Contact Lens Update
CLINICAL INSIGHTS BASED IN CURRENT RESEARCH

Contact lens biosensors: Can we sense our tears?

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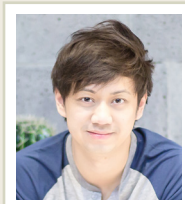

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Introduction

The last decade has ushered in an age of smart devices and wearables that have rapidly changed the way we live. Not surprisingly, this movement also has inspired the contact lens market, with over 140 million wearers worldwide,[1] to ponder what else can we do with contact lenses aside from vision correction. Researchers across the world are developing 'smart contact lenses' for ocular drug delivery,[2] myopia control,[3] visual displays,[4] and biosensing of tear film components.[5] While all of these developments are equally exciting, this overview will only address contact lenses for biosensing.

If the eyes are the windows to the soul, then the tear film is the window to the body. Tears contain not only water and salts, but also very complex proteins, enzymes, polysaccharides and lipids.[6] Even small changes in the composition of these tear components can trigger or indicate a state of disease.[7, 8] In other words, tears contain a wealth of information about our health; the challenge is how to detect and make sense of it all.

The traditional approach for analysis of bodily fluid involves collecting samples from the subject, and then analyzing them at a lab. This approach however, while highly accurate, only provides a snap-shot in time. For many diseases such as glaucoma and diabetes, the factors that need to be monitored can fluctuate immensely throughout the day, and a one-point measurement will likely miss these transient changes. The advantage of a contact lens biosensor is that it sits right in the tear film, thereby being able to provide real-time and continuous monitoring. In addition, contact lenses are also non-invasive and relatively more comfortable than current invasive methods for monitoring diseases. Therefore, a contact lens biosensor could significantly improve the management of diseases that require continuous monitoring.

Sensimed – first smart contact lens for assessment of IOP

More than 67 million people worldwide are affected by glaucoma, the second leading cause of blindness in the world.[9] The monitoring and management of intraocular pressure (IOP) is key to the successful treatment of glaucoma. Goldmann applanation tonometry (GAT) has been considered the gold standard for measuring IOP, which measures the applanation of the cornea. The limitation of this approach is that GAT can only provide a one-time measure of the IOP, which is taken typically during the day. As a result, it can easily miss transient changes in IOP, especially during the night time where the IOP is highest.[10]

Considering that a contact lens rests on the cornea, it made perfect sense to include a sensor that could potentially measure changes in IOP. In 2009, Sensimed AG (Lausanne, Switzerland) was the first company to successfully commercialize a contact lens sensor for IOP measurement (the Triggerfish® lens).[11-13] The sensor contains four circular strain gauges embedded in the lens that can sense minor changes in the circumference at

the limbus.[11-13] Consequently, IOP is measured indirectly by volume changes in the eye, in contrast to measuring the pressure via corneal applanation.[11-13] While there was initial skepticism as to how accurate this approach would be, Triggerfish® has gone through tremendous amounts of peer review to date to prove its accuracy and reliability.[11-20]

The biosensor is integrated with a wireless microprocessor and antenna for power and data transmission. The entire platform is mounted on a single-use silicone contact lens and can be worn for an entire day.[11-13] The 24-h data generated by Triggerfish® provides the clinician with a wealth of information they can use to effectively provide appropriate management for the patient's glaucoma care. More interestingly, this device has also created opportunities to study IOP fluctuations in other everyday scenarios, such as during exercise,[16] playing wind instruments,[18] and post-surgery.[17] These collective data and future data on IOP using the Triggerfish® will help shed more light on the underlying causes of glaucoma.

Evolution of the glucose-sensing smart contact lens

Diabetes affects more than 382 million people globally.[21] Control and monitoring of blood glucose is the cornerstone of successful diabetic management, which significantly improves quality of life for those affected.[22, 23] The traditional approach uses a finger prick method to sample blood glucose, which is painful, prone to infections, and inconvenient.[24] Interestingly, glucose is also present in tear fluid, and in significantly higher concentration in diabetic individuals compared to normal individuals.[25] This finding has sparked numerous attempts to develop contact lens for glucose monitoring.[4, 24, 26-39]

Initial attempts at creating a glucose-monitoring contact lens utilized optical changes in the contact lens to measure glucose concentration. One approach utilized boronic acids, which bind to glucose to provide a unique colorimetric or fluorescence change.[26, 27] Another similar method utilized concanavalin A, a protein which binds to glucose and increases in fluorescence in response to glucose concentration.[28, 29] In these approaches, the patient would need to use a hand-held device to manually measure the changes in colour or fluorescence of their lens. Since optical responses to glucose changes are difficult to quantify, these lenses would be to indicate whether an excess amount of glucose is present in the tears or not.[30]

Perhaps the most promising development in this area was spearheaded by one of Google's subsidiary, X (formerly Google X). Their approach took advantage of an enzyme-electrode-based mechanism for glucose detection. In brief, an enzyme known as glucose oxidase breaks down glucose in a series of chemical reactions into hydrogen, oxygen, and free electrons. The free electrons produce an electric current, which correlate to the glucose concentration. While this mechanism was reported as early as 1962,[40] the real challenge came in how to couple this process with electronics that could fit onto a contact lens.

It was more than a half century later that Liao et al. described a platform that could couple a glucose sensor with an antenna and wireless powering system, and also was small enough to fit onto a contact lens.[31, 32] This development ignited numerous smart contact lens projects for glucose detection, the most prominent one being led by a collaboration between Google and Novartis in 2014.[33] If successful, the contact lens biosensor would continuously monitor glucose in the tears and transmit this information in real-time to a smart phone. A smart app would then record this data and determine the appropriate response, such as telling the patient to inject their insulin, or notifying their physician.

One of the main disadvantages of using an enzymatic based system is long term stability. Enzymes are also easily affected by common sterilization methods used in the contact lens industry.[34] These limitations can be addressed by using non-enzymatic electrochemical sensors consisting of metals, such as platinum,[34] copper oxide,[35] or gold.[36] However, these sensors are naturally not as sensitive or specific as an enzyme. As a result, there has been a great deal of research in nanotechnology to produce accurate non-enzymatic glucose sensors

for smart contact lenses.[4, 24, 34-39]

Despite significant efforts by numerous researchers, experts, and global "giants" like Google and Novartis, the commercialization for a glucose sensing contact lens has still not yet materialized. In fact, the excitement behind Google and Novartis seemed to have stopped by 2018, when they announced that the development of the glucose contact lens was put on hold.[41] It seems that although there has been tremendous progress in both biosensors and the accompanying microelectronics, the underlying problem may be that measuring glucose in tears is simply not as reliable as measuring glucose in blood. For instance, there is a lag time between glucose in blood and tears that cannot be overcome with technology.[33, 42-44] Furthermore, the measurements in tears can easily be affected by environmental factors such as temperature and humidity, or interference by other biomolecules in the tears.[41] So while glucose detection with a contact lens is certainly possible, the question is whether the information is reliable enough to lead to actionable outcomes. Only time will tell.

Non-continuous sensing opportunities

While many of the current developments for smart lenses are focusing on continuous monitoring, there are also opportunities to use traditional contact lenses as a one-time diagnostic tool. A contact lens worn throughout the day absorbs significant amounts of tear components that could be analyzed for certain biomarkers indicative of diseases.[45, 46] Of significant interests are biomarkers related to dry eyes[47, 48] and cancer.[49-51] Therefore, it may be of future interest to design contact lenses with materials or nanoparticles that could bind specific biomarkers, which can then be analyzed post-wear for a particular disease.

Challenges to smart contact lenses

There are several technical challenges that need to be solved for the successful commercialization of a smart contact lens. For instance, the biosensor must be sensitive enough to detect small changes of the analyte of interest in the tear fluid. Furthermore, it needs to be integrated with an antenna and a power source in a form factor that can fit a contact lens. The entire system must also be thin and flexible enough to be comfortable to wear. Another important factor is whether the biomarker in the tear can be used as a reliable indicator. For example, for glucose there is a lag time of 20 minutes between tear glucose and blood glucose.[33, 42-44] This lag time is long enough to give the wrong information to the patient. A final consideration is the actual costs of these devices. While expensive smart lenses may be adopted by the wealthy, the innovators, and early adopters, they may not be widely accepted by the general public – which makes them a gimmick rather than a useful application.

Final thoughts

The tremendous amount of work already expended on creating a smart contact lens biosensor has created so much excitement that it has expanded to other areas, such as drug delivery and augmented reality. After all, the same platform developed to sense biomarkers in the tears could be used for a wide array of other applications in the eye. For instance, even though the Google glucose contact lens has been put on hold, the same research groups are now working on smart accommodating contact lenses and intraocular lenses.[41] The success with Sensimed Triggerfish® for measuring IOP has shown that a smart contact lens is not just science fiction, but a reality that can drastically change the ways diseases are treated. So despite all the hiccups thus far, the future for smart sensing contact lenses is looking as clear as ever.

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