

The Applications of Electrochemical Biosensors in Blood Glucose Monitoring

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Abstract. In recent years, more and more people are aware about their health conditions, and the measures and technologies of monitoring people's health conditions have updated at the same time. Diabetes is a type of disease that would cause severe effects to other organs in the human body and there is an increasing number of patients with diabetes in recent years. Hence preventing diabetes or monitoring the glucose content in diabetes patients is crucial. Electrochemical biosensors are the devices that can be used for disease monitoring, diabetes is the disease that is included. For monitoring the glucose levels continuously and providing comprehensive safeguarding to the patients, Continuous Glucose Monitoring (CGM) which is based on the electrochemical technology is employed. This essay gives a general introduction to electrochemical biosensors and their relative practical applications. Overall, the electrochemical biosensor demonstrates its application in a real-time monitoring of the glucose level in the human body. This research focuses on the principles of converting information from the working electrodes in electrochemical biosensors into electrical signals, the principle of recognizing target analyte in the testing sample and the principle of CGM system and its practical performance.

Keywords: Diabetes, Electrochemical sensor, CGM.

1. Introduction

The latest information about the worldwide number of patients who have diabetes, given from the International Diabetes Federation (IDF), shows that there are 11.1% of the adults who aged from 20 to 79 years old are suffering from diabetes. The predicted number of people who have diabetes in 2050 would increase significantly, which will reach a number that is approximately 853 million [1]. Type 2 diabetes could increase the risks of cardiovascular disease, stroke and atherosclerosis, which will damage a patient's heart and blood vessels. The blood vessels and lens in patient's eyes could also be damaged, the diseases called glaucoma and cataracts which can lead to blindness may also occur. Obviously, diabetes is a disease which is harmful to many organs. Consequently, it will cause a significant decrease in the life quality of patients. Therefore, preventing diabetes and controlling the blood glucose level in an individual's daily life is essential.

Continuous Glucose Monitoring (CGM) is a useful tool for preventing diabetes and reducing the negative effects from the diabetes by detecting the blood glucose content continuously and reminding users to control their blood glucose level. The patients with diabetes should have several blood glucose content monitoring every day, the time is dependent on the type of diabetes of the patients. Therefore the CGM system plays a key role in monitoring the patient's blood glucose content. The component for detecting glucose level in the human body is electrochemical biosensor, which employs the electrochemical technology for converting the information from chemical reaction into the electrical signals. For instance, in the chemical reaction (redox reaction), there is a transfer of the electrons, which will generate a current as an electrical signal that can be detected, and the magnitude of the current can reflect the concentration of the target analyte in the sample solution. Mostly, some biological molecules such as enzymes, antigens and antibodies are immobilized on the surface of the working electrodes in the electrochemical biosensors. These biological molecules act as bio recognition elements because they can only bind to specific molecules, which indicates that the specificity of electrochemical biosensors can be guaranteed. Besides, the time taken for response of the electrochemical biosensors is short and this type of biosensors have a good limit of detection

(LOD), these facts imply that the electrochemical biosensors can give reliable information on the concentration of the blood glucose [2].

Firstly, the second section in this essay gives information on the working principles of various types of electrochemical biosensors, including enzyme-based biosensor, non-enzymatic biosensor and non-invasive biosensor, the different methods of generating electrical signals. Secondly, in the third section, the working principle of the CGM system, the methods the non-invasive sensor monitors the glucose level and the practical performance of the CGM system are introduced. The fourth section mainly discusses about the technical challenge the electrochemical biosensors currently face are introduced in the third section, the materials of producing the working electrodes which can help in maximizing the sensitivity of electrochemical biosensors are also included in this section. The future perspectives of the currently used electrochemical biosensors are discussed in section five. Including the environmental impact the biosensors will cause, the psychological impacts to patients who wear CGM sensors and the ability of reducing the effects from interferons that electrochemical biosensors should improve further in the future.

2. Principle of Electrochemical Biosensors

2.1. Electrochemical Biosensors and Their Principles

Based on the methods for generating electrical signals, the electrochemical biosensors are categorized into three main types: amperometric, potentiometric and impedimetric biosensors [3]. In addition, electrochemical biosensors can also be classified according to the type of bioreceptor used. This section mainly discusses the types and operating principles of various electrochemical biosensors.

2.1.1 Potentiometric biosensors

A biosensor that uses the potentiometric technique is called potentiometric biosensor. For detecting electrical signals, ion-selective electrodes (ISEs) and ion-sensitive field-effect transistors (ISFETs) are used to detect electrical signals. When ions in the solution accumulate at the ion-selective electrode, an electrical signal can be detected [3]. A potentiometric biosensor measures the electromotive force (EMF) or the potential difference between the working electrode and a reference electrode under conditions of the current is approximately zero. The measured potential difference is correlated with the concentration of a target ion in the detected solution [2]. For practical applications that require the support of real-time data, a potentiometric biosensor is an appropriate choice. In addition, since no continuous flow of current is required, the sample solution undergoes minimal change.

2.1.2 Amperometric biosensors

An amperometric biosensor detects the current which is generated from the reduction or oxidation of an electroactive substance under a potential difference applied with a constant value [2]. Amperometric biosensors have higher sensitivity and are more suitable for being produced in a large-scale production than the potentiometric biosensor [3]. Due to their relatively high accuracy, they can detect current even when the analyte is present at very low abundance. However, these biosensors can be susceptible to background signals [4].

2.1.3 Impedimetric biosensors

The working principle of an impedimetric biosensor involves applying a small AC voltage to the working and counter electrode, with different potentials between the working electrode and the reference, then measuring the resulting AC response, and determine the impedance of the electrochemical cell from the difference between the working and reference electrodes [2].

2.2. Types, Immobilization and Using of Bioreceptor

Bioreceptors used in electrochemical biosensors include biological molecules such as enzymes, antibodies and nucleic acids. They exhibit high selectivity which means they bind only to specific biological targets, and this selectivity will result in the accuracy of the biosensors. Immobilization of the bioreceptor is an essential step in producing the biosensors. For immobilizing the enzymes, both covalent and non-covalent immobilization methods are the most common methods, including covalent binding and physical entrapment. When immobilizing the enzymes, their active sites should remain exposed to ensure the function of enzymes can work normally [5].

2.3. Principle and Applications of Enzyme-based Biosensors

In enzyme-based biosensors, enzymes act as bioreceptors. These enzymes integrate with the transducers of the biosensor to convert the information from the redox reaction of the electroactive substances into electrical signals. Immunosensor and glucose biosensors have been developed using this technique. In immunosensors, antibodies or antigens are immobilized on the surface of the electrodes, the binding of the antigens and antibodies will generate electrical signals, which can be analyzed to gain the results [4].

2.4. Non-enzymatic Electrochemical Biosensors

Non-enzymatic biosensors do not have any biological elements such as enzymes. Instead, the functionalized nanomaterials are used as catalysts or as platforms for immobilizing the analyte. The stability of this type of biosensor is higher than the enzymatic biosensors due to the absence of the easily denatured enzymes [6].

3. Applications in Glucose Monitoring System

3.1. Principle of CGM

Continuous Glucose Monitoring (CGM) is a technique that measures the glucose content in humans and records the glucose content with maximum 1,440 glucose readings every day, with sensors measuring at this glucose value with an interval of 1-5 minutes. A CGM system includes a sensor, a transmitter, and a receiver. The sensor can be either enzymatic or non-enzymatic electrochemical biosensor. The sensor is typically worn on the subcutaneous tissue of the arm. After measuring the glucose levels in the tissue, the transmitter processes and transmits the glucose information to the receiver. The receiver, such as a mobile phone application, reader device and insulin pump receives the glucose data and makes a response to the patient if the glucose levels are abnormal [7]. In affinity-based CGM systems, interactions between the glucose and the glucose oxidase or other glucose binding proteins are used. After these glucose-affinity molecules bind to the glucose, the electrical signals can be then generated. These signals are proportional to glucose concentration, consequently, the glucose level in the human body to be determined. Since biological molecules are used, affinity-based sensors can be affected by the pH value and the temperature [8].

3.2. Non-invasive CGM sensor

In order to collect and monitor glucose levels in the human body precisely, choosing the sample from skin interstitial fluid is essential. This is because the interstitial fluid carries nutrients. However, the interstitial fluid is located in subcutaneous tissue. In order to detect the glucose levels from those interstitial fluids without invasions puncturing the skin, extracting those interstitial fluids to the skin surface is crucial. Several methods are available for extracting the interstitial fluid from subcutaneous tissue, including reverse iontophoresis, remote intradermal, and transdermal iontophoresis. In the transdermal iontophoresis, a small current is applied to two electrodes which are attached to the skin, causing ions to move. Positively charged sodium ions migrate toward the cathode of the neutral glucose molecules in the same direction [9]. In addition, detecting the glucose molecules by using

sweat provides an alternative approach. In wearable sensors, glucose can be detected through electrocatalytic oxidation of glucose under the alkaline conditions occurs in a wearable sensor. A highly negative pretreatment potential is applied to reduce the proton concentration in sweat. A positive potential is then applied to detect glucose [10].

3.3. Practical Performance and the Benefits of CGM System

The anti-interference capability of the CGM system reflects its measurement accuracy. The CGM biosensors are often affected by the biological molecules, temperature fluctuations, and electromagnetic disturbances. As previously mentioned, the CGM systems can monitor the glucose levels continuously throughout the day, with the readings updated frequently. In addition, the CGM systems support taking action to prevent hypoglycemia [7].

4. Technical Challenges and Limitations

4.1. Stability, Life Span and Performance of Electrochemical Biosensors

The electrodes in an electrochemical biosensor are the key components responsible for detection. As time passes by, the electrodes will become less sensitive. This decline occurs because the performance of electrochemical sensors is affected by environmental factors such as temperature fluctuations, pH variations and the presence of interfering molecules or substances. As previously mentioned, biological molecules are immobilized on the electrodes of electrochemical biosensors, where chemical reactions between the biological molecules and the analytes occur in the electrodes of the biosensor. Therefore, the choosing of materials used for making the electrode is crucial. In other words, the sensitivity of an electrochemical biosensor relies on the properties of the working electrodes. Materials which have porous structure are suitable for constructing working electrodes. This is because a porous structure indicates the material has high surface area, facilitating chemical reactions to occur [11]. The nanomaterials can enhance the adsorption capacity of the biological molecules and simultaneously improve the response time of the device can be also improved [12]. Fabricating the electrodes of electrochemical biosensors by using the carbon nanofibers (CNF) is an effective strategy to enhance the working performance of the biosensor. This is because they have porous structure, stable mechanical characteristics, and high electrical conductivity [13]. Moreover, CNFs enhance the electrocatalytic activity, which indicates that this property can improve the practical performance of the electrochemical biosensors [6].

The forth-generation of CGM sensors represents a type of electrochemical biosensor designed for detecting glucose levels. This generation of CGM sensors employ non-enzymatic technology, generating electrical signals through the direct oxidation of the glucose molecules. Since the charge is transferred directly in this CGM sensor, its performance in the detection of glucose is improved. However, the susceptibility to the electrical noises may result in gaining the incorrect or inaccurate results [8]. In addition, most of the CGM sensors are designed for a limited wear period, typically ranging from 7 to 15 days [7].

4.2. The Impact of Interference

Apart from the intrinsic stability of electrode materials, another major challenge influencing the accuracy of electrochemical biosensors is the interference from non-target substances in biological samples. For the enzyme-based electrochemical biosensors, the pH value of the sample is crucial to the accuracy of the results and the life span of the biosensor. The enzymes may be denatured if the pH value of the sample is extreme or deviates from the optimum pH range for the enzyme immobilized on the surface of the biosensor. As previously mentioned, the electrochemical biosensors detect electrical signals generated from the redox reaction of the analytes. Therefore, if non-target ions are present in the sample solution, the result of detection gained will be inaccurate because the unwanted redox reactions may occur [4].

4.3. Limitations in Clinical Uses

4.3.1 Skin responses to the CGM wearable sensors

For CGM systems, wearable glucose sensors may cause several adverse skin reactions in patients. For instance, patients may experience non-specific cutaneous conditions [7].

4.3.2 Using problems and challenges to the patients

Since individual health conditions vary, applying alarms and setting the same threshold value for alarming the patient is not suitable, and may lead to alarm fatigue. Another big barrier to the clinical adoption of CGM systems is to provide education to the patients. Patients should understand the components of the CGM system as well as the methods of reading and understanding the data from the CGM system. In addition, overcoming the negative psychological impacts is a tough task to the patient, as some patients may feel uncomfortable with the appearance of wearing a glucose sensor [7]. This psychological issue will cause a decrease in the probability of patients who are willing to use the CGM system to monitor their glucose level.

5. Perspectives

5.1. The Uses of New Materials and Technologies in Detecting Blood Glucose Content

Although recent electrochemical biosensors have high sensitivity, selectivity and real-time monitoring capabilities, there are still some challenges. Since there is an increasing demand for disposable electrochemical biosensors, the public should pay more attention to their biodegradation of the disposable electrochemical biosensors [14]. Developing environmentally friendly electrochemical sensors is necessary and this aim can be achieved by employing or developing new materials for producing the electrodes. In addition, applying AI algorithms to the CGM system to process and analyze the electrical signals can reduce the negative effects the interferons bring efficiently, hence a more accurate and reliable glucose level result can be obtained.

5.2. Perspectives in Using the CGM Sensors in Clinical Field in a Large-scale

One of the most important factors for large-scale clinical adoption of CGM sensors is the extent of the acceptance of the patients. In other words, patients should receive a proper CGM system education before using a CGM system and gain a thorough understanding of how the CGM sensors and the overall system function. They need to clearly understand the components of the CGM device, therefore they can correctly wear and remove it. In addition, the ability to interpret CGM data is also essential for patients to monitor their current blood glucose levels and address potential safety issues. CGM systems also play a crucial role in strengthening the awareness of hypoglycemia and reminding the individuals with diabetes to better control their daily glucose intake [7]. Apart from providing education to the patients, choosing another material the sensor used, which is comfort and the patients are not allergic to is crucial for improving the wearing feedback. In addition, customizing alarm settings can reduce the probability the sensor gives an inappropriate alarm to the patient. The CGM system should set different safety glucose content ranges to different patients, hence more reliable and accurate data can be obtained. Given these benefits, CGM systems have a strong potential for large-scale clinical application, provided that patient education is also implemented.

6. Conclusion

This review mainly outlined the current types of electrochemical biosensors and their working principles for generating electrical signals, the introduction to the CGM system and highlights the critical role of electrochemical biosensors in glucose monitoring and diabetes management. Based on the methods of generating the electrical signals, these electrochemical biosensors can be categorized into 3 main types, which are amperometric, potentiometers and impedimetric biosensors. All of these

3 types of electrochemical biosensors convert the information from the reaction on the electrodes in biosensors into electrical signals, hence people can gain the information on the content of the analytes from the sample, in this case, the glucose content in the human body could be determined. In the most common electrochemical biosensors, biological molecules are immobilized on the surface of the working electrodes in the electrochemical biosensors. These biological molecules can help in recognizing the presence of target molecules in the sample. For improving the stability of electrochemical biosensors, removing the biological molecules such as enzymes, immobilized on the electrodes, and choosing a material with porous structure could be good ideas. For collecting the sample from the human body, an invasive method can let the electrochemical biosensor measure the glucose level in the human body directly. However, a non-invasive method for determining the glucose level would cause a little damage to the skin. For example, this method extracts the interstitial fluids from the subcutaneous tissue and then starts detection.

The glucose level of patients with diabetes should be monitored under a system which provides support from monitoring glucose level continuously to sending alarms to the patients if the glucose content is beyond the safe range. This system is a CGM system. This can be used for controlling the glucose level in humans and it also plays a significant role in preventing diabetes and hypoglycemia. Moreover, providing the education of the CGM system to the users can improve the effect of using feedback, the CGM system can work in a more efficient way.

The future developments of both the electrochemical biosensor and the CGM system should focus on the following key issues: The stability and the accuracy of the electrochemical biosensors should be further improved, applying AI algorithms to the CGM system to process and analyze the electrical signals, employing or developing new materials are appropriate choices. Consequently, people can gain more reliable information about their glucose levels, and a more effective treatment for the patients can be implemented. Besides, for giving a more efficient glucose level monitoring, providing comprehensive understanding of the CGM system to the patients or the CGM system users is a crucial part. As the glucose monitoring technology develops, some of the negative effects brought from the drawbacks of electrochemical biosensors could be reduced in the future. In addition, humans can gain more accurate and reliable data on their glucose levels in blood as the electrochemical technology improves in the future.

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