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Electrochemical Glucose Biosensors, Recent Advances, Advanced Nanosystems and Evolution of Biosensor Platforms

Mustafa Abbas Mohammed[1], Hassan Ali Shaheed[2], Ahmed Khalaf Jaber[3], Mustafa Hussein Amana Aboud[4], Mujtaba Abbas Mohammed[5]

[1,2,3,4,5]Medical Devices Technology Engineering, University of Hillah, Iraq

Abstract:
Since the advent of sophisticated nanostructures and nano-composites, a plethora of sensing platforms have been developed through rigorous investigation into different immobilisation techniques and the enhancement of electron transfer efficiency between the enzyme and the electrode. Several nanomaterials and composites have found use in biosensors, such as carbon nanotubes, gold nanoparticles, chitosan hydrogel composites, and carbon/graphene quantum dots, which have enhanced the immobilisation process or demonstrated electrocatalytic activity towards glucose. Since traditional glucose meters use human blood or serum as their sample medium, they necessitate intrusive sampling procedures. Researchers have shifted their attention to non-invasive sensing platforms that may detect glucose from various physiological fluids such as saliva, perspiration, or tears, in an effort to alleviate the pain and discomfort associated with these invasive approaches. These innovative developments in miniaturised technologies for painless, non-invasive glucose testing have the potential to revolutionise diabetes control and management. Also, other potential target analytes could have their point-of-care devices developed as a result of these accomplishments. One of the best examples of a device that can be used at the point of care is the personal glucose meter. Because of its portability, user-friendliness, quantitative results, and accuracy, commercially accessible glucose meters have seen extensive application. Whole blood glucose detection is accomplished using these instruments. But the brilliant thought of reusing the PGMs opens the door to developing sensing platforms for non-glucose targets to use as POC devices. A plethora of new techniques for detecting bacteria, DNA, illness biomarkers, and other substances in the presence of the invertase enzyme have been created using personal glucose meters. Research on the limitations of portable glucose meters, such as their small linear range and the impact of naturally existing glucose in biological samples, is necessary before these devices may find widespread use. There are, of course, a plethora of additional untested approaches as well. Therefore, for the early-stage identification of biomarkers linked to a variety of malignancies and diseases (e.g., Alzheimer's, multiple sclerosis, etc.), there is a strong need for inexpensive sensing devices that are durable, accurate, sensitive, selective, and reasonably priced. It is worth mentioning that another significant difficulty in the field of diabetes control is the creation of sensors that can reliably, continuously, and quickly monitor glucose levels in real-time while maintaining high selectivity. These days, electrochemical biosensors are all the rage due to their selectivity, sensitivity, ease of use, and speed of response.

Keywords: Glucose Biosensors, Nanosystems, Recent Advances, Biosensor Platforms

Corresponding Author: Mustafa Abbas Mohammed†, Medical Devices Technology Engineering, University of Hillah, Iraq

Introduction

The device's foundation was an oxygen electrode and a semipermeable dialysis membrane that included glucose oxidase. After that, in 1970, Clark's patent proved that enzymes could change electro-inactive substrates into electroactive compounds. Two separate electrode systems were utilised by this system [1, 2]. In order to transform the substrate into an electroactive substance even when species interfered, the first electrode system—which included an enzyme in a capillary thin layer between the electrode and the membrane—was employed. There were organisms in the sample that could interfere with the second electrode system. Glucose levels were successfully monitored using Clark's patented device by subtracting the current measurements from the first and second electrode systems. An epidemic of diabetes mellitus affects people all over the globe. In terms of global mortality and disability rates, it ranks high. Hyperglycemia and insulin insufficiency cause this metabolic disease. Close monitoring of blood glucose levels is an essential part of diagnosing and managing diabetes mellitus. Glucose is the most frequently measured analyte since millions of diabetics check their levels every day [3, 4]. A large amount of research is still focused on the difficulty of providing such tight and dependable glycaemic control. In this regard, electrochemical glucose biosensors are pioneers. Extensive research has thus been conducted on amperometric enzyme electrodes, which rely on glucose oxidase (GOx) attached to electrode transducers. Ever since Clark and Lyons initially suggested the idea of glucose enzyme electrodes [5-7]. A variety of ways have been investigated in the operation of glucose enzyme electrodes. Such devices show enormous potential for a variety of critical applications, including diabetes control, bioprocess monitoring, and food analysis. Because glucose is so crucial, it has been the subject of a deluge of research articles, and this trend shows no signs of abating. Although glucose biosensors have come a long way, there are still a lot of obstacles to overcome before we can achieve tight glycaemic monitoring that is clinically accurate.

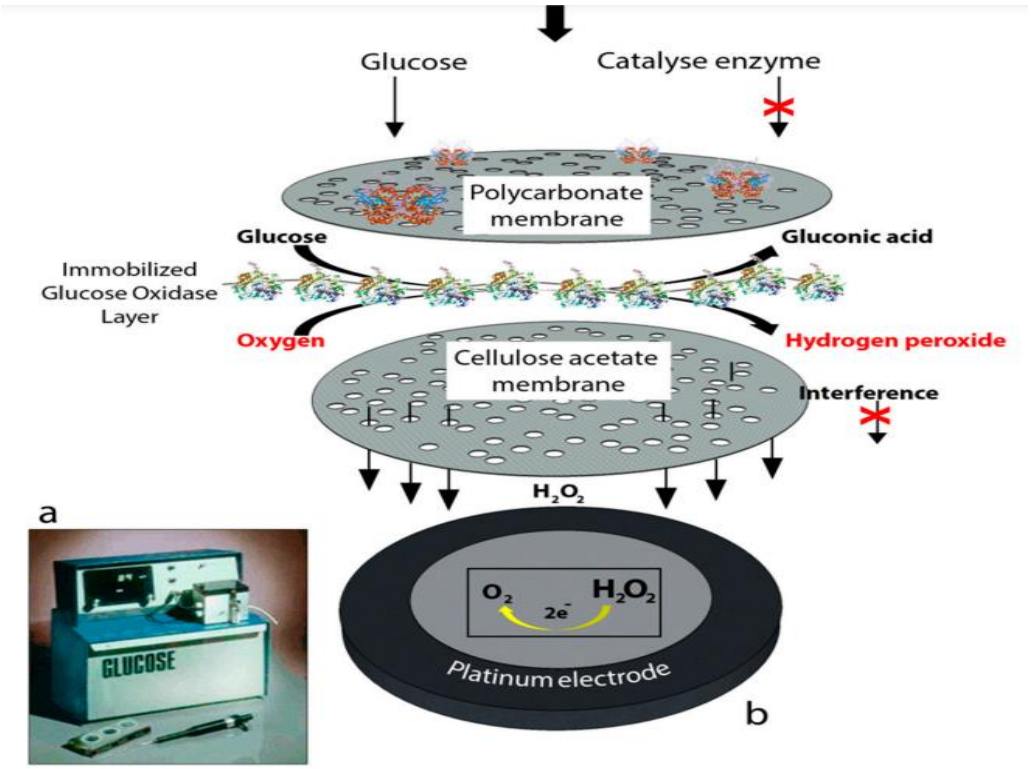

Figure 1. (a) YSI 23A glucose biosensor and (b) sensor probe with immobilized enzyme membrane for the Yellow Springs Instruments.

Biosensors of the second generation: This latter factor being taken into account, there have been significant advancements in the development of commercial electrochemical glucose biosensors due to the maturation of surface chemistry, screen printing, and semiconductor integration technologies, as well as the use of synthetic electron acceptors. To facilitate electron shuttles between the enzyme's redox centre and the electrode surface, synthetic redox couples or mediators can be employed. To facilitate the glucose catalytic reaction by glucose oxidase, a number of inorganic redox couples and organic dyes have been effectively utilised. This approach was also demonstrated to be insensitive to the content of dissolved [8-10] oxygen and to be effective at lower applied potentials, resulting in reduced interference effects. Amperometric biosensors needed disposable, tiny, miniaturised, sturdy, and inexpensive electrodes, hence screen printing techniques were adopted for this purpose. A breakthrough in home-use blood glucose biosensor technology was born out of these two ground-breaking research projects, which used screen-printed electrodes and mediators. In 1987, these biosensors were introduced to the market by the MediSense Company, formerly known as Genetics International, a joint venture between Cranfield and Oxford universities. The brand name used was ExacTech. One may argue that the employment of mediators and screen-printed electrodes was a huge leap forward for the creation of commercial home-use devices and amperometric biosensors.

FIRST-GENERATION GLUCOSE BIOSENSORS

Hydrogen peroxide production and detection, as well as the utilisation of the naturally occurring oxygen cosubstratum, have been the backbone of devices of the first generation. One benefit of these peroxide formation measures is how easy they are to implement, particularly with the use of little sensors. The YSI probe is a popular design that entraps GOx between two membranes: one that limits diffusion and is biocompatible and another that acts as an anti-interference. Endogenous reducing species, including ascorbic and uric acids, as well as certain medications (e.g., paracetamol), are electroactive, which is necessary for the amperometric detection of hydrogen peroxide [11, 12]. These and other oxidisable components of biological fluids can have anodic contributions that reduce selectivity and, by extension, overall accuracy. In the 1980s, researchers focused heavily on ways to reduce electroactive interference errors in glucose electrodes. The application of a permselective coating, which prevents these substances from reaching the transducer surface, is one practical approach. So far, electroactive substances that coexist have been discriminated against by means of various polymers, multilayers, and mixed layers that exhibit transport behaviours depending on size, charge, or polarity. In addition to being more stable, these films do not contain surface-active macromolecules. High selectivity (based on size exclusion) and surface confinement of Gox have been demonstrated to be achieved through the use of electropolymerized films, in particular poly (phenelendiamine) and overoxidized polypyrrole. Coatings such as size-exclusion cellulose acetate films, hydrophobic alkanethiol or lipid layers, and negatively charged sulfonated Nafion or Kodak AQ ionomers are also commonly utilised. More benefits can be obtained by combining the qualities of various films through the usage of layered multilayers. To eliminate the interference of the neutral acetaminophen and the negatively charged ascorbic and uric acids, respectively, alternating deposition of Nafi on and cellulose acetate was chosen as an example. The preferred electrocatalytic detection of the released hydrogen peroxide was the primary focus of efforts in the 1990s. As a result, the detection potential has been fine-tuned to precisely the range (_0.0 to _0.20 V versus Ag/AgCl) where the majority of undesired background reactions are practically nonexistent. A rapid and sensitive response accompanied the extremely high selectivity that was achieved in this way. To improve selectivity towards the desired glucose substrate, transducers based on metal-(Ru, Rh,)-carbon or metalhexacyanoferrate have proven to be very effective [13, 14]. Adding a discriminative layer, such as rhodium particles dispersed within a Nafion film, to this selective catalytic activity can further improve the film. The stoichiometric limitation of oxygen and variations in oxygen tension can introduce errors into oxidase-based devices since they employ oxygen as the physiological electron acceptor. Some of these issues include a lower upper limit of linearity and variations in the sensor's response. Because typical oxygen concentrations are around a factor of ten lower than the physiological glucose level, this restriction—called the "oxygen deficit"—reflects this reality. There are a number of possible ways to overcome this oxygen shortage. One method involves improving the oxygen/glucose permeability ratio by manipulating the flux of the two substances using mass-transport limiting coatings like polyurethane or polycarbonate.

Particularly appealing for resolving the oxygen deficiency is a two-dimensional cylindrical electrode developed by Gough's group. This electrode permits two-way diffusion of oxygen into the enzyme region of the sensor [15-19], but only one-way diffusion of glucose. An oxygen-rich carbon paste enzyme electrode was designed to alleviate the oxygen restriction of glucose biosensors. A fluorocarbon paste liquid (Kel-F oil) is the basis of such a biosensor. It acts as an internal source of oxygen due to its very high oxygen solubility. Thus, even in glucose solutions devoid of oxygen, the enzymatic reaction can be supported by the internal flux of oxygen. Substituting glucose dehydrogenase (GDH), which does not necessitate an oxygen cofactor, for GOx is another way to avoid the oxygen demand problem.

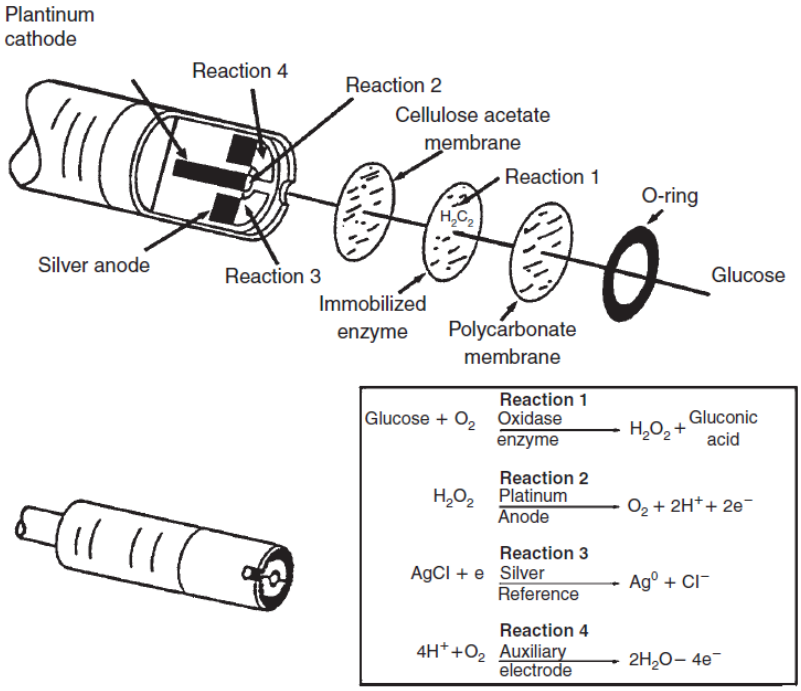

Figure 2. Schematic of a "first-generation" glucose biosensor.

Second-Generation Glucose Biosensors

Electron transfer between GOx and electrode surfaces

Substituting a synthetic, non-physiological electron acceptor for the oxygen allows for additional enhancements (and correction of the aforementioned mistakes) by transferring electrons from the enzyme's redox centre to the electrode surface.Because of the thick protein covering that surrounds its flavin redox centre, glucose oxidase is unable to directly transmit electrons to ordinary electrodes.

Installation of relays for electron transfer

Heller's team came up with a clever, non-diffusional way to connect GOx to electrodes; they "wired" the enzyme to the surface using a long, flexible poly-pyridine polymer that had a dense array of osmium complex electron relays. In addition to stabilising the mediator to electrode surfaces, the resultant three-dimensional redox-polymer/enzyme networks provide large current outputs. One new way to make it easier for electrons to go from GOx's redox centre to the electrode surface is to chemically modify it with electron-relay groups. Willner and colleagues detailed a sophisticated method for integrating electron relays into GOx modifications. To achieve this, an electron-mediating ferrocene unit had to be positioned before the enzyme could be reconstituted, which required removing the FAD active centre of the enzyme. Another possible approach to achieving low electron-transfer distances is to attach electron-transfer relays to the enzyme's periphery [20-23]. For the purpose of interfacing GOx with the electrode support, more advanced bioelectronic systems have been created. These systems rely on organised enzyme networks on solid electrodes and patterned monolayer or multilayer assemblies to enhance the electrical response.For the purpose of creating GOx/mediator networks layer-by-layer (LBL), functionalised alkanethiol modified gold surfaces have proven to be quite appealing.

Progress in electrochemical glucose sensors in recent times:

From biological applications to ecological techniques, glucose sensing is a highly significant field. One of the top global killers and disability-inducing conditions, diabetes mellitus is a major player in clinical medicine. Hyperglycemia, a metabolic disease caused by insulin insufficiency, manifests as blood glucose values greater than the normal range of around 3.9-6.2 mM (empty stomach) or 3.9-7.8 mM (2 hours after food). One of the most important therapeutic applications of quantitative blood glucose monitoring is the prevention of diabetic complications such as cardiovascular disease, kidney failure, and blindness [24-27]. A plethora of optical and electrochemical glucose monitoring techniques have been developed. It goes without saying that optical technologies measure photons and electrochemistry measures electrons. Bioimaging and in vivo biosensing are both greatly facilitated by optical technologies due to their wireless nature. Readers interested in learning more about the several optical approaches that have proven efficient for glucose sensing can peruse pertinent articles and reviews. These methods include fluorescence, surface plasmon resonance (SPR), absorption (and reflectometry), and others. Glucose sensing has made extensive use of electrochemical approaches, particularly amperometric methods. One of the most studied and used types of glucose sensing is enzymatic biosensing, whereas the other is nonenzymatic sensing. The direct electrochemical oxidation of glucose, the basis for amperometric nonenzymatic glucose sensors, has attracted considerable interest and has seen extensive exploitation [28-32]. The main benefit of amperometric nonenzymatic glucose sensing over enzymatic biosensing is that the former has solved the issue of inadequate long-term stability, the most prevalent and significant difficulty with enzymatic glucose sensors caused by the inherent characteristics of enzymes. Noble metals (e.g., Au and Pt) and their alloys are among the many metals that have found extensive use as electrode materials in nonenzymatic glucose sensing because of their excellent selectivity, sensitivity, and electrocatalytic activity for glucose electrooxidation.

Electrochemical glucose sensors that do not need enzymes

An efficient and quick method for nonenzymatic glucose sensing is the direct electrochemistry of glucose, whether it be oxidation or reduction. Nonenzymatic sensors were initially developed using composites of noble metals (Pt15,17,45, Au46,47) and other similar elements. In a recent review, Park et al. and Toghill et al. discussed nonenzymatic electrochemical strategies for glucose sensing. There are three main issues with using a traditional noble metal electrode to directly oxidise glucose: firstly, the sensitivity of glucose sensing is limited due to the slow kinetics of glucose electro-oxidation on these electrodes. Secondly, noble metal electrodes are often hindered in their activity by adsorbed chloride ions and irreversibly adsorbed oxidation intermediates of glucose. To address this, we recommend a permselective film against anionic Cl2 as a solution. Lastly, nonenzymatic glucose sensors have poor selectivity because other sugars and endogenous interfering species can also be oxidised within the potential range of glucose oxidation. Being a prerequisite step in the highly sensitive and selective electro-oxidation of glucose, a high real surface area (with a high roughness factor) of an electrode is likely to be beneficial. On the other hand [33-37], the diffusion-controlled electro-oxidation of interfering electroactive species such as ascorbic acid, uric acid, and p-acetamedophenol is independent of the electrode roughness. There have been a lot of recent efforts to create new nanomaterials with unique properties in the hopes of opening up new avenues for the fabrication of innovative nonenzymatic glucose sensors. However, the rough electrode surface exhibits substantial chloride adsorption. Given that the OH group is already present on the electrode surface, it was found that chloride can be effectively removed by subjecting the system to an alkaline environment. 53 It is generally believed that the rate-determining step in the catalytic process of glucose electro-oxidation occurs during the simultaneous adsorption of organic species and the hemiacetalic abstraction of hydrogen atoms, which is an integral part of the catalytic process of nonenzymatic glucose oxidation. The development of hydroxide premonolayers was shown to be an important step in the electrocatalytic process of glucose, and Burke put out the "incipient hydrous oxide adatom mediator" (IHOAM) hypothesis to explain this. 54 It is well-known that the electro-oxidation of glucose and numerous other organic compounds relies on the presence of "active" hydroxide anions close to the electrode surface, which are formed when water dissociates.

The chemisorbed MOHads are thought to be involved in the glucose oxidation process, which is a slow stage. The aforementioned equations clearly show that MOHad production is enhanced as the OH2 concentration increases. The sensitivity of nonenzymatic glucose sensing is typically found to be higher in environments with a higher pH, as this reaction is pH-dependent and thrives in an alkaline environment. A wide range of nanomaterials have been developed

for use as electrocatalysts in nonenzymatic glucose sensing in alkaline media. These include palladium nanoparticles supported on functional carbon nanotubes, Ti/TiO2 nanotube array/Ni composites, boron-doped diamond nanorods, electrospun palladium (IV)-doped copper oxide composites nanofibers [38-41], three-dimensionally ordered macroporous platinum templates, polycrystalline Pt electrodes, nanoporous Au,58 Cu nanoclusters/multiwalled carbon nanotubes (MWCNTs) composites, and graphite-like carbon film electrodes with embedded Ni nanoparticles. A method for nonenzymatic glucose sensing in 0.10 M pH 8.1 PBS was also developed using porous tubular palladium nanostructures. 61 It was also found that surface-bound Ni2+/Ni3+ and Cu2+/Cu3+ redox couples at Ni and Cu electrodes significantly improve the nonenzymatic electro-oxidation of glucose when compared to Pt and Au electrodes. 62,63 pages When exposed to glucose electro-oxidation in acidic solutions, all of the aforementioned nanomaterials react selectively and sensibly, with MOHads being more readily formed and Cl2 adsorption being significantly reduced in the presence of copious OH2. Because of their stability and superior catalysis at high pH settings, carbon-based nanomaterials, as well as Pt, Au, Cu, Ni, Pd, Ti, TiO2, and carbon-based nanomaterials, can be used for nonenzymatic glucose sensing in alkaline media. On the other hand, electrocatalysts may have their lifetime reduced due to surface deterioration caused by the acidic environment [42, 43]. Furthermore, nonenzymatic glucose sensors are typically evaluated in neutral physiological media for their efficiency. However, glucose adsorption in neutral media can be significantly suppressed by physiological Cl2 concentrations, and the electrocatalytic activity of the metal electrode in glucose oxidation is also significantly affected by physiological pH. There have been reports of various nanomaterials that can effectively detect glucose in neutral medium as well. As an example, it was shown that electrodes made of well ordered Pt nanotube arrays could detect nonenzymatic glucose with sufficient sensitivity, selectivity, and stability. The mesoporous surface of the enzyme-free glucose sensor developed by Park et al.17 gave it great anti-poison ability [44, 45]; even in the presence of extremely high concentrations of chloride ions (0.10 M KCl), the sensor maintained enough sensitivity. Wang et al.'s synthesisednanoporousPtPb networks14 exhibited great sensitivity, selectivity, and resistance to Cl2 poisoning. Sun et al. also found that Pt-Pb alloy (Pt2Pb) electrodes can selectively electro-oxidize glucose at much more negative potentials than pure Pt surfaces. The high surface roughness factor and unique nanostructure of Pt2Pb allow for more stable and larger responses.

GLUCOSE TESTING IN VIVO

When it comes to home glucose testing, electrochemical biosensors are perfect. Disposable (screen-printed) enzyme electrode test strips form the basis of most personal blood glucose meters. Using thick film (screen-printing) microfabrication technology, these disposable electrode strips are mass-produced for one-time use. Screen printing uses conductive and insulating patterns printed onto flat (ceramic or plastic) surfaces. Working electrodes are coated with the appropriate reagents (enzyme, mediator, stabiliser, linking and binding agents, etc.) and reference electrodes are printed on each strip. These days, inkjet printing is all the rage for dispensing these kinds of chemicals. It is possible to incorporate a counter and an extra ("baseline") working electrode. Avoiding issues with carryover, contamination, or drift is made easy with these single-use devices. The test strips are designed with multiple layers of membranes (mesh) and surfactants to ensure a consistent sample coverage [45-48]. The control meter is usually made of compact, lightweight, battery-operated components that work together to perform a potential-step (chronoamperometric) operation and a brief incubation (reaction) step. These devices show great potential for acquiring the needed clinical data more quickly, cheaply, and with less effort than conventional assays. Medisense Inc. debuted their initial invention, the ExactechTM, a pen-style device that utilised a ferrocenederivative mediator, in 1987. Numerous commercial strips and pocket-sized meters for self-monitoring of blood glucose have been launched since then, all utilising ferricyanide or ferrocene as mediators. Still, Abbott, Bayer, Life Scan, and Roche Diagnostics all hold over 90% of the market [49-51]. Every time, the diabetic patient just needs to prick their finger, place the tiny drop of blood on the sensor strip, and within 5-30 seconds, they can see their blood glucose concentration on an LC display. In addition to fast response and small size, such modern personal glucose meters have features such as extended memory capacity and computer downloading capabilities.

Real-Time In-Vivo Monitoring in Continuous Flow

Even though self-testing has been a huge step forward in glucose monitoring, there is a daily limit to how many tests you can do. Patients are less likely to undergo regular monitoring due to the hassle of conventional finger-stick sampling. Such testing may provide an inaccurate estimate of blood glucose fluctuations since it does not account for variations over the night. In order to make accurate treatment decisions, it is necessary to maintain tight glycaemic control by measuring glucose levels more frequently or continuously. This will allow for the detection of sudden spikes or dips in glucose levels and the right triggering of alarms in cases of hypo- or hyperglycemia. Therefore, glucose biosensors play an essential role in glycaemic control systems that are closed-loop. In order to keep glucose levels close to normal, researchers have investigated a variety of in-vivo glucose biosensors [52-57]. A platinum anode maintained at _0.6 V (instead of a silver cathode) was used to monitor the enzymatically produced hydrogen peroxide in his needle-type glucose sensor. Coatings of cellulose-diacetate, heparin, and polyurethane allowed for the trapping of the enzyme, glucose oxidase. When it comes to in-vivo glucose sensors, the vast majority rely on the GOx-catalyzed oxidation of glucose by oxygen. The ideal dimensions and form factor for the sensor would allow for its easy implantation with little to no discomfort. For a sensor to be biocompatible, its impact on the in-vivo environment and the environment's impact on the sensor's performance must be considered. The development of dependable implanted devices has been largely hampered by issues with biocompatibility. In order to work reliably for an extended period of time in whole blood, most glucose biosensors do not meet the biocompatibility requirements. This has led to an increase in research into alternative sensing sites, most notably subcutaneous tissue. The aforementioned problems are serious, however there has been great strides in the area of continuous glucose monitoring.

Carbon Nanofiber Nanocomposites-Based Non-Enzymatic Electrochemical Glucose Biosensors

Diabetes mellitus has exploded in prevalence during the past few decades. Reports indicate that diabetes will surpass all other diseases as the sixth most common cause of death worldwide by the year 2030. A normal blood glucose range is often below 100 mg/dL. A patient is diagnosed with diabetes if their blood glucose level exceeds 126 mg/dL on two separate fasting blood glucose tests. There are two distinct kinds of glucose levels in a human body. To begin, very low blood sugar levels, or hypoglycemia, can cause a variety of symptoms, including dizziness, unconsciousness, and death. As a second undesirable occurrence, hyperglycemia causes abnormally high blood sugar levels, which in turn affect the kidneys, eyes, nerves, and blood vessels. Hyperglycemia, or a high blood glucose level, is the hallmark of diabetes, which can develop when the body either does not make enough insulin (Type-1 diabetes) or is unable to effectively use the insulin it does produce (Type-2 diabetes). The hormone insulin facilitates glucose absorption by the body's cells. Without insulin, blood glucose levels in Type-1 and Type-2 diabetes can rise to dangerous levels, endangering the kidneys, eyes, nerves, and heart. The development of highly sensitive and selective glucose biosensors for quick detection is a direct result of the rising global patient population with diabetes. Biological events can be converted into electrical signals by use of biosensors. Electrochemical biosensors are the gold standard for glucose monitoring since they are simple, inexpensive, and can be integrated with mobile devices for numerical analysis [58-60]. However, there are other methods that have been suggested. One can choose between enzymatic and non-enzymatic electrochemical glucose biosensors. The glucose oxidase enzyme (GOx) is utilised in enzymatic biosensors to detect glucose, while electrocatalytic activities form the basis of the glucose detection process in non-enzymatic biosensors. Carbon nanofiber (CNF) is structurally and functionally comparable to carbon nanotubes (CNTs), but it is more practical, cheaper, and easier to manufacture. CNFs are carbon nanoparticles that have micron-sized lengths and nanometer-sized diameters. Because of their remarkable characteristics, nanocomposites have garnered a lot of interest. By combining the best features of nanomaterials and matrices, nanocomposite materials can be used to modify bare electrode surfaces. Biosensors and actuators are only two of the many biomedical uses for conductive nanocomposites. CNFs are great for synthesising CNF-based nanocomposites because they have high surface area, strong electrical conductivity, high porosity, and good thermal conductivity. For non-enzymatic biosensors, CNFs are a solid substrate due to their large specific surface area, high electrical conductivity, and easy production procedure. Another option is to make CNF-based electrodes that can stand on their own, eliminating the need for a binder or glassy carbon electrode (GCE) strip that attaches to the glucometer. Two commonly used techniques for creating CNFs are electrospinning and CVD. Nanofibers are created by the electrospinning process by uniaxially stretching a viscoelastic fluid. Electrospinning differs from dry-spinning and melt-spinning in that it employs electrostatic forces to stretch the fluid during solidification. When the electrospinning jet is supplied with

enough solution, fibres can be created by pulling the solution. With the electrospinning jet running continuously, fibre production is thus unbroken. Nonwoven mats (webs) and yarns are two examples of the many forms that electrospinning has taken in the production of nanofibers made of different polymers. Their diameters range from tens of nanometres to a few micrometres. This straightforward and inexpensive process can be used to create continuous nanofibers from polymer melts or solutions. Electrospuncarbonised nanofibers, or CNFs [61-63], are a convenient byproduct of the electrospinning process that involves carbonising polymer nanofibers. Because of its high carbon yield, simple processing, and great mechanical characteristics, polyacrylonitrile (PAN) has become the polymer precursor of choice for electrospinning carbon nanofibers. Direct carbonisation of various polymers, including cellulose, chitin, lignin, and chitosan NFs, can also be employed to produce CNFs. CVD can also produce carbon nanofibers with different structures and properties from those made by electrospinning, called vapor-grown carbon fibers (VGCF). Catalysed thermal deposition (CVD) is a method for synthesising CNFs by growing carbon on a substrate in a 2D pattern. Supercapacitors, batteries, biomedicine, textiles, filtration, drug delivery, and biosensing are just a few of the many possible uses for CNFs due to their large specific surface area, high electrical conductivity, and mechanical characteristics.

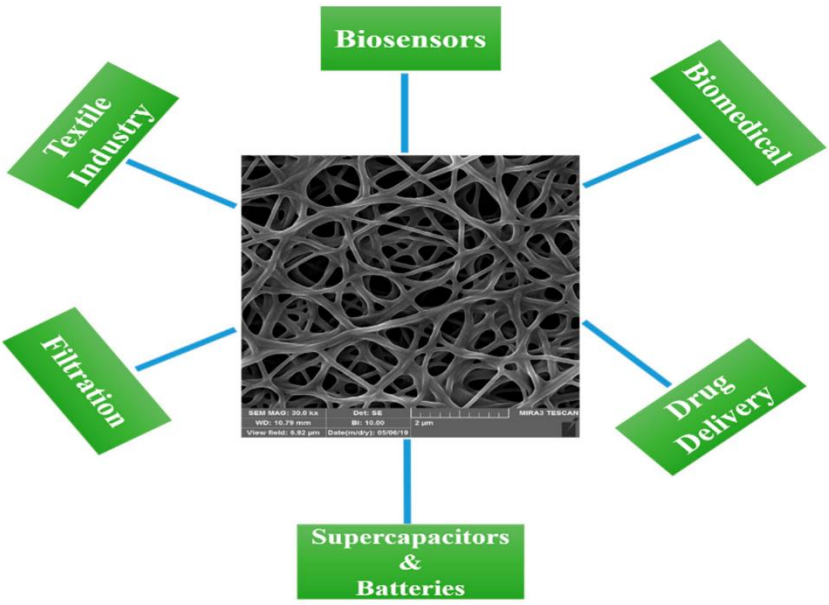

Figure 3. Displays the properties of CNFs that render them very suitable for use as biosensor diagnostic electrodes. Increased biosensor sensitivity is a direct outcome of CNFs' enhanced conductivity, which speeds up and simplifies electron flow in the electrode.

Electrochemical Biosensors that Do Not Require Enzymes for Glucose Measurement

The non-enzymatic glucose sensors are becoming more popular as an alternative to conventional enzymatic glucose biosensors, which have a number of drawbacks such as high production costs, low enzyme stability, dependence on pH values, and other specific constraints. Researchers are working on new electrochemical biosensors that do not use any biological components, such as enzymes, in order to circumvent the limitations of enzyme-based biosensors. The issue of enzyme immobilisation is not a concern with non-enzymatic glucose biosensors, in contrast to enzymatic sensors. Also, because enzymes aren't present, non-enzymatic biosensors are more stable. Functionalised nanomaterials can be used as catalysts or immobilisation platforms to improve detection sensitivity and specificity. Newer generations of glucose biosensors use enzyme-free materials that are based on straight glucose electro-oxidation. These biosensors have far better electrocatalytic activity for glucose detection than enzymes because the electrode surfaces are coated with nanostructured metal or metal oxide. Choosing the right catalyst for glucose detection is the most important part of developing non-enzymatic biosensors. Extensive research has demonstrated the sensitivity, selectivity, and stability of specific non-enzymatic electrochemical glucose biosensors. Also, unlike enzyme immobilisation approaches, non-enzymatic glucose biosensors are easy to create, stable, reproducible, and

inexpensive. Metallic nanoparticles, oxide nanoparticles, bimetallic/alloys nanostructures, carbon nanomaterials, and metal/carbon nanomaterial-based nanocomposites are among the several kinds of non-enzymatic electro-catalysts.

Biosensors for Non-Enzymatic Glucose Metabolism Derived from CNF Nanocomposites

The large specific surface area, porosity, mechanical characteristics, and electrical conductivity of CNFs have led to their recent recognition as ideal substrates for incorporating metal and metal oxide nanoparticles into sensitive nanocomposites for biosensors. Biosensor electrodes made of CNFs have seen extensive use due to their many desirable properties, including high conductivity, surface area, porosity, and an easy and eco-friendly production procedure. Because of its huge specific surface area, CNFs can have a lot of catalysts and nanoparticles attached to them, which improves their electrocatalytic performance when reacting with analytes of interest. The electrocatalytic activity and performance of the biosensor, including its limit of detection (LOD), linear range (LR), and sensitivity, are improved by including metal or metal oxide nanoparticles into the CNF matrix. The need for an accurate blood glucose monitor is rising in tandem with the number of people diagnosed with diabetes. It is common practice to treat commercial glucometer strips with enzymes. Scientists have been working on non-enzymatic biosensors for a while now due to enzyme instability in the environment, enzyme immobilisation challenges, and enzyme cost. For biosensors that don't use enzymes, a substrate is necessary to implant the catalyst. The large specific surface area, high electrical conductivity, and facile production method of carbon nanofibers (CNFs) make them an ideal substrate for non-enzymatic biosensors. It is also possible to make CNF-based electrodes independently, without the use of a binder or GCE, so that they can be used as strips with the actual glucometer. Noble metals, nickel-based nanoparticles, cobalt-based nanoparticles, and copper-based nanoparticles are among the nanostructures that have been electro-catalyzed onto the CNF surface.

Compact Nanoparticle/CNF Hybrid An Alternative to Enzymatic Glucose Biosensor Utilising Nanocomposites

In order to improve the properties of single-component nanoparticles, accomplish novel properties that are not achievable with single-component nanoparticles, and achieve multiple functionalities, researchers have concentrated on developing hybrid nanostructures made of two or more distinct materials. Compared to nanoparticles made of a single component, nanostructures with a hybrid composition have better electrochemical characteristics. These outcomes are the consequence of a synergistic impact among the constituent parts. Therefore, it is anticipated that a novel method for producing electrode materials for non-enzymatic glucose detection may involve combining ECNF matrices with two or more nanoparticles. A nanocomposite combining electrospun ECNFs and CoFe2O4 nanoparticles was created by Ding et al. [107] by use of a heat treatment procedure. In order to improve the dispersion of CoFe2O4 and provide a superior electron transportation path, ECNFs with outstanding conductivity served as a substrate that guided the formation of CoFe2O4 particles. Due to their huge surface area, electrical conductivity, and wide electrochemical window, electrospun nanofibers can also be utilised as electron transport channels in the electrocatalytic reaction processes involving CoFe2O4. The incorporation of CoFe2O4 nanoparticles and an ECNF matrix into the suggested nanocomposite electrode results in outstanding detection capabilities. This features a low limit of detection (LOD) of 3.25 × 10−4 mM, a wide range of detection (LR) from 10−2 to 3.52 mM, and a sufficient sensitivity (318 μA·mM−1·cm−2). For non-enzymatic glucose biosensors, Li et al. synthesisedMCo nanoparticles (where M = Cu, Fe, Ni, and Mn) and implanted them in CNFs. Heat treatment transforms PVP nanofibers into CNFs, as seen in the image. As the temperature rises, a metal concentration gradient exists between the bulk and surface of the CNFs, allowing metal nanoparticles to diffuse from the inside to the outside. The electrocatalytic characteristics of the electrode surface in the reaction with the glucose analyte are improved and the biosensor's performance is enhanced by the presence of nanoparticles on the surface of CNFs. Given these findings, the order of catalytic capacity is as follows: CuCo/CNFs, Co/CNFs, NiCo/CNFs, FeCo/CNFs, and MnCo/CNFs. With a LOD of 10−3 mM, a high sensitivity of 507 μA·mM−1·cm−2, and an LR of 0.02-11 mM, the biosensor that has been suggested is an excellent choice. In addition to being highly selective, the suggested biosensor is also inert to other blood-borne species that could interfere with its performance.

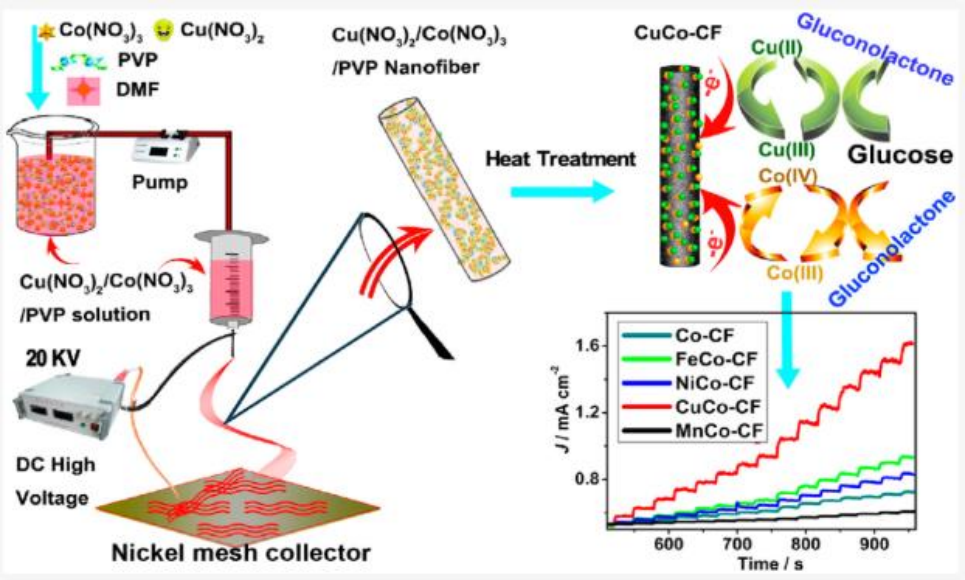

Figure 4. Biosensor amperometric findings, electrochemical mechanism of electrodes, and processes for synthesising Co/CNFs and MCo/CNFs (where M = Fe, Ni, Cu, and Mn) nanocomposites.

The appealing qualities of CNFs, including their high surface area, superior conductivity, and high porosity, have led to the construction of a variety of electrochemical biosensors with outstanding analytical performance. Biosensor performance is enhanced by CNFs due to their high electrical conductivity. The performance and electrocatalytic activity of the biosensor are enhanced by the addition of metal oxide or metal nanoparticles to the CNF matrix. Metals (Ni, Cu, Co, Pt, and Pd) and compounds (NiO, CuO, and CoO) were initially incorporated into a CNF matrix to create nanocomposite electrodes in the earlier experiments. The synergistic effects and outstanding electrocatalytic performance of metal compound combinations, including alloys and bimetallic nanoparticles embedded within CNFs, have recently attracted a lot of attention. Most non-enzymatic glucose biosensors are unable to catalyse glucose oxidation under physiological settings, which is a big hurdle to utilising these biosensors with blood samples. Since blood has a physiological pH of 7.4, the majority of non-enzymatic glucose biosensors showcased in the literature rely on alkaline medium to identify glucose. Despite their high sensitivity, this is especially important for Cu, Ni, metal oxide, and carbon nanomaterial electrodes. Therefore, prior blood preparation is required to utilise these electrodes for direct diabetes diagnosis. Selectivity is another important consideration when developing non-enzymatic glucose biosensors. Although the GOx enzyme is highly specific for glucose detection in enzymatic glucose biosensors, non-enzymatic glucose biosensors are susceptible to errors in blood glucose detection due to interactions between the electrode surface and interfering species in the blood, such as dopamine, uric acid, and ascorbic acid. Because of this, picking a catalyst with great electrocatalytic characteristics is crucial. While studies into non-enzymatic biosensors are continuing, the fourth generation of electrochemical glucose biosensors, which use electrodes with various electro-catalysts, still require further research before they can be commercialised. The main issue with commercialising non-enzymatic electrodes is their fabrication cost. Consequently, this kind of CNF-based biosensor has received comparatively little attention in the scientific community. It would be wise to do additional research utilising novel nanostructured materials as reaction catalysts. Nevertheless, numerous researchers have taken an interest in this biosensor type in the past ten years. Research and development (R&D) has not yet progressed to the commercialisation level for non-enzymatic glucose biosensors.

CONCLUSIONS

Electrochemical biosensors utilising sophisticated nanostructures and miniature devices provide crucial sensing and diagnostic tools with excellent selectivity and sensitivity for a wide range of target analytes, as has been demonstrated by the majority of research. There have been several ground-breaking developments in biosensor technology since its first discovery, all with the goal of making these sensing devices better. There have been several detailed descriptions of first-, second-, and third-generation glucose biosensors that employ nanoparticles or integrated polymeric matrices.

Emerging nanostructures, hybrid materials, and micro-or nano technologies have been utilised to improve the sensitivity of glucose biosensors. Graphene, graphene derivatives, carbon quantum dots, graphene nanotubes, gold nanostructures, biocompatible hydrogel chitosan, and nano-bio-composites of these are all examples of carbon-based nanomaterials. Research into nanotechnology has recently accelerated the creation of glucose sensors that do not require enzymes and have outstanding analytical performances. Glucose sensors made of metal or metal oxide nanostructures have a higher sensitivity and a larger electroactive surface area. There are still obstacles to overcome in the areas of biocompatibility, lifespan, and selectivity for both enzymatic and non-enzymatic sensing platforms. A new generation of (integrated) electrochemical biosensors for the detection of multiple analytes may make use of glucose oxidase-based biosensors, since these sensors have been utilised as idealised model systems for the fabrication of various sensing platforms. A low-cost method for detecting miRNAs, for instance, involves integrating an electrochemical glucose biosensor with sophisticated DNA technology on a compact microfluidic chip. There has been great advancement in the development of electrochemical glucose biosensors during the past 40 years. Thanks to a plethora of technical advancements and refined studies on novel sensing principles, electrochemical glucose biosensors are now finding extensive use. These devices make for to 85% of the biosensor market globally. The accuracy and precision of glucose testing instruments have been greatly improved in recent years. Exciting new possibilities for study and substantial economic growth have prompted such a flurry of endeavour. There has been a lot of interest in developing in-vitro and in-vivo devices to monitor additional chemicals that are physiologically significant, thanks to the success of glucose blood meters. Tight, steady, and dependable glycaemic monitoring remains a challenging goal, despite significant advancements in glucose biosensors. As a result, many scientists are still devoted to finding better glucose biosensors. We anticipate substantial attempts to integrate basic sciences with technological developments as this area enters its fifth decade of vigorous research. Research that pushes the boundaries of what is possible will lead to a variety of exciting developments, such as: improved electrical contact between electrode surfaces and GOx's redox centre; improved "genetically engineered" GOx; new "painless" in vitro testing; artificial (biomimetic) glucose receptors; advanced biocompatible membrane materials; the integration of minimally invasive monitoring with a compact insulin delivery system; novel non-invasive monitoring approaches; and miniaturised long-term implants. The management and control of diabetes will be substantially enhanced by these and comparable advancements.

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