Review

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Lab on the eye: A review of tear-based wearable devices for medical use and health management

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Summary **Wearable sensors have garnered considerable interest because of their great promise in terms of personalized health and disease management. Tears are a superior target for wireless, non-invasive wearable devices, and tear-based platforms have developed rapidly over the past decade. Although an increasing number of tear analytes have been found to be associated with multiple diseases, glucose still serves as a main target for tear-based wearable devices. There has been much investment and efforts to develop tear-based wearable biosensors, with contact lens-based and spring-like sensors flourishing commercially. Current efforts have moved past ocular and systematic disease markers to nutrients and chemicals. Moreover, tear-based wearable devices also have the potential to treat some ocular diseases. This review discusses aspects of tear-based wearable devices and it emphasizes that strict clinical validation is needed before such platforms enter the market. Multifunctional and theranostic strategies would further broaden their clinical use in the future.**

Keywords: Wearable devices, tears, health monitoring, disease management

1. Introduction

Wearable devices utilize sensors to monitor analytes in human biofluids to reflect physiological performance in sports or an aberrant component imbalance in diseases such as diabetes mellitus and cystic fibrosis (*1-3*). Such devices have the potential to revolutionize healthcare and disease management as a surrogate strategy for measuring circulating analyte concentrations in the blood, and especially in a dynamic, noninvasive manner (*4-6*).

Recent advances have led to multiple sensors for mechanoelectrical transduction using nanoparticles, carbon nanotubes, liquid metals, and ionic liquids (*7-10*). The key developments to date have mainly focused on skin interstitial fluid (ISF), tears, saliva, and sweat (*11-16*). Tears have substantial advantage over other biofluids, and tear-based wearable devices have emerged as a promising strategy for monitoring both ocular and common diseases.

The current review summarizes the most recent developments in tear-based wearable devices, and it emphasizes their potential uses in health status management and clinical management.

2. Advantages of tears as a biomarker source

Tears are secreted by the lachrymal gland as a protective film and are part of the anti-fouling mechanism of the eye. Tears are superior to other biological fluids as a target for wearable devices (*17*). Biomarker molecules in tears diffuse directly from the blood and their concentrations in the blood are more closely correlated than those of other biofluids such as sweat (*18*). Unlike sweat that lacks protein biomarkers, tears contain a wide variety of components including proteins, peptides, lipids, metabolites, and electrolytes and are also less complex than blood because of the blood-tear barrier (*18*). Tears possess unique merits in diagnosing specific ocular diseases and also reveal useful information on systemic disorders.

However, *in vitro* diagnoses using reflex tears,

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which are generated during emotional or mechanical stimulation, still have considerable issues due to the small sample volume, ease of evaporation, and variations in production among individuals (*19*). In contrast, basal tears that act as the protective film covering the eye surface at all times have a stable blood-related composition. Therefore, these characteristics make basal tears an attractive target for bloodless diagnosis.

Currently, tear-based sensors have focused primarily on glucose monitoring but show considerable promise for detecting other physiologically important biomarkers. The scope of new tear analytes can be expanded to include additional metabolites and key electrolytes with concentrations in tears that are closely related to those in the blood. For example, direct tear-based noninvasive assays of catecholamines may improve the diagnosis of glaucoma (*20*). Since tear fluid contains thousands of proteins – the most abundant of which are lysozyme, lactoferrin, and albumin – noninvasive tear monitoring could also be used to detect protein biomarkers correlated with various diseases. Proteomic analysis of tear samples may be one approach to identify biomarkers linked to ocular diseases (*21-25*). However, the correlation between the concentration in tears and blood and its relevance to disease progression must be extensively validated before using novel tear analytes.

3. Tear biomarkers associated with health status and diseases

Most diseases-specific biomarkers in tears have been identified using comparative proteomic profiles of diseases-related and healthy tears. Numerous novel protein biomarkers in tear fluid have been found to be correlated with some specific ocular diseases (such as dry eye syndrome, trachoma, glaucoma, keratoconus, and thyroid- associated orbitopathy) and systematic disorders (such as diabetes mellitus, cancer, systemic or multiple sclerosis, cystic fibrosis, Parkinson's disease, and sclerosis) (*17*). Cytokines, growth factors, and mucins are the most frequently validated tear biomarkers. A previous study investigated the endogenous metabolites in the tears of patients with keratoconus, and it found highly abnormal levels of tear metabolites in the urea cycle, tricarboxylic acid (TCA) cycle, and oxidative stress (*26*).

Although various potential biomarkers have been screened, none have been used clinically because their diagnostic power still needs to be validated in large cohorts. Currently, only several long-established tear analytes such as glucose and lactate have been used as targets of wearable devices.

4. Tear-based sensors for continuous analyte monitoring

4.1. *Strip-based sensors*

The earliest tear-based wearable devices were developed using electrochemical sensors on flexible or stretchable strips. Kudo *et al*. (*27*) fabricated a glucose oxidase (GOx)-based glucose sensor on a flexible PDMS substrate coated with a hydrogen peroxide permeable poly membrane to measure tear glucose concentration amperometrically. In a later study, this strategy was further improved by combining film printing technology to develop low-cost and high-fidelity ocular sensors (*28*). Although strip-based ocular sensors have been used in keratoconjunctivitis sicca, transcutaneous oxygen, and glucose monitoring, they lack the integration of sensor and data processing. Moreover, strip-shaped sensors are difficult to keep in place, and hard plastic substrates usually cause eye irritation and the subsequent formation of reflex tears, thus making them less attractive for use as a wearable device.

4.2. *Contact lens-based sensors*

Contact lens systems provide an attractive platform for fabricating tear-based sensors due to the comfort to the wearer, a consistent yield of tear fluid, excellent oxygen permeability, and the ability to provide accurate continuous monitoring.

Currently, two types of contact lens-based sensors, optical and electrochemical biosensing, have been developed (*29*). The earliest optical sensors measured tear glucose by detecting the fluorescence of molecules that competitively bind with glucose such as concanavalin A or phenylboronic acid derivatives (*29*). Several teams developed contact lenses embedded with fluorescent nanoparticles or boronic acid-containing fluorophores to obtain the glucose concentration by measuring the fluorescence intensity and resonance energy transfer. More recently, a colloidal crystal array (CCA) contact lens was able to selectively detect a visible color change reflecting variation in the glucose concentration (*30*).

Another important advance in contact lens-based sensors is electrochemical biosensing. Parviz *et al*. first used an amperometric glucose sensor based on GOx with an in-built wireless readout chip in a contact lens (*31*). Later, they incorporated a dual sensor strategy consisting of activated and deactivated GOx to minimize the interference effect (*32*). Kajisa *et al*. (*33*) developed a highly sensitive hydrogel field effect transistor (FET) glucose sensor electrode suitable for use as a tear-based wearable device. The sensor electrode can significantly suppress the signal noise caused by nonspecific adsorption.

4.3. *Spring-like sensors*

A small spring-like electrochemical sensor coated with a protective polysaccharide-based hydrogel material has been designed by NovioSense (*34*). This sensor can be placed behind the eyelid without irritation. When

coupled with wireless data transmission, this device can measure tear glucose.

4.4. *Eyeglasses-based tear biosensing systems*

Most recently, Sempionatto *et al*. (*35*) integrated a microfluidic electrochemical detector into the nose-bridge pad of eyeglasses to non-invasively monitor tear biomarkers. Unlike other basal tear-based platforms, this system directly collected and measured stimulated tears. Their work was the first to demonstrate that a wearable device could monitor tear analytes outside the eye region, therefore addressing the faults of contact lenses systems, *i.e*. the high risk of infection and vision impairment.

5. Use in healthcare and disease management

5.1. *Glucose monitoring*

Continuous glucose monitoring is particularly important for the successful management of diabetes. The convention finger prick blood test causes frequent pain and inconvenience, so monitoring the glucose level in other body fluids, and particularly in tear fluid, has emerged as a promising strategy. Glucose monitoring is the most widely applicable field of tear-based wearable devices (*36*). Two devices are preparing to enter the commercial market. The concept of a soft contact lens with integrated wireless electrochemistry electronics is now being developed by Google and Novartis, which represents an endeavor to bring contact lens-based wearable devices to the commercial market (*4*). The aforementioned tear glucose monitoring device worn under the lower eye lid developed by NovioSense is now in a phase II clinical trial involving six patients with type 1 diabetes mellitus, and a close correlation between glucose concentrations in tears and blood has been noted in animals and humans (*4,37*).

5.2. *Lactate monitoring*

Lactate is a metabolite associated with an oxygen deficiency, and lactic acidosis characterized by a persistent accumulation of lactate can lead to several life-threatening conditions. Lactate monitoring is of great importance to evaluating an oxygen deficiency in conditions such as cancers, bacterial or fungal infections, cerebral stroke, and trauma (*37-39*). Moreover, continuous lactate monitoring could also expand to sports medicine to indicate the level of an athlete's physical training. Currently, most of the lactate biosensing strategies use two enzymes, lactate oxidase (LOx) and lactate dehydrogenase (LDH) (*37*). Lactate is a main component in basal tears, and it mainly comes from the corneal epithelium. Variation in tear lactate levels is closely associated with many ocular diseases. For example, tear lactate levels decrease in deepithelialized cornea. Thomas *et al*. (*40*) developed a LOx and contact lens-based lactate sensor for real-time monitoring of lactate in tear fluid, and the sensor has a good response time, a high level of sensitivity, and a high level of stability. This device represents a promising step towards the integration of biosensors to measure tear lactate. Unlike efforts at glucose measurement, however, few efforts have been made to fabricate innovative wearable device targeting lactate.

5.3. *Ocular pressure monitoring*

Intraocular pressure is a significant indicator of ocular diseases (*41-43*). For example, increased intraocular pressure is the highest risk factor for glaucoma, which represents the most frequent cause of blindness, so timely monitoring of variations in intraocular pressure is extremely important to early diagnosis and treatment of glaucoma (*44,45*). Kim *et al*. (*46*) developed a multifunctional contact lens sensor to simultaneously monitor tear glucose and intraocular pressure. This system is based on independent different electrical responses, with one element responding to glucose binding and two other elements reflecting structural changes, thus enabling the measurement of intraocular pressure.

5.4. *Alcohol and vitamin detection*

Wearable sensing devices provide a good opportunity for the continuous and real-time monitoring of alcohol intake and intoxication. The first proof of concept of detection of alcohol in tears was performed using a thermal resistivity sensor in vapors above the eyes in the 1980s by Giles *et al*. (*47*). Recently, Sempionatto *et al*. (*35*) indicated that a wearable eyeglasses-based alcohol bioelectronic platform can be used to monitor alcohol in stimulated tears. More importantly, they found a close correlation between alcohol levels in tears and blood. An eyeglasses-based sensing platform has also been used to measure glucose and vitamin concentrations (*35*). Using rapid square wave voltammetry technology, this platform is capable of sensing multi-vitamins, which also represents a major step towards tear-based wearable devices that can monitor personal nutrition (*35*).

5.5. *Theranostic platform for modulation and detection of viral infections*

Mak *et al*. (*48*) proposed and confirmed a new concept of a wearable theranostic device targeting tears. Unlike most other monitoring strategies, this platform is both able to measure interleukin 1 alpha (IL-1α) levels and able to effectively measure herpes simplex virus type 1 (HSV-1) activity in the cornea. This device is based on a contact lens with an anti-viral coating, thus

Table 1. List of tear-targeted wearable devices that have been developed

Year	Analytes & targets	Wearable platform	Monitoring mechanism	Medical use	*Ref.*
2006	glucose	contact lens	optical (fluorescence signal)	glucose monitoring	(*29*)
2006 & 2008	glucose	strip-based sensor	electrochemical	glucose monitoring	(*27,28*)
2011	glucose	contact lens	electrochemical (GOx)	glucose monitoring	(*31*)
2012	glucose	contact lens	electrochemical (dual GOx sensors)	glucose monitoring	(*32*)
2012	lactate	contact lens	electrochemical (LOx)	lactate monitoring	(*40*)
2015	IL-1α (detection), HSV-1 (therapy)	contact lens	surface engineering technique	theranostic	(*48*)
2017	glucose	contact lens	electrochemical (FET)	glucose monitoring	(*33*)
2017	glucose	contact lens	optical (fluorescence signal)	glucose monitoring	(*30*)
2017	glucose, ocular pressure	contact lens	multifunctional electrical response elements	glucose monitoring, and intraocular pressure	(*46*)
2018	glucose	spring-like sensor	electrochemical	glucose monitoring	(*34*)
2019	alcohol, glucose, vitamins	eyeglasses	electrochemical	analyte monitoring	(*35*)

providing a defense against ocular infection. Therefore, the theranostic contact lens holds immense promise as a next-generation wearable device to diagnose ocular diseases.

6. Challenges and perspectives

With the entry of large industrial players like Google, the field of innovative wearable devices targeting tears is expected to grow rapidly, but these products are still in clinical trials and their commercial release is still a ways off. This indicates that some challenges still need to be addressed to successfully achieve a high level of sensitivity, linearity, and accuracy in detecting tear analytes (*49,50*). First, a better understanding of the correlation between analyte concentrations and variations in tear and blood is needed to improve reliability. Second, large, multi-center cohort studies need to validate the performance of tear-based wearable devices before they are used clinically.

Although some obstacles remain, tear-based wearable devices are a potentially cost-effective solution with great prospects for personalized health monitoring. An increasing number of tear biomarkers will presumably soon be used in wearable biosensing platforms. Most of the current systems focus on individual analytes, so the development of multifunctional devices targeting two or more analytes would further enhance the power of diagnosis and monitoring. As miniaturization proceeds and functional improvements are made in electronic interfaces and power sources, such wearable devices systems would represent a great benefit in therapeutic use or monitoring of drug concentrations.

Monitoring harmful chemicals in the human body or from the surrounding environment is crucial to maintaining health (*51*). A panel of organic transistor-based sensors that detect various chemicals such as sulfur dioxide and volatile organics in the human body *via* sweat and urine has been developed (*51*), but analysis of chemicals in tears has yet to be explored. Environmental chemicals might be a key target for tear-based wearable electronic devices in the future.

7. Conclusions

This review has described recent advances in wearable devices targeting tears for continuous personalized health monitoring and management of ocular and systemic diseases (as summarized in Table 1). Currently, such platforms have great prospects in various fields, and this is particularly true for multi-functional and theranostic strategies. Advances in new materials and techniques would greatly benefit the selectivity, stability, reliability, and lifetime of tear-based wearable sensors. However, great challenges still need to be overcome to achieve better performance before validated and reliable data can be obtained. The wearable sensor market is expected to grow rapidly, and particular attention should be paid and considerable efforts should be made to develop tear-based platforms.

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