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REVIEW ARTICLE

Progress in the study of enzyme-free glucose electrochemical sensors

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ABSTRACT

The detection mechanism of enzyme-free glucose electrochemical sensors, the research progress of enzyme-free glucose sensors based on composite materials such as noble metals, transition metals and doped carbon nanomaterials, and the latest progress of new wearable enzyme-free glucose detection devices are reviewed. With the development of science and technology, enzyme-free glucose sensors will potentially be applied to the in vivo detection of animal and plant species, which will become a hot spot for new research.

Keywords: enzyme-free; glucose sensor; electrode modification; in vivo detection

1. Introduction

Glucose is an important component of carbohydrates in plants and animals. The development of new devices and instruments for the quantitative determination of glucose in living organisms is of great importance for advancing research in the field of in vivo glucose detection. The development of new and efficient enzyme-free glucose sensors is a key issue in the field of sensor development. The development of new and efficient enzyme-free glucose sensors is a key issue in the field of sensor research and development. However, research into the real-time monitoring of glucose levels in living plants and animals is still in its infancy and is the focus of research and development by scientists.

In 1962, Clark and Lyons first introduced the concept of using glucoamylase electrodes in electrochemical assays and prepared the first glucoamylase electrode[1]. After decades of development, glucose sensor technology has become more mature and is widely used in clinical medicine and phycological testing, for example, in the detection of blood glucose levels during the treatment of diabetes. According to Grand View, a leading global research institute, the market for Continuous Glucose Monitoring (CGM) sensors in China will reach US$55 million by 2024. Therefore, the development and application of glucose sensors is of increasing interest to researchers.

This paper provides an overview of how electrochemical glucose sensors work, discusses their current status and recent developments, and outlines

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the main challenges and opportunities for their further development and use, with a focus on the application of enzyme-free glucose sensors for in vivo detection.

2. Development of glucose sensors

2.1. Enzyme-based glucose sensor

For the classification of glucose sensors, the common electrochemical glucose sensors can be divided into enzyme-based glucose sensors and non-enzymatic glucose sensors (NEG), depending on whether enzymes are used. Depending on the type of electronic medium used, enzyme-based glucose sensors can also be subdivided into three generations of sensors. Throughout the development of glucose sensors, the first to third generations of sensors have been based on the principle of bio-enzyme catalysis as the core of the reaction, with improvements focused on increasing the electron migration rate at the reaction interface.

The first generation of enzyme-based glucose sensors used the immobilisation of an enzyme on an electrode enzyme[2]. Glucose Oxidase (GOx) uses Flavin Adenine Dinucleotide (FAD) as a carrier for the redox reaction. Oxidation of glucose to gluconolactone and hydrogen peroxide, while obtaining the reduced form of the enzyme GOx ($FADH_2$). GOx ($FADH_2$) reacts with dissolved oxygen to produce hydrogen peroxide. The concentration of glucose in the initial sample can be determined by measuring the consumption of oxygen or the production of hydrogen peroxide[3,5].

Equations involved in the catalytic reaction of the first generation of glucose sensors:

$$GOx(FAD) + glucose \rightarrow GOx(FADH_2) + gluconolactone$$
$$GOx(FADH_2) + O_2 \rightarrow GOx(FAD) + H_2O_2$$

There are two main problems with first generation glucose sensors: Firstly, the presence of many electroactive interfering substances in the blood that can be oxidised, and the relatively high detection potential of H_2O_2, at which the interfering substances are co-oxidised, leading to interference with the experimental results; and secondly, the reliance on free oxygen as a catalytic medium. The former produces interference effects that reduce the selectivity of the sensor, while the latter makes the sensor ineffective in detecting defective oxygen samples[3,5]. Therefore, the first generation of sensors is not suitable for analysis of practical applications[5].

The researchers have improved on the first generation of sensors by replacing the biological mediator oxygen with an artificial mediator to develop a second generation of glucose sensors. The second-generation glucose sensor technology uses a non-physiological artificial medium to speed up the electron transfer process and overcome the interference problems of the first generation[4]. The reaction equations involved in second generation glucose sensors are as follows:

$$GO_x(FAD) + glucose \rightarrow GOx(FADH_2) + gluconolactone$$

$$GOx(FADH_2) + Med_{(ox)} \rightarrow GOx(FAD) + Med_{(red)}$$

In the reaction equation, $Med_{(ox)}$ is the oxygenated medium and $Med_{(red)}$ is the reduced medium.

The electron transfer rate between the enzyme and the electrode is increased due to the replacement of the artificial medium, but the medium is still required. The media may still react with interfering substances in the blood, affecting accuracy and efficiency. It is very difficult to maintain the presence of the mediator near the surface of the electrode and enzyme[5]. Therefore, scientists set out to study new glucose sensors that do not require the introduction of external media.

With the further development of new nano-functional materials, direct electron transfer (DET) between enzymes and electrodes becomes possible, and the third generation of glucose sensors emerges as the times require. This type of sensor immobilizes the enzyme directly on the electrode surface, which further improves the free electron transfer rate between the electrode and the enzyme.

No medium is the main advantage of the third-generation sensor. There is no interference from electroactive substances during the reaction process, and there is no dependence on dissolved oxygen. At the same time, the interference effect caused by the competition between the dissolved oxygen and the electrode to regenerate enzymes is greatly reduced[5].

The reaction equation involved in the third-generation glucose sensor is as follows:

$$glucose + FAD \rightarrow gluconic\ acid + FADH_2$$

The principle of the third-generation enzyme-based glucose sensor is shown in **Figure 1**. Although the enzyme-based glucose sensor occupies the main market in the glucose sensor industry, it still cannot get rid of the influence of environmental factors on the activity of the enzyme, such as ambient temperature, humidity, pH value, etc., because its sensitivity depends largely on the activity of the enzyme[4]. The stability of the enzyme has also become a great obstacle in the development and application of enzyme-based glucose sensors.

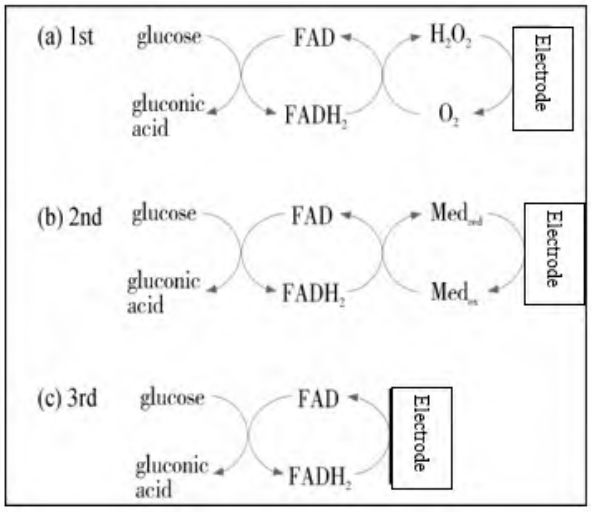

Figure 1. Principles of the first, second and third generation enzymatic glucose sensors[2].

2.2. Enzyme-free electrochemical glucose sensor

Enzyme-free electrochemical glucose sensors are based on electrodes or modified materials on electrodes to replace biological enzymes to generate electrocatalysis. Compared with enzyme-based glucose sensors, its biggest advantage is that it is easy to achieve long-term and stable target detection, breaks through the limitation that biological enzymes are susceptible to failure due to environmental temperature, pH value and other factors, and provides an optimized interface for rapid electron migration. It can provide support for high-performance continuous monitoring application scenarios.

Currently, two models exist for explaining the mechanism of non-enzymatic electrochemical glucose sensors: The activated chemisorption model (**Figure 2**) and the Incipient Hydrous Oxide Adatom Mediator (IHOAM) (**Figure 3**). The former proposes that the electrocatalytic reaction requires the adsorption of the substrate (glucose) to the catalyst surface (electrode surface) to form bonds with the unfilled d orbitals of the catalyst. The latter is a model proposed by Burke, demonstrating that the formation of a monomolecular front layer of hydroxide is one of the keys to the electrocatalytic process of glucose. The active hydroxide ions generated after the dissociation of water on the electrode surface are involved in the electro-oxidation process of glucose and many organic small molecules, so the enzyme-free glucose sensor can show high sensitivity under alkaline conditions[2,4,6].

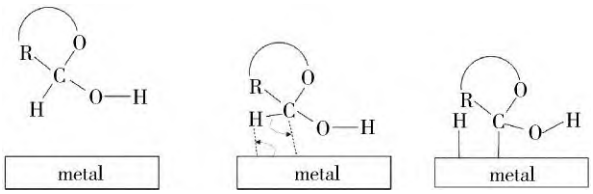

Figure 2. Activated chemisorption model[4].

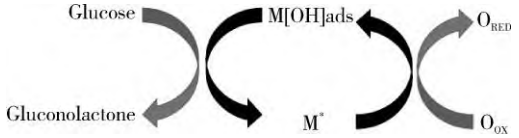

Figure 3. IHOAM model[4].

The emergence of non-enzymatic glucose sensors has provided more choices in the selection of materials for glucose sensors, and the way to increase the effective surface area is no longer limited

to the stacking of enzymes. Due to the advantages of high catalysis and high sensitivity for the oxidation of glucose, such as noble metal materials, transition metals and composite materials doped with carbon nanomaterials, etc. Therefore, their selection as modification materials to modify the electrodes of glucose sensors has also become an effective way to enhance the effective area of the glucose sensor reaction and the interfacial electron migration rate. The catalytic ability of the working electrode is also no longer limited to biological enzymes, and the application of noble metals, transition metals and doped carbon materials will lead to further enhancement of the detection performance of glucose sensors.

3. Research progress of electrode modification methods

At present, in the field of electrochemical sensors, carbon electrodes are widely used because of their advantages of good chemical stability, wide electrochemical stability window, and low background current. Commonly used carbon electrodes are glassy carbon electrodes and carbon paste electrodes[7]. However, due to the defects of bare electrodes, modifiers are required to improve performance. This paper mainly describes the research progress of modified electrodes synthesized by noble metals, transition metals, and composite materials doped with carbon nanomaterials. These modification methods provide reliable ideas for the application of enzyme-free glucose sensors in in vivo detection.

3.1. Sensors decorated with precious metal materials

Platinum (Pt), gold (Au) and other noble metal materials have excellent catalytic properties, and their nanoparticles are often used to modify electrodes to promote the catalytic oxidation of glucose. Pt has high catalytic activity for compounds such as glucose and hydrogen peroxide. Porous nano-Pt has the characteristics of high sensitivity and strong anti-interference ability, and has excellent selectivity and catalytic activity to glucose[8]. Wesley et al.[8] used $H_{14}Cl_{16}O_6Pt/CuSO_4$ solution as electrolyte and used cyclic voltammetry to electrodeposit porous nano-Pt films on screen-printed carbon electrodes for the fabrication of glucose sensors. As shown in **Figure 4**, it has good chemical stability, a wide linear range (up to 13 mM, as shown in **Figure 5**), and a short response time (less than 5 s).

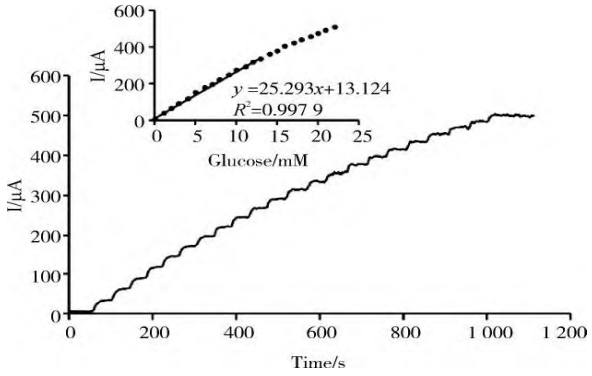

Figure 4. The current response of the nanopore electrode to the continuous addition of 1 mM glucose (0.4 V) to PBS buffer (0.1 M). Insert: Calibration curve for amperometric response[8].

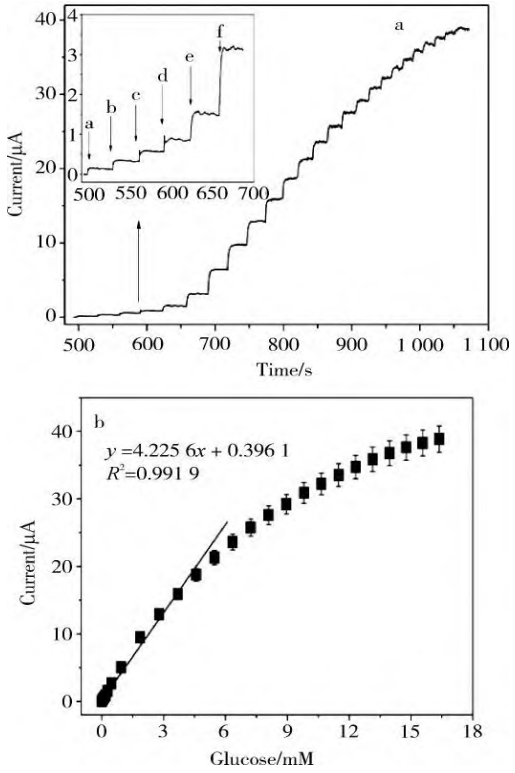

Figure 5. (a) GO-COOAu/GCE at + 0.35 V on grape Amperometric responses of sugar additions of 0.02 (a), 0.04 (b), 0.06 (c), 0.08 (d), 0.1 (e) and 0.2 mM glucose (f). **(b)** Calibration curve of the amperometric glucose assay[9].

In alkaline medium, the rate of Au catalyzing the oxidation of glucose is better than that of other Group VII noble metals such as Pt. Therefore, Au is also an excellent modifier for the preparation of enzyme-free glucose sensors[9]. Yusuf et al.[9] de-

posited Au nanoparticles on carboxylated graphene oxide (GO-COOH) and modified them on glassy carbon electrodes as working electrodes for glucose sensors. The sensitivity of the sensor prepared by the GO-COO-Au glassy carbon electrode reached 20.218 μA/(mMcm2). As shown in **Figure 5**, in an alkaline environment, the linear range is 0.02 to 4.48 mM under the condition of + 0.35V, which broadens the Linear range with detection limits down to 6 μA. However, the sensor showed almost no response in neutral glucose solution, and only showed excellent performance under alkaline conditions, which would be limited for in vivo detection of plants with a pH value of less than 7.

3.2. Sensors decorated with transition metalsand their oxides and hydroxides

The transition metals Cu, Ni, oxide Cu_XO, NiO and hydroxide materials all have good selectivity and stability for the catalytic oxidation of glucose, and they have a very large price advantage. Therefore, such modified materials are widely used in electrode modification of glucose sensors at this stage. Cobalt oxide has good bio-compatibility, wide band gap, high stability, low cost and good reproducibility. At the same time, the electrochemical performance of cobalt oxide and its selectivity to glucose can be improved by doping Since its porous with other nanomaterials[10]. The preparation cost of nickel is low and the preparation is simple. Under alkaline conditions, it has a high electrocatalytic ability for glucose[11]. Xu[10] used a hydrothermal method to fabricate 3D Co_3O_4/Ni heterostructures on porous Ni materials, as shown in **Figure 6**.

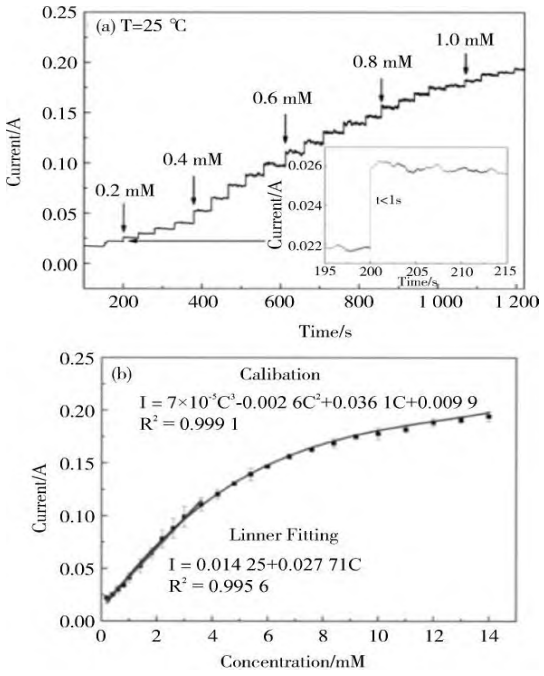

Figure 6. (a) The current responses of the glucose sensor based on the 3D Co3O4/Ni heterostructure sensing electrode to different glucose concentrations at room temperature. Inserted is the response time of the sensor to changes in glucose concentration. **(b)** Measured data and the amperometric response calibration curve of the sensor to glucose concentration. Each concentration was repeated three times, and error bars indicate deviations[10].

Since its porous structure provides multiple electroactive sites, it is favourable for the oxidation reaction of the electrode surface with glucose. The sensor has a sensitivity of 13,855 μA/(mMcm2). The detection limit was reduced to 1 μM. The detection limit is an important performance parameter of the sensor, and how to optimize the detection limit has always been a focus of researchers in the sensor field. Moreover, metallic nickel has the characteristics of non-toxicity[11], so it is expected to be used in the detection of living organisms. However, since nickel only exhibits excellent catalytic activity under alkaline conditions, how to apply it to the in vivo detection of acidic fruits and vegetables requires further exploration by scientists.

CuO has received extensive attention from scientists due to its good electrochemical activity and low overvoltage during electron transfer[12]. In 2019, Cheng et al.[12] applied transition metal-containing porous organic frameworks (MOFs) to the construction of enzyme-free glucose sensors, and constructed the MOF structure of porous CuO

polyhedrons on carbon cloth. The sensor has a sensitivity of 13,575 μA/(mMcm2) and a detection limit of 0.46 μM, which further reduces the detection limit. In 2020, Ashwini et al.[13] used gold nanowire electrodeposition to modify the CuO nanoelectrode on the basis of the same use of CuO nanomaterials to catalyze glucose. This structure further increases the specific surface area of the electrode, improves the catalytic activity, the sensitivity is 1,591.44 μA/(mMcm2), and the detection limit is greatly reduced to 0.3 μM. In the same year, Luo et al.[14] used Cu-MOF microcrystals as raw materials to prepare a porous nanolayered CuO structure as a catalytic material for the working electrode of an enzyme-free glucose sensor. The sensitivity of the sensor is 1,806.1 μA/(mMcm^2), the linear range is 0–6.535 mM, and the detection limit drops to 0.15 μM, which reduces the detection limit of the sensor again. The optimization of these properties benefits from its porous hierarchical structure.

3.3. Composite-modified sensor doped with carbon nanomaterials

Carbon nanomaterials have become one of the latest research hotspots in the field of glucose sensors due to their excellent performance in glucose catalysis. According to its morphology, it can be divided into one-dimensional (such as carbon nanotubes) and two-dimensional (such as graphene oxide). Carbon nanotubes have large specific surface area, excellent electrical properties and good biocompatibility[15]. Zhao[16] et al. used carbon nanotubes to prepare a carbon nanotube-nickel/boron-doped diamond composite electrode (CNTs-Ni/BDD), Ni nanoparticles themselves can catalyze glucose, and the composite carbon nanotubes increase the specific surface area and electrode active sites of the BDD electrode, and at the same time, the carbon nanotubes enhance the electronic conductivity. Therefore, using the composite material to modify the electrode greatly improves the catalytic activity of the electrode to glucose, and its sensitivity is 0.005–0.02 mM, 0.02–1 mM, 1.0–5.5 mM, respectively, at the glucose concentration. The linear range of mM was 475, 42, 19 μA/(mMcm2), respectively, and the detection limit was 0.42 μM. Hun et al.[17] developed a 3D material based on nitrogen-doped graphene-carbon nanotubes and gold nanoparticles and applied it to an enzyme-free glucose sensor. The introduction of carbon nanotubes between graphene nanosheets can avoid the problem of large charge transfer resistance of graphene, good dispersion of carbon nanotubes can avoid the aggregation of graphene, and graphene nanosheets as "surfactant" can disperse carbon nanometers tube, forming a network structure with large specific surface area and excellent electrical conductivity. As shown in **Figure 7**, the modified electrode has excellent performance, with a linear range of 2 μM to 19.6 mM, a sensitivity of 0.9824 μA/(mMcm2), and a detection limit of 500 nM, which further improves the sensitivity and reduces the detection limit.

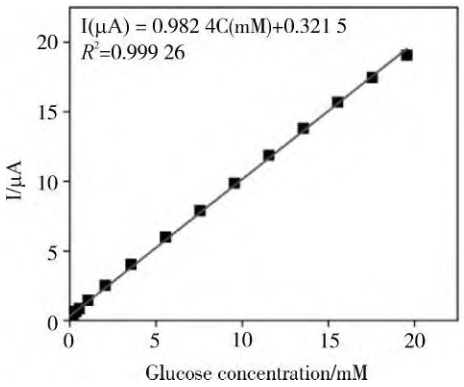

Figure 7. The relationship between current and glucose concentration[17].

The two-dimensional nanomaterial graphene has good electrical conductivity, large specific surface area, and its honeycomb two-dimensional structure can increase the electron transfer rate.

Graphene oxide also has the characteristics of being easy to combine with other materials, so that it can be prepared into functional composite materials with good comprehensive properties[18,19]. For example, Xue[20] et al. prepared persimmon tannin-reduced graphene oxide-platinum-palladium alloy (PT-RGO-Pt-Pd) nanocomposite. graphene oxide is easily combined with other materials, combined with persimmon tannin to form a thin film,

wrapping metal particles, enhancing the stability of the composite material, and graphene oxide itself has excellent electrical conductivity, so it improves the catalytic conductivity of the electrode. The sensor modified by the composite material has high stability and fast response (<3 s), with a detection limit of 1.43 μM and a linear range of 0.01 to 0.40 mM, as shown in **Figure 8(a)**. The electrode is suitable for a neutral detection environment with a pH of 7 to 8. As shown in **Figure 8 (b)**, at pH=6 (Curve a), pH=7 (Curve b), and pH=8 (Curve c), pH=9 (Curve d), pH=10 (Curve e) in the PBS solution using time amperometric method to detect glucose, the large current value appears between Curve e and Curve d, that is, the pH value is between 7 and 8.

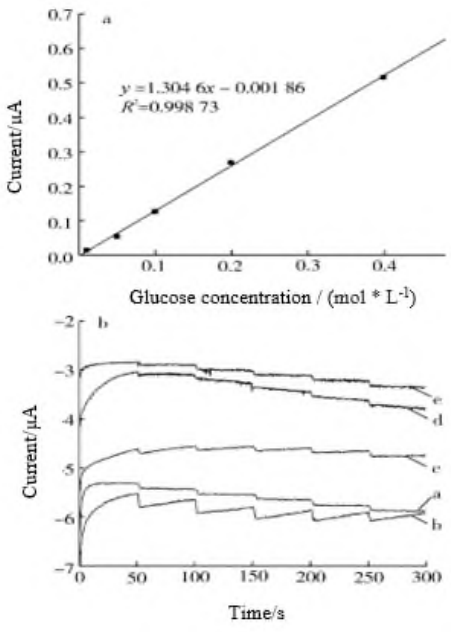

Figure 8. (a) Effects of different pH on the performance of persimmon tannin-reduced graphene oxide-Pt-Pd enzyme-free blood glucose sensor. **(b)** Glucose standard curve[20].

This is a major breakthrough compared to previous sensors, many of which only showed excellent performance under alkaline conditions. There are organic acids in the fruits of many crops, and the juice is acidic. Therefore, the application of non-enzymatic glucose sensors to the in vivo detection of plant fruits needs to overcome the limitation that many current electrodes are only suitable for alkaline environments. The development of an enzyme-free glucose sensor that can be used in acidic conditions will further promote its application in vivo detection.

Carbon nanomaterials are easy to combine with other materials, and composite materials doped with carbon nanomaterials have many advantages for modifying non-enzyme glucose sensors, such as enhancing electrode specific surface area, enhancing current, etc. Therefore, there are many studies on doping carbon nanomaterials in modified materials to improve the performance of sensors. In the modification process of composite materials, attention should be paid to how to make various materials compatible with each other to form a stable structure, and some materials will be difficult to modify on the electrode. For example, Zhao et al.[16] needed to overcome the difficulty of co-modifying BDD with Ni nanoparticles and carbon nanotubes when preparing carbon nanotube-nickel/boron-doped diamond composite electrodes (CNTs-Ni/BDD).

4. Application of non-enzymatic glucose sensor in vivo detection

Enzyme-free glucose sensors have a series of advantages, such as high specificity, fast detection speed, portability, low cost, and low power consumption. In recent years, glucose sensors have developed rapidly and have deep applications in agriculture, biotechnology, medicine and many other fields. At the same time, scientists have gradually developed new sensor structures for the detection of living organisms, such as minimally invasive painless devices, wearable flexible devices, etc. The above-mentioned various electrode modification methods provide ideas for in vivo detection. Most of them use carbon electrodes or metal electrodes as electrode substrates, and on this basis, modify the materials to improve their performance. Difficulties encountered in applying non-enzymatic glucose sensors to in vivo detection of animals and plants. For example, how to replace the base electrode in the existing research to make it suitable for living body detection, how to make the sensor fit with the living body, and how to ensure that the sensor

living body detection is not toxic to the living body, etc., are the research hotspots of scientists.

4.1. In vivo detection in animals

In 2015, Lee et al.[21] developed a new patch-type enzyme-free biosensor for painless continuous blood glucose monitoring, which used a platinum black sensing electrode layer micro-needle array. Micro-needle arrays were fabricated using micro-machining techniques and 316 L commercial stainless steel. They inserted the sensor part into rabbits and performed blood glucose monitoring experiments in rabbits. The sensor was able to operate normally for four days, with a sensitivity of 1.62 μA/mM and a linearity of 0.9939. In 2018, Li et al.[22] established an enzyme-free Online Electrochemical System (OECS) for the first time, as shown in **Figure 9**. The sensor can be used for the continuous determination of glucose in animal brain systems, an in vivo application of an enzyme-free glucose sensor. In the same year, Yoon et al.[23] developed a wearable enzyme-free glucose detection system, and through two animal experiments, proved that the system has good bio-compatibility. With the further in-depth research, more and more wearable devices for animal live detection are gradually being developed.

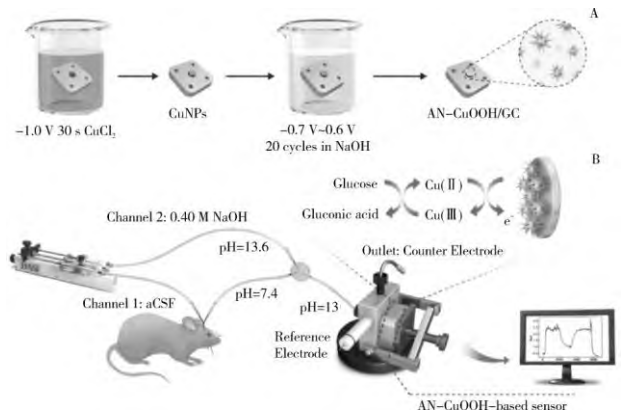

Figure 9. Schematic diagram of continuous monitoring of rat striatal glucose by non-enzymatic electroanalysis system based on OECS[22].

4.2. Human wearable enzyme-free glucose sensor

In the medical field, the application of sensors in blood sugar detection of diabetic patients is one of the hotspots. Diabetes is a disease caused by insufficient insulin production or ineffective use of insulin in the body, and its incidence has continued to rise in recent decades. Currently, there are two drawbacks to the traditional glucose monitoring methods on the market. One of the disadvantages is that most blood glucose monitoring systems on the market rely on enzymes to catalyze glucose oxidation, and the disadvantage of enzymatic sensors is that their performance is easily affected by the environment, such as pH, temperature, humidity, etc. This disadvantage has been mentioned above, and it is very disadvantageous for patients to monitor their glucose levels in real time. The second disadvantage is that the traditional glucose monitoring method usually samples the blood from the fingertip of the patient first, and then tests the blood glucose of the sample, which will cause certain damage to the physical and mental health of the patient.

For the first disadvantage, compared with enzyme-based sensors, enzyme-free sensors are not constrained by the constraints brought by enzymes, and have many advantages, such as high stability, simple preparation, strong reproducibility, and no oxygen limitation. Therefore, an enzyme-free glucose sensor is more beneficial for diabetic patients to monitor glucose levels stably in real time. For the second disadvantage, non-invasive biosensors currently under development can solve this problem. To address the above shortcomings, researchers are focusing on combining non-invasive and non-enzymatic glucose sensors.

Wearable biosensors are non-invasive sensors that have attracted much attention due to their ability to provide continuous, real-time physiological information through dynamic, non-invasive measurement of biochemical markers in biological fluids such as sweat, tears, saliva, and tissue fluids[23]. Most of the current wearable glucose sensors require the use of enzymes (mainly glucose oxidase), there are still few mature wearable non-enzymatic glucose sensors for human blood glucose detection, and there are many studies on in vivo detection in

animals, and wearable sensor devices are gradually being developed.

In 2017, Munje et al.[24] studied a sweat-based wearable diagnostic biosensor made of room temperature ionic liquid, which used a ZnO thin film deposited on a nanoporous polyamide film. It is demonstrated that ionic liquids can enhance the stability of wearable sensor devices. With the birth of wearable sensor devices, it has also been applied in the detection of glucose, which has replaced the method of fingertip blood collection to a certain extent. Sampling in a non-invasive way can avoid damage to the stratum corneum, the outermost protective layer of human skin, and avoid direct contact between the device and blood. Therefore, the non-invasive detection method brings less harm and less risk of wound infection in patients.

In addition, the breakthrough in the development of flexible electrodes combined with non-invasive glucose detection is also conducive to further reducing the discomfort caused by patients during the glucose detection process. Through the use of advanced materials and sophisticated design, wearable devices have certain flexibility and stretch-ability to achieve patient body compliance and reduce wearer discomfort[23].

In 2018, Zhu et al.[25] prepared a wristband-type wearable enzyme-free glucose by covering fluorocarbon-based materials on gold electrodes. The sensor, shown in **Figure 10**, is used to monitor the glucose concentration in human sweat in real time and upload the detection results to a smartphone app via Bluetooth. During monitoring, multiple different potentials are used on the Au electrode corresponding to different uses. Among them, the high negative potential is used for sample pre-treatment, which generates alkaline conditions on the local surface of the electrode; the medium potential is used to detect the glucose concentration in the sample, and needs to be used in the sample. carried out in an alkaline environment. A positive potential is used to clean the electrode surface. The detection limit is 15 μM, and the sensitivity can reach 114 μA/(mMcm2). The birth of the wearable glucose sensor has greatly influenced the home blood glucose monitoring method of diabetic patients.

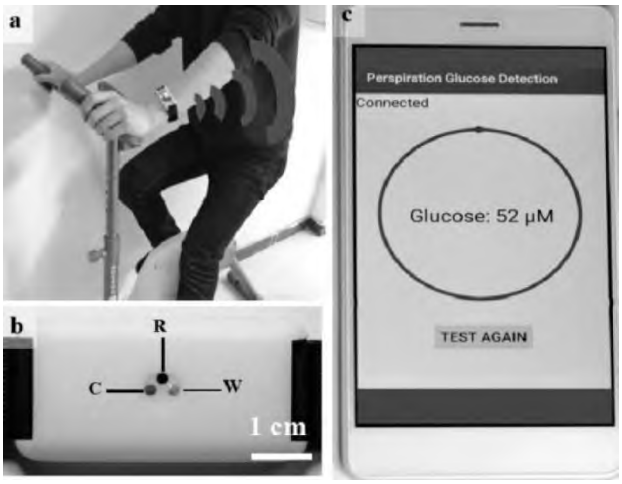

Figure 10. (a) Sweat glucose analysis during physical activity using a wristband-based electrochemical sensor. (b) physical image of the wrist-worn electrochemical sensor used to analyze glucose in sweat. (c) An application of a smartphone for analyzing glucose in sweat, the sensor is connected to the smartphone via Bluetooth[25].

In 2019, Ali et al.[26] used chemical methods to synthesize Ni-SnOx, PANI and CuO nanoparticles on the surface of cotton fabrics to prepare a flexible and high-performance enzyme-free glucose sensor. The sensor has a wide linear range from 0.001 to 10 mM, a detection limit as low as 130 nM, long-term stability and re-usability, and excellent performance.

In the application of living body detection, wearable glucose sensor technology has developed rapidly in the past few years, and a lot of research work has been done on flexible sensors that apply it to human blood glucose level monitoring. The application of glucose sensors in the medical field has only just started, and its application in physiological research needs to be further developed, and the performance of flexible wearable glucose sensors needs to be further improved. In general, due to the current need for such technology in medical or biological detection, this technology still has great potential for development, and more new non-enzymatic glucose sensor devices will also be developed[27].

5. Conclusions

In this paper, the development of glucose sensors in past generations is discussed, and the research results of non-enzymatic glucose sensors in electrode modification materials, new sensor structures and their in vivo detection applications in recent years are reviewed. Enzyme-free glucose sensors are increasingly the focus of attention due to their excellent properties. The working electrode modification materials of the enzyme-free glucose sensor are mainly nanoparticles such as noble metals, transition metals, and composite materials doped with carbon nanomaterials. It has also become a research direction for scientists to improve the performance of the sensor around the modified materials. The research on electrode modification of glucose sensor also provides ideas for its application in in vivo detection. In terms of in vivo detection, glucose sensors are mostly used in the detection of human blood sugar levels. New flexible electrodes are still to be developed. After the technology is further matured and popularized, it will become a great boon for diabetic patients. Moreover, there are few studies on non-enzymatic glucose sensors applied to agricultural living detection, which still requires further exploration by scientists to promote the development of agricultural intelligence.

Conflict of interest

The authors declare no conflict of interest.

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