycolide in the final material.⁶⁷ Several ophthalmic drugs, including econazole, latanoprost, fluorescein, and ciprofloxacin, have been individually incorporated into PLGA and then encapsulated into 2 sides of a hydrogel material to create a contact lens drug delivery device.⁶⁸⁻⁷⁰ By dissociating the desired drug-release characteristics from necessarily being borne by the contact lens material and instead being taken up by a substance engineered for this purpose, substantial tailoring of the amount and rate of drug release can be achieved, with in vitro and in vivo reports suggesting that relevant release rates can be sustained for 1 month or more.⁷⁰ Unfortunately, the addition of a PLGA drug-release component significantly detracts from the application of these devices as contact lenses because PLGA, even in very thin layers, is at best translucent and does not transmit visible light as effectively as the hydrogel material itself.⁶⁸⁻⁷⁰ Incorporation of PLGA also has the detrimental effect of increasing the overall thickness of the lens.

CONCLUSIONS

In conclusion, the future of contact lenses seems to remain bright, with many potential innovative applications under consideration and development, by both researchers and the contact lens industry. In the short term, results from ongoing studies on the use of various optical designs and filters for myopia control probably hold the most promise. In the medium term, development of lenses that can adequately deliver topical drugs and assist with management of ocular surface diseases seems possible. In the long term, issues associated with biosensors will likely hold up the development of lenses for internet medical devices. A review of the technologies under development certainly suggests that contact lenses in 10 years will be quite different from those found at present.

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