Comparison of the Structure, Working Principle, Materials, Advantages, Disadvantages, and Performance of Four Generations of Glucose Biosensors

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Abstract. This paper mainly introduced the history of development and applications of glucose biosensors. The article first explains the basic composition and principles of biosensors, focusing on the role of glucose oxidase in blood glucose detection. Subsequently the paper systematically sorted out the evolution of four generations of glucose biosensors: The first generation of sensors relied on oxygen and were susceptible to interference, resulting in insufficient accuracy of the final results; the second generation added artificial media to improve stability and response speed; the third generation enhanced specificity and accuracy by achieving direct electron transfer between enzymes and electrodes, but it was very complex; the latest fourth generation adopted an enzyme-free design, using metal nanoparticles as electrocatalysts, with high sensitivity, low cost and excellent stability, overcoming limitations such as enzyme degradation.

Keywords: Biosensor Glucose; Generation; Nanomaterials; Electron Transform.

1. Introduction

A biosensor is a device capable of converting biological responses into electrical signals. It is an integrated receptor-transducer system with many applications, particularly in diagnosing and treating medical conditions [1]. A typical biosensor consists of five fundamental components: the analyte — the substance to be detected, the bioreceptor — a biological recognition element that interacts specifically with the analyte, the transducer — which converts the biorecognition event into a measurable signal, the electronics — responsible for signal amplification and processing, and the display — which presents the final results in a readable format [2]. Glucose biosensors are essential for diabetes care, yet non-invasive monitoring remains underdeveloped. This research gap presents opportunities for progress, with advances in nanomaterials and wearable technologies offering a foundation for future innovation, as shown in Figure 1.

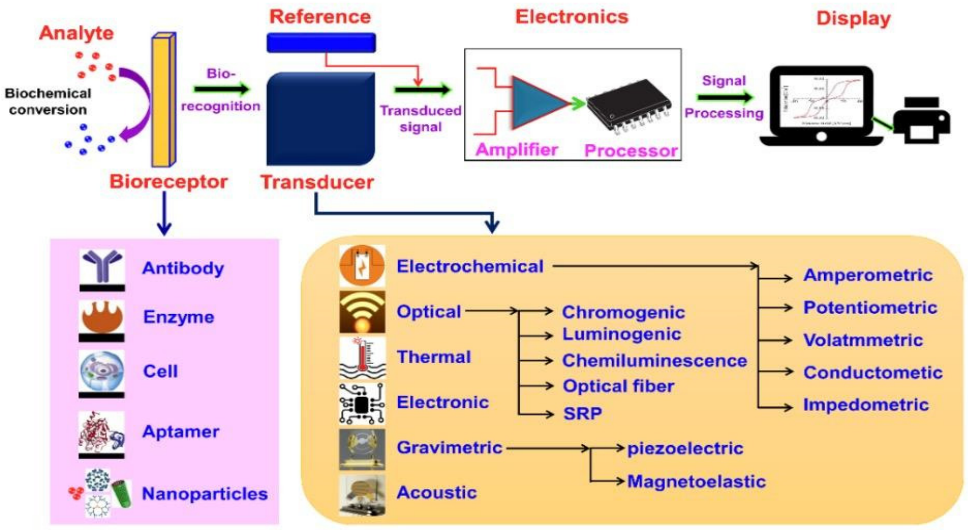

Figure 1. Key components of a biosensor, including the analyte, bioreceptor, electronics, and display. [1]

This review aims to provide a comprehensive understanding of the development and progression of glucose biosensors, highlighting how each generation has addressed the limitations of its previous generation. Given the global prevalence of diabetes and the critical role of accurate blood glucose monitoring in disease management, research in this field is of considerable importance. Advances in biosensor technology improve patient outcomes and contribute to the broader pursuit of accessible and reliable healthcare solutions. Therefore, this study aims to analyze the evolution of glucose biosensors, evaluate the strengths and limitations of each generation, and consider future directions that may lead to more effective, stable, and user-friendly devices.

This passage will focus exclusively on the glucose biosensor.

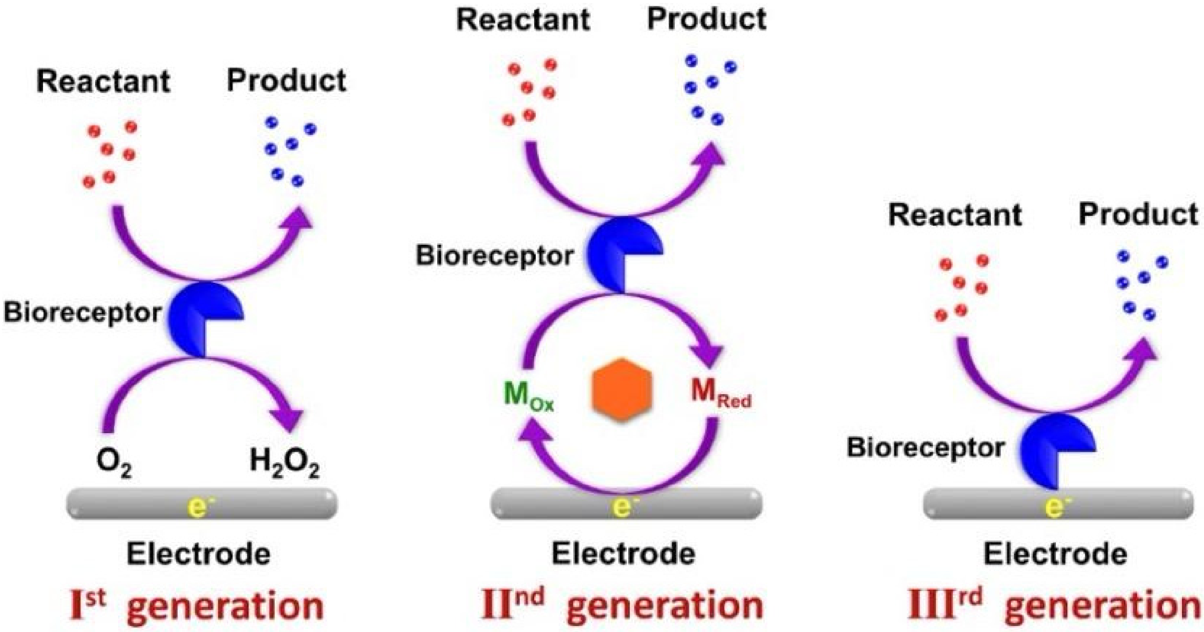

Figure 2. Illustration of the three generations of biosensors.[1]

2. Development of Glucose Biosensors

Various glucose biosensors have been developed over the past several years, each with distinct working principles, materials, and technological advancements. In the following sections, this passage will explain each type in detail, highlighting their structure, mechanism of action, and practical applications. A glucose biosensor is an analytical device that combines a biological sensing element, such as glucose oxidase, with a physicochemical transducer to detect and measure glucose concentration. This type of biosensor is widely used in clinical diagnostics, especially for monitoring blood glucose levels in patients with diabetes [3]. In 1976, Clemens et al. applied the glucose biosensor to develop a “bedside artificial pancreas.” [4,5] Additionally, the LA 640 lactate analyzer is an improved device that enhances the transfer of electrons from lactate dehydrogenase to the electrode, enabling accurate and efficient measurement of lactate level [6]. In 1987, researchers at Cambridge University in the United States developed a pen-shaped glucose meter to measure blood glucose levels quickly and conveniently.

2.1 The First-generation Biosensor

The first type of glucose biosensor operates by detecting either the concentration of the analyte—glucose in this case—or the molecular products generated from its enzymatic reaction. These molecules diffuse to the sensor's surface, undergoing electrochemical reactions that produce an electrical signal. The magnitude of this signal is directly proportional to the glucose concentration in the sample [7]. This type of biosensor is referred to as a mediator-less amperometric biosensor because it does not utilize artificial electron mediators; instead, it relies on natural electron acceptors such as oxygen. The enzyme glucose oxidase catalyzes glucose oxidation to gluconic acid in this system. During this enzymatic reaction, oxygen is reduced to hydrogen peroxide (H_2O_2). The hydrogen peroxide produced, or oxygen consumption, is then electrochemically detected at the electrode surface. This generates an electrical current that is directly proportional to the glucose concentration in the sample. This method was first described experimentally by Leland C. Clark Jr. in 1962, following his earlier foundational work on the oxygen electrode published in 1956[8].

2.2 The Second-generation Biosensor

The working principle of the second-generation glucose biosensor involves integrating artificial electron mediators into the sensor's biological recognition layer. These mediators are typically small molecules with redox activity, such as nanomaterials acting as electron shuttles. They transfer electrons from the active site of enzymes—such as glucose oxidase, catalyzing glucose oxidation—to the artificial mediators. During this redox reaction, electrons move from the glucose molecule to the enzyme and then to the mediator. The electrons are transferred directly to the electrode, generating an electrical signal. The current produced is proportional to the glucose concentration in the sample. This design enhances analytical efficiency, particularly regarding response speed and signal strength.[4,5]

2.3 The Third-generation Biosensor

In the third-generation glucose biosensors, a direct electron transfer is established between the enzyme and the electrode, eliminating the need for intermediate electron carriers such as mediators or nanomaterials. The enzyme is immobilized onto the electrode surface, allowing efficient direct electron transfer between the enzyme’s active site and the electrode without needing oxygen or artificial mediators and eliminating any intermediate electron-transfer steps. This direct interaction transfers electrons straight from the enzyme’s active site to the electrode surface. This approach improves the specificity and stability of the sensor by simplifying the electron transfer pathway and reducing interference from external substances. The design often involves modifying the electrode surface with conductive materials or nanostructures to facilitate efficient electron tunneling between the enzyme and electrode [9,10].

2.4 The Fourth-generation Biosensor

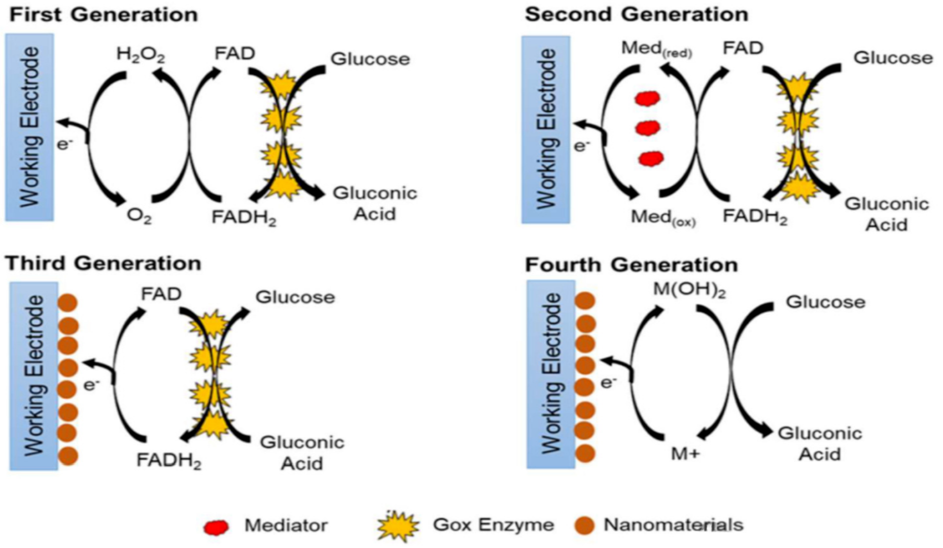

Figure 3. This picture illustrates the evolution of glucose biosensors from the first to the fourth generation. Technological advancements have made glucose biosensors increasingly efficient, offering faster response times and greater convenience in glucose detection.[1]

The most recent development in glucose biosensors is the fourth-generation glucose biosensor. Ghasemi et al. presented a novel non-enzymatic glucose sensor type, which significantly departs from traditional enzyme-based designs. This sensor is based on gold–nickel bimetallic nanoparticles embedded in an aluminosilicate framework, which was synthesized from agricultural waste material, making the approach cost-effective and environmentally friendly.

Instead of relying on enzyme-catalyzed redox reactions, this biosensor uses metallic nanoparticles as electrocatalysts to oxidize glucose directly. Electrons are transferred directly to the electrode surface through the nanostructured material, generating an electrical signal. The device demonstrated a wide linear detection range and a low detection limit, key indicators of its high analytical performance. This structure improves sensitivity and stability and eliminates the drawbacks of enzyme degradation and interference from other biomolecules [11].

3. Limitations and Future Prospects

3.1 Limitations

Despite the glucose biosensor's significant process improvements over four generations, several critical limitations remain unresolved. Noninvasive monitoring, though highly attractive, continues to face difficulties related to measurement accuracy, long-term stability, and user comfort. Enzyme-based sensors, while offering high specificity, are constrained by enzyme degradation and interference from coexisting biomolecules, compromising their durability and reliability. These persistent issues indicate that future sensitivity, selectivity, and operational robustness improvements are still urgently required.

3.2 Future Prospects

New approaches have emerged to address these challenges. For noninvasive monitoring, optical or chemical platforms based on nanomaterials can provide higher accuracy and stability, using other, more stable and predictable materials. Metal nanoparticles are being tested to overcome enzymatic degradation and see if they can offer greater durability and interference resistance. Furthermore, advances in microsensor and wireless communication technologies transform biosensors into wearable and implantable devices, achieving greater flexibility and enabling continuous, real-time blood glucose monitoring.

4. Conclusion

Glucose biosensors have developed significantly from the first to the fourth generation, becoming increasingly advanced and convenient. The first-generation sensors had the simplest structure but were highly susceptible to oxygen interference, often leading to inaccurate measurement results. The second-generation devices introduced artificial mediators to replace oxygen as the electron acceptor. This enhancement improved the stability of the sensors and allowed them to function more reliably under a broader range of conditions.

The third-generation biosensors further advanced the technology by enabling direct electron transfer between the enzyme and the electrode. This eliminated the need for mediators, increased specificity, and improved the accuracy of glucose detection. However, more complex electrode surface modifications were required to ensure effective electron transfer. Most recently, fourth-generation glucose biosensors have moved away from enzymatic systems entirely. These non-enzymatic sensors utilize metal nanoparticles as catalysts, offering high stability, low production cost, and the ability to operate without biological enzymes. As a result, they are well-suited for industrial applications and harsh environmental conditions, where traditional enzyme-based sensors may fail. As glucose biosensors continue to develop, future research will focus on improving their measurement accuracy, making them more compact, and enabling them to connect to phones. One of the most critical areas is the possibility of making glucose biosensors wearable or implantable. This will allow more detailed and real-time monitoring of diabetic patients, and there is hope for non-invasive use.

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