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Advances in Smart Contact Lenses for Tear Glucose Monitoring: A Review

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Abstract

Diabetes mellitus, a chronic metabolic disorder affecting a growing global population, demands accurate real-time glucose monitoring for effective management. Traditional finger-prick blood glucose testing is invasive, painful, and incapable of long-term continuous monitoring, driving the development of non-invasive alternatives. Tear glucose monitoring via smart contact lenses has emerged as a promising approach due to its non-invasiveness, real-time responsiveness, and improved patient compliance. This review systematically summarizes recent progress in smart contact lens technology for tear glucose sensing.

Keywords

Diabetes Mellitus, Smart Contact Lenses, Tear Glucose Monitoring, Electrochemical Sensors.

1. Introduction

All Diabetes mellitus is a chronic metabolic disease, and the number of patients worldwide has been on a steady rise over the years. Diabetes can lead to a series of serious complications, such as cardiovascular diseases, renal failure, vision loss, and lower limb amputation [1, 2], imposing a heavy burden on both patients and society. Therefore, how to efficiently and accurately manage blood glucose levels has become the core issue in the field of diabetes research.

Traditional blood glucose monitoring methods typically involve fingertip blood sampling. This approach not only causes inconvenience and pain to patients but also affects their quality of life to a certain extent. Additionally, this method cannot achieve long-term, real-time blood glucose monitoring. Therefore, the development of rapid, painless, and frequently performable blood glucose measurement technologies is of great significance for personal health management, improvement of medical services, and optimization of social medical resources. In this context, non-invasive blood glucose monitoring technologies have gradually become the focus of attention for researchers [3].In recent years, tears, as a non-invasive body fluid, have emerged as a new approach for blood glucose monitoring due to their stable composition and convenient collection [4]. Studies have shown that there is a strong positive correlation between glucose concentration in tears and that in blood, which lays the foundation for the application of tears in diabetes monitoring [5, 6]. Furthermore, tears contain abundant biomarkers such as amino acids, enzymes, and small molecules, which can be used for various diagnostic purposes[7-10].

In recent years, with the development of the Internet of Things, materials science, and miniaturized sensing technologies [11-13], smart contact lenses with real-time monitoring capabilities have gradually evolves from a concept to reality. Breaking through the limitation of traditional contact lenses that only serve for vision correction, smart contact lenses can realize real-time monitoring of glucose levels in tears by integrating advanced sensing technologies and communication functions, providing a convenient and non-invasive blood glucose monitoring method for diabetic patients. Of course, as a contact lens that directly contacts the ocular surface, its preparation materials play a crucial role. They not only directly determine the optical performance and wearing comfort of the lens but also serve as key elements of non-invasive monitoring technology. The biocompatibility and mechanical flexibility of contact lens materials are the core factors for achieving long-term wearing safety and comfort, which directly determine the scope of application in clinical promotion and the tolerance level of patients [14]. Studies have shown that the use of high-oxygen permeability polymeric materials can significantly improve the oxygen metabolism level of corneal tissue[15], which is of special importance for smart contact lenses requiring continuous monitoring of physiological indicators. This can effectively prevent iatrogenic complications such as corneal edema [16] and neovascularization [17] caused by corneal hypoxia. Additionally, the mechanical strength and fatigue resistance of materials are key parameters to ensure the long-term reliable operation of the device. They directly affect the signal drift characteristics of embedded sensors and ultimately determine the data accuracy and long-term stability of the monitoring system. It is worth noting that with the deep integration of sensing technology and contact lenses, breakthroughs in materials science, such as the application of technologies like surface functionalization modification [18], nanocomposite enhancement strategies [19], and biomimetic microstructure design [20], can significantly expand the performance boundaries of devices. These provide new material solutions for achieving highly sensitive detection, low-power operation, and wireless real-time data transmission. Therefore, the performance of contact lens materials not only relates to biocompatibility and wearing comfort but also serves as a core factor in promoting the clinical practicalization of non-invasive monitoring technologies[21].

Based on this, this review will comprehensively introduce tear glucose monitoring technology based on smart contact lenses, including its detection principles, key technologies, material selection, and the challenges it faces (**Figure 1**). Meanwhile, this paper also discusses the potential of smart contact lenses in diabetes management and future development directions.

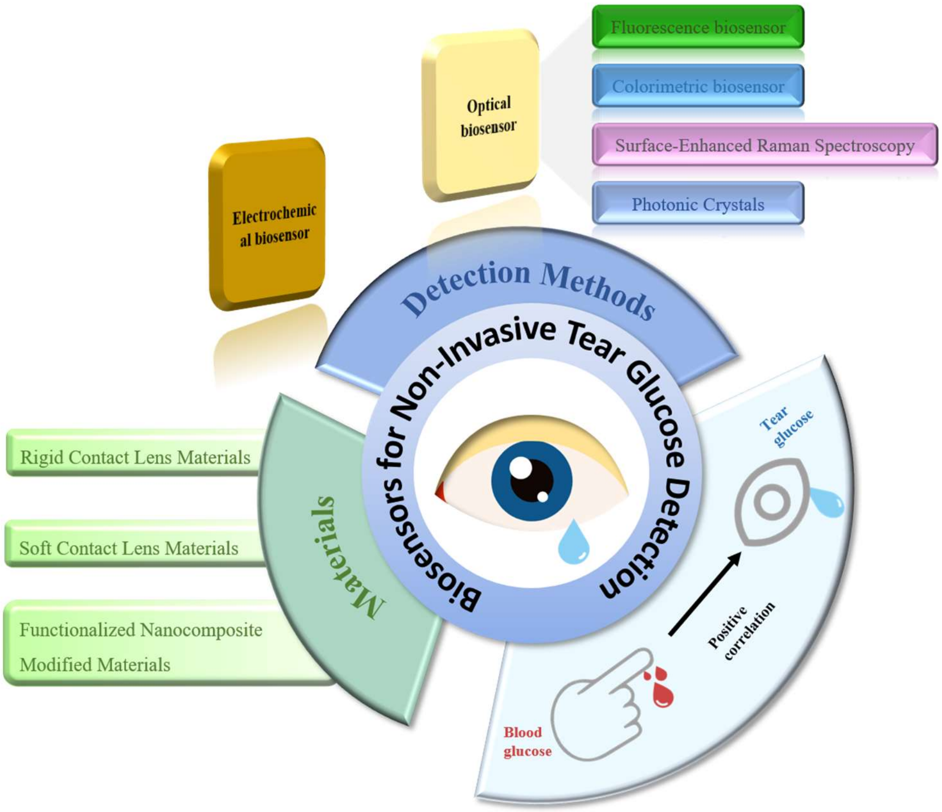

Figure 1. Detection mechanism of tear glucose and materials of contact lenses.

2. Electrochemical Methods

Electrochemical sensing technology has become one of the important methods in the field of glucose detection due to its advantages of high sensitivity, fast response, and miniaturization. In recent years, researchers have made significant progress in developing smart contact lenses capable of continuously monitoring glucose levels in tears [22-24].

Enzyme-based electrochemical sensors, utilizing the high specificity and high catalytic efficiency of enzymes, are currently the most in-depth studied and technologically mature technologies for tear glucose detection. The core of this technology resides in glucose oxidase (GOx) immobilized on the surface of the working electrode. GOx can specifically catalyze the oxidation of glucose, yielding gluconic acid and hydrogen peroxide (H_2O_2)[25, 26]. The signal transduction of the sensor is primarily achieved by detecting the changes in electrical signals during this reaction. However, it is susceptible to factors such as temperature, pH, and inactivation caused by long-term use. As Yan et al. fixed GOx on a chitosan-carbon paste electrode, the detection limit reached 0.1 mM, but enzyme activity decreased by 40% after 24 hours of wearing [27].

In view of this, to overcome the drawbacks of enzyme dependency, researchers have dedicated themselves to developing non-enzymatic electrochemical sensors[28, 29]. These sensors typically rely on materials with special properties, such as metal oxides, carbon nanomaterials, and conductive polymers, which can directly undergo electrochemical reactions with glucose without relying on enzymatic catalysis. For example, Zhou et al. [30] successfully prepared a composite material based on Fe/Co bimetal and reduced graphene oxide, using a flexible electrode to detect glucose in tears. The results showed that the flexible electrochemical sensor could quickly and sensitively detect tear glucose, providing valuable references for non-invasive diabetes diagnosis.

Compared with the high specificity of enzymes, nanocatalysts are usually susceptible to interference from other electroactive substances in tears, leading to inaccurate signals. Therefore, the current focus of research is on designing and synthesizing new types of nanocomposites to enhance their catalytic selectivity and sensitivity to glucose[31, 32]. Li et al.[33] developed a self-powered glucose-sensing contact lens. Using PB as the core electrochromic material, they constructed a sensing system by combining it with GOx, and realized glucose detection through the synergistic effect of enzymatic reaction and electrochromic effect. Through the integration of a power-free design, a multi-thickness electrode array, and color quantitative analysis, this study built a tear glucose detection device with low cost, high stability, and practicality, providing an important technical reference for the development of non-invasive wearable medical monitoring equipment. Kim et al. [34] developed hyaluronic acid -modified gold-platinum bimetallic nanocatalysts (HA-Au@Pt BiNCs) and immobilized them in a nanoporous hydrogel. By optimizing the electronic structure of Pt to enhance catalytic activity and leveraging the porous structure to accelerate mass diffusion, the team significantly improved the sensitivity and response speed of electrochemical sensing while reducing detection lag. Concurrently, the detection accuracy was validated in accordance with clinical standards such as the Clarke error grid analysis.

3. Optical Methods

Existing contact lens-type glucose monitors based on wearable electronic devices have numerous problems, such as opaque electronic materials, difficulty in integrating with soft materials, requirement for power sources, and expensive signal measurement equipment. Optical glucose sensors have been widely studied due to their convenient and rapid detection.

These methods generally do not rely on enzymatic reactions but detect glucose by analyzing the specific response of glucose molecules in tears to light.

3.1. Fluorescence Methods

Fluorescence spectroscopy, a technology based on molecules emitting longer-wavelength light after absorbing specific-wavelength light, has been widely applied in biosensing and diagnosis. Many researchers have developed smart contact lenses using the chemical properties of fluorescence for monitoring glucose, pH, and ion concentrations in tears. Although fluorescence methods have extensive applications in biosensing and diagnosis, they also have some defects. For example, most fluorescent sensors suffer from insufficient sensitivity, and given the low glucose concentration in tears, improving the sensor's sensitivity to low-concentration glucose is particularly important. Chen et al. [35] designed a fluorescence resonance energy transfer (FRET) pair composed of donor CdSe/ZnS quantum dots and acceptor dextran-conjugated malachite green (MG-dextran), which was combined with concanavalin A (Con A) with specific affinity for glucose. The nanostructured FRET sensor was assembled on a patterned ZnO nanorod array deposited on synthetic silicone hydrogel, enabling dual-modulation detection of tear glucose. The photoluminescence showed a linear correlation with glucose concentration in the range of 0.03–3 mmol/L, allowing rapid monitoring of glucose in small amounts of tears. Deng et al. [36] elected boronic acid-modified anthracene derivatives as glucose probes (GS) and rhodamine fluorophores (RDMA) as reference probes, incorporating them into a HEMA hydrogel network to design and prepare contact lenses for high-resolution tear glucose detection. By capturing fluorescent images with a smartphone and converting them into RGB signals, glucose levels were quantified. Although this simplifies the detection process, it is still affected by ambient light during practical use.

3.2. Colorimetric Methods

Colorimetric detection of tear glucose mainly utilizes specific chemical reactions to make glucose in tears act with chromogenic reagents, producing color changes, and realizes detection through the corresponding relationship between color depth and glucose concentration. The common one is the enzyme-catalyzed reaction system based on glucose oxidase. Seo et al. [37] functionalized contact lenses through a two-step method. First, the contact lens surface was coated with polytannic acid (pTA), and then 4-mercaptobenzeneboronic acid (4-MPBA) was covalently bound to pTA to obtain pTA-BA contact lenses. The contact lens can capture glucose through the reversible binding of boric acid and glucose, and then use glucose oxidase and peroxidase to make the released glucose undergo a color reaction, and reflect the glucose content through color changes.

With the development of nanomaterials, some nanomaterials also play such a role in colorimetric detection of tear glucose. For example, Jeon et al.[38] proposed detecting tear glucose based on nanoparticles embedded in contact lenses. They used contact lenses containing cerium oxide nanoparticles (CNPs), chemically conjugating CNPs with GOx. GOx catalyzes the reaction of glucose to generate hydrogen peroxide, which oxidizes colorless Ce^{3+} to yellow Ce^{4+}, achieving colorimetric detection of tear glucose.

3.3. Surface-Enhanced Raman Spectroscopy

Raman spectroscopy is a molecular vibrational spectroscopy technique that can provide "fingerprint" information of molecules with high specificity[39, 40]. However, ordinary Raman signals are extremely weak. Surface-Enhanced Raman Spectroscopy (SERS) technology can amplify the Raman signals by several orders of magnitude by adsorbing the molecules to be detected on the surface of rough noble metal nanostructures, thereby enabling trace detection[41, 42]. Integrating SERS-active substrates into contact lenses allows for the direct detection of the characteristic Raman peaks of glucose molecules in tears, achieving label-free and highly specific detection[43]. Lee et al.[44] developed a novel layered surface-enhanced Raman scattering contact lens material (SERS-LM), which integrated silk fibroin (SF) layer, 4-MPBA-modified silver nanowire (AgNWs-MPBA) layer, and protective film (PF) in a layered structure. By combining the chemical recognition capability of MPBA with the SERS signal enhancement effect of silver nanowires, a highly sensitive detection system was constructed, with a limit of detection as low as 211 nM and good linearity in the concentration range of 500 nM to 1 mM.

3.4. Photonic Crystals

Photonic crystals are artificial microstructures composed of periodic arrangements of media with different refractive indices. The sensing functionality of photonic crystals is rooted in their ability to finely modulate light. When the lattice constant of photonic crystals (i.e., the spacing of their periodic structures) is on the same order of magnitude as the wavelength of light, Bragg diffraction occurs, forming the so-called photonic bandgap (PBG). This bandgap forbids the propagation of light with specific frequencies (wavelengths) within the crystal, thereby generating a peak in the reflectance spectrum. The wavelength (λ) corresponding to this peak adheres to a modified form of Bragg's diffraction law:

$$m\lambda = 2\mathrm{d}\sqrt{(n\_eff^2 - sin^2\theta)} \tag{1}$$

Here, d denotes the lattice plane spacing, n_eff is the effective refractive index of the photonic crystal, and θ is the incident angle. For sensors embedded in contact lenses, observations are generally conducted under near-normal incidence conditions. As a result, any minor variations in d or n_eff directly induce a shift in the reflected wavelength λ, manifesting as a color change.

To enable photonic crystals to "recognize" glucose, researchers typically incorporate glucose-sensitive functional molecules into their structures. The most commonly used among these are phenylboronic acid (PBA) and its derivatives. PBA can undergo reversible covalent esterification reactions with molecules containing vicinal diols, such as glucose. When photonic crystals are combined with hydrogels containing PBA groups, the binding of glucose may lead to volume phase transition of the hydrogel or effective refractive index change. Ruan et al. [45] embedded three-dimensional polystyrene (PS) colloidal crystal arrays (3D CCAs) into 4-borobenzaldehyde (4-BBA)-modified polyvinyl alcohol (PVA) hydrogels and attached them to PMMA rigid gas-permeable contact lenses. The reversible binding of 4-BBA with glucose changes the volume of the hydrogel matrix, inducing Bragg diffraction and color changes in photonic crystals to monitor tear glucose concentration. Although this sensing device improves glucose detection sensitivity and selectivity, its sensing capability is limited because the volume change of the hydrogel is restricted by the PMMA rigid lens. The drawbacks of 3D colloidal crystal arrays include difficulties in obtaining ordered arrays, poor selectivity, and cumbersome self-assembly procedures. In recent years, monolayer colloidal crystal materials (2D PC) have gained wider attention due to their simple and rapid preparation. The research group then embedded PS-based 2D PC into 4-BBA-functionalized PVA hydrogels to construct a novel hydrogel monolayer colloidal crystal (GMCC) sensor for semi-quantitative detection of tear glucose [46]. When the glucose concentration varies within 0–20 mM, the sensor effectively diffracts visible light, and its structural color changes from red to yellow and green can be rapidly distinguished within 180 seconds.

Although the 2D PC strategy effectively optimizes preparation processes and monitoring sensitivity, obtaining visual quantitative readings remains an urgent issue in practical applications. Recently, Elsherif et al. [47, 48] successfully developed a wearable contact lens biosensor for continuous glucose monitoring using a smartphone. This system is based on onedimensional holographic polymer crystal colloidal arrays (1D PC), printing photonic crystals with 1.6 μm periodic structures on phenylboronic acid-functionalized glucose-selective hydrogel membranes and integrating them with commercial lenses. Upon binding with glucose, the gel undergoes micro-volume swelling, altering the periodic constant, thus establishing a correlation between the periodic constant and glucose concentration within 0 - 50 mM.

4. Comparison of the Limitations of Methods

Tear glucose detection based on smart contact lenses mainly relies on two core technical routes, namely electrochemical sensing and optical sensing. By integrating the principles of materials science, electrochemistry, optics, and biomedical engineering, each route has formed a relatively mature methodological system. Table 1 shows the application of smart contact lenses in different sensing mechanisms and their performances.

Although the electrochemical method can achieve rapid response through the electrical signals generated by the glucose oxidation reaction, it has weak anti-interference ability[49]. Components such as ascorbic acid and proteins in tears can undergo non-specific reactions with electrodes, leading to detection errors. Furthermore, the glucose oxidase it relies on is easily degraded by tear proteases and inactivated by fluctuations in the temperature and humidity of the ocular surface. Integrating rigid electronic components with soft, breathable, and biocompatible hydrogel contact lens materials poses a significant technical challenge. This not only requires a high degree of miniaturization but also demands solutions to a series of engineering issues such as power supply and wireless data transmission, while ensuring the flexibility, comfort, and safety of the entire device[50]. In contrast, although the optical method can achieve anti-interference detection through changes in refractive index, diffraction peaks, and other properties caused by glucose, it suffers from insufficient sensitivity[51]. Moreover, its response, which relies on the physical interaction between glucose and the sensing material, takes 15-30 minutes, which making it unable to capture rapid fluctuations in blood glucose[52, 53]. It is also susceptible to interference from ambient light and changes in the tear film on the ocular surface. Additionally, it requires regular calibration using external equipment, which is cumbersome and disrupts the continuity of monitoring. Differences in corneal refractive index among different users further increase the difficulty of calibration. These limitations of the two mainstream detection routes not only restrict their individual clinical translation potential but also highlight the necessity of exploring synergistic strategies that leverage the strengths of both technologies to address the unmet needs of non-invasive, real-time, and reliable tear glucose monitoring.

Table 1. Application of smart contact lenses in different sensing mechanisms and their performances.

Sensing mechanism	Doped materials	Detection range	Limit of detection	Reference
Electrochemical	PB	0.18–0.7 mM	0.02 mM	[54]
	HA-Au@Pt BiNCs	5 - 50 mg·dl^{-1}	0.01 mg·dl^{-1}	[34]
	Au@Pt	1 - 50 mg/dL	1 mg/dL	[55]
	PtNW,CNT	0.05 – 2 mM	0.05 mM	[56]
	ITO,PB	0.16 – 0.5 mM	0.05 mM	[33]
Fluorescence	CdSe/ZnS	0.03 – 3 mM	0.03 mM	[35]
	GS-NHS	0.1 – 10 mM	9.3 mM	[36]
Colorimetric	CeO_2	0.1 – 9.6 mM	> 0.1mM	[57]
SERS	AgNWs-MPBA	500nM - 1 mM	211 nM	[44]
Photonic Crystals	4-BBA	0 -50 mM	0.05 mM	[45]

5. Conclusion

Electrochemical and optical methods each exhibit distinct advantages in tear glucose detection, yet both face inherent limitations. Electrochemical techniques offer high sensitivity and quantitative measurement capabilities but typically rely on enzymes, presenting challenges in sensor stability and calibration. Optical methods, conversely, are enzyme-independent, easily integrated into wearable devices, and operationally simple, though they still face hurdles in sensitivity and quantitative accuracy.

Enhancing sensor stability, optimizing calibration procedures, and developing novel sensor materials represent critical steps toward commercialization. Tear glucose monitoring, as a pivotal direction in non-invasive blood glucose sensing, demonstrates enormous potential through smart contact lens technology. The advancement of smart contact lenses hinges on continuous innovations in contact lens materials to ensure wearing comfort and safety while enabling sensor integration and functional expansion. In terms of detection methods, electrochemical and optical approaches have their respective strengths. Electrochemical methods are highly sensitive but struggle with enzyme stability, while optical methods offer operational simplicity but require improved sensitivity and quantitative capability. Current technologies still face challenges in sensor stability, calibration mechanisms, device integration, and precise analysis of the tear-glucose relationship.

Future research should prioritize the development of hybrid systems integrating both technologies, leveraging the advantages of electrochemical and optical sensors to provide more accurate and reliable glucose monitoring data. The field of tear glucose monitoring via smart contact lenses is evolving toward multimodal sensing fusion and AI-assisted calibration. Multimodal fusion integrates the strengths of different detection methods by simultaneously acquiring multiple physiological parameters and signals, enhancing monitoring accuracy and reliability. AI-assisted calibration utilizes big data and advanced algorithms to account for individual differences and the complexity of the tear-glucose relationship, optimizing calibration models for improved measurement precision.

Furthermore, with continuous advancements in materials science, micro-nano manufacturing technologies, and communication technologies, smart contact lenses are expected to become more miniaturized, integrated, and intelligent. These advancements will reduce costs, enhance mass-production capabilities, and strengthen market competitiveness, propelling the transition from laboratory research to widespread commercialization and clinical application. This progression will provide diabetic patients with more convenient and precise blood glucose monitoring, improve quality of life, and contribute to global diabetes management.

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