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Revolutionizing Diabates Management and Advances in Nanomaterials for Electrochemical Non-Enzymatic Glucose Biosensors

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Abstract

In recent years, portable, cost-effective, and user-friendly electrochemical biosensors have gained popularity for medical diagnostics and environmental monitoring. Electrochemical sensing technologies are promising due to their sensitivity, selectivity, and downsizing for portable devices. Electrochemical biosensors focus on glucose detection, a critical biomarker in medical diagnostics, especially for diabetes management. Sensor design, materials science, and fabrication have greatly advanced glucose biosensors. Enzymatic biosensors are unstable, prone to interference, and expensive to make. These restrictions have led to interest in non-enzymatic electrochemical biosensors due to their promise of stability, selectivity, and cost-effectiveness. Nanostructured materials boost non-enzymatic glucose biosensor performance. Gold, silver, and platinum nanoparticles electrooxidize glucose due to their high surface-to-volume ratios and catalytic characteristics.

Tin oxide and zinc oxide conduct well, and electro catalyze glucose oxidation. Carbon nanomaterials, including graphene, carbon nanotubes, and carbon nanofibers, are attractive sensor platforms due to their electrical conductivity and biocompatibility. Surface science has improved our understanding of nanoscale electron transport mechanisms, allowing us to rationally develop nanostructured materials with specific electrocatalytic capabilities. Adding nanomaterials to sensing platforms has improved glucose biosensor sensitivity, selectivity, and reaction time. As non-enzymatic glucose biosensing electrocatalysts, each nanostructured material has pros and cons. non-enzymatic electrochemical glucose biosensors have a bright future for commercial and basic research. Continued advances in nanomaterial production, surface engineering, and sensor integration should increase sensitivity, selectivity, and stability. These advances will lead to affordable, compact, and widely accessible glucose monitoring devices that will revolutionize diabetes treatment and control.

Keywords: Electrochemical biosensors; Enzymatic biosensors; non-enzymatic biosensors; Carbon nanoparticles; Oxidation potentials; Metallic nanoparticles

Abbreviations: CGM: Continuous Glucose Monitoring; Gox: Glucose Oxidase; GDH: Glucose-1-Dehydrogenase; SMBG: Blood Glucose Self-Monitoring; AA: Ascorbic Acid; UA: Uric Acid; ITO: Indium Tetra Oxide; Sams: Self-Assembled Monolayers; Pd: Palladium; Glassy Carbon Electrodes; Ni: Nickel; Cuo: Copper Oxide; LOD: Limit Of Detection; CPE: Carbon Paste Electrodes; Mwcnts: Multiwalled Carbon Nanotubes; Ruo2: Ruthenium Dioxide; Mpcs: Metallo Phthalocyanines; BDD: Boron-Doped Diamond; BDDNF: Boron-Doped Diamond Nanoforest

Introduction

Over the past 50 years, glucose biosensor technology has transformed diabetes management. Diabetes, a chronic metabolic illness with high blood sugar, requires close monitoring and massnagement to reduce complications and improve outcomes. The autoimmune death of pancreatic beta cells causes Type 1 diabetes, often diagnosed in infancy or adolescence, and leads to insulin insufficiency. Type 1 diabetics without exogenous insulin cannot regulate their blood glucose levels, which can cause hyperglycemia, ketoacidosis, retinopathy, neuropathy, and cardiovascular disease. The development of glucose biosensors has made blood glucose monitoring and insulin administration

easier and more accurate for type 1 diabetics [1]. By allowing frequent home blood glucose monitoring, glucose biosensors help type 1 diabetics make informed decisions about insulin dosing, diet, and physical activity, optimizing glycemic control and reducing the risk of acute and chronic complications. Insulin resistance and a relative insulin shortage characterize type 2 diabetes, which accounts for 90% of diabetes cases. Insulin resistance impairs glucose absorption and raises blood sugar. As pancreatic beta cells fail to compensate for insulin resistance, insulin output may decline [2]. Obesity, sedentary lifestyle, and genetic predisposition are associated with type 2 diabetes, which can lead to cardiovascular disease, stroke, kidney failure, and other consequences. Like type 1 diabetes, type 2 diabetes cares require regular blood glucose monitoring to guide lifestyle changes, oral medicines, and insulin therapy. Glucose biosensors help type 2 diabetics identify hyperglycemia and hypoglycemia early and adapt treatment regimens [3].

Since its invention 50 years ago, the glucose biosensor has advanced in technology, miniaturization, and accuracy, becoming the cornerstone of current diabetes management. These tiny, user-friendly gadgets detect blood glucose levels in real time using enzymatic or non-enzymatic electrochemical technologies, empowering diabetics to manage their health. Because of their widespread use and proven efficacy, glucose biosensors have become essential tools in clinical practice, home monitoring, research, and industry, dominating the global biosensor market. Future glucose biosensor research focuses on improving accuracy, reliability, usability, and cost while reducing complexity [4]. Wearable biosensors, continuous glucose monitoring

systems, and digital health platform integration could revolutionize diabetes care and improve outcomes for millions of people. By using glucose biosensors and technology, we may create a future where diabetes management is individualized, proactive, and empowering, improving the lives of patients with this common and difficult condition. Beyond blood glucose measurement, glucose biosensors are used in bio industrial process monitoring, quality control, and fuel cell technology. Enzymatic glucose sensors have traditionally dominated the market, but non-enzymatic glucose sensors, especially those using nanomaterials, have garnered scholarly attention in recent years. Nanotechnology is driving glucose sensing innovation, enabling inventive and high-performance biosensors [5]. Nanomaterial-based non-enzymatic biosensors have a lot of potential because they are more sensitive, last longer, and can fix problems in enzymatic systems. Nanostructured electrocatalysts solve non-enzymatic glucose sensing selectivity and surface fouling difficulties. Nanomaterial-based non-enzymatic glucose sensors have seen increased investigation in the past decade. This emerging literature acknowledges nanotechnology as a critical facilitator of next generation biosensing platforms Figure 1.

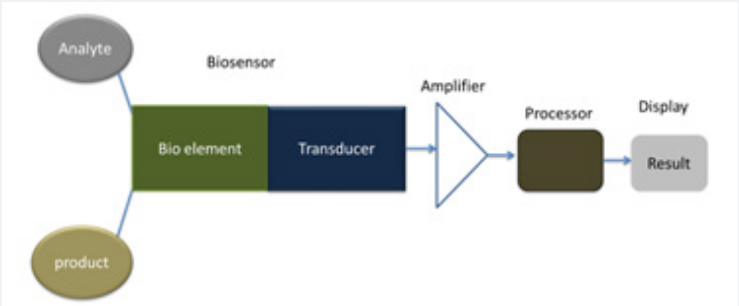

Figure 1: Schematic diagram of sensor.

The rise of nanomaterial-based glucose sensors emphasizes the need for a comprehensive evaluation of the current advances, methods, and trends in this quickly growing field. Electrochemical non-enzymatic glucose sensors are dynamic; therefore, a new assessment is needed to reflect recent advances. Park et al. and Toghill et al. gave useful insights [6]. The exponential development of nanomaterial-based, non-enzymatic glucose sensor research articles over the past two years makes such a review urgent and relevant. This study synthesizes and analyzes the latest advances in nanomaterial-based glucose sensing to provide a thorough overview and highlight areas for future research and innovation. Researchers like Wang and Heller et al. pioneered electrochemical enzymatic glucose biosensors. Their groundbreaking work has advanced biosensor technology and inspired new glucose-detecting methods. This study looks at the history and latest progress in both enzymatic and non-enzymatic glucose sensing to give a full picture of biosensor research and what it means for medicine, business, and other areas [7].

Sensors

Sensors shape our environment and improve our daily lives nowadays. Sensors in homes, workplaces, cars, and other places enable automation, efficiency, safety, and comfort by monitoring our modern ecology. Sensors detect and respond to physical changes. These alterations can affect motion, temperature, pressure, light intensity, sound, proximity, and chemical

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composition. Sensors convert these changes into electrical or optical signals that electronic systems might use to operate, offer feedback, or set alarms. Consider a simple but effective motion sensor- operated lighting system. A motion sensor activates lights as we enter a room, providing quick illumination without manual intervention. By simply turning on lights when needed, this improves convenience while reducing energy use and environmental effects [8]. By monitoring and adjusting temperature and humidity, sensors help regulate indoor settings. Sensor-equipped thermostats optimize energy use and lower utility costs by automatically adjusting heating and cooling systems to a comfortable indoor climate. Sensors can detect smoke or fire in home or business environments, triggering alarms and alerting inhabitants to potential hazards, improving safety, and reducing risks.

Sensors in cars perform everything from proximity detection for parking assistance to collision avoidance systems that notify drivers of potential risks. Proximity sensors in automobile doors can detect objects and obstructions, preventing parking accidents and damage. Sensors in advanced driver assistance systems (ADAS) can monitor traffic, detect lane deviations, and aid autonomous driving, improving road safety and convenience. Sensors also enable many more uses that improve our lives and simplify activities. Sensors can manage appliances, monitor water usage, and detect leaks and floods in homes, saving resources and property damage. Sensors allow firms to manage inventories, monitor equipment, and secure them with surveillance and access control [9].

Sensors are essential to modern life, advancing efficiency, convenience, and creativity. Sensors enable automated responses to environmental changes, allowing us to maximize our surroundings, safety, and quality of life. We should expect further sensory enhancements and better experiences as we invent and use sensor technology [10].

Nano sensor

Nano sensors have great potential in nanotechnology, materials research, healthcare, environmental monitoring, and more. Nano sensors detect and analyze the chemical and physical properties of materials, nanoparticles, and biological organisms with unparalleled sensitivity, resolution, and adaptability. We use nano sensors to characterize and manipulate materials. Nano sensors reveal material structure, composition, and surface morphology, mechanical, optical, and electrical properties. This information is required for designing and engineering innovative materials with specific features and increased performance. Nano sensors speed up the creation of new materials for electronics, photonics, catalysis, energy storage, and medicinal devices. Nano sensors could revolutionize healthcare diagnostics, treatments, and personalized medicine [11]. These small devices can detect proteins, nucleic acids, and metabolites with high sensitivity and specificity, enabling early disease detection, therapeutic response monitoring, and targeted drug delivery. Nano sensors in wearable and implantable devices analyze physiological indicators in real time, aiding disease management and prevention. Nano sensors are also used for environmental monitoring Figure 2. These instruments accurately and efficiently identify and quantify pollutants, poisons, and pathogens in air, water, soil, and food samples.

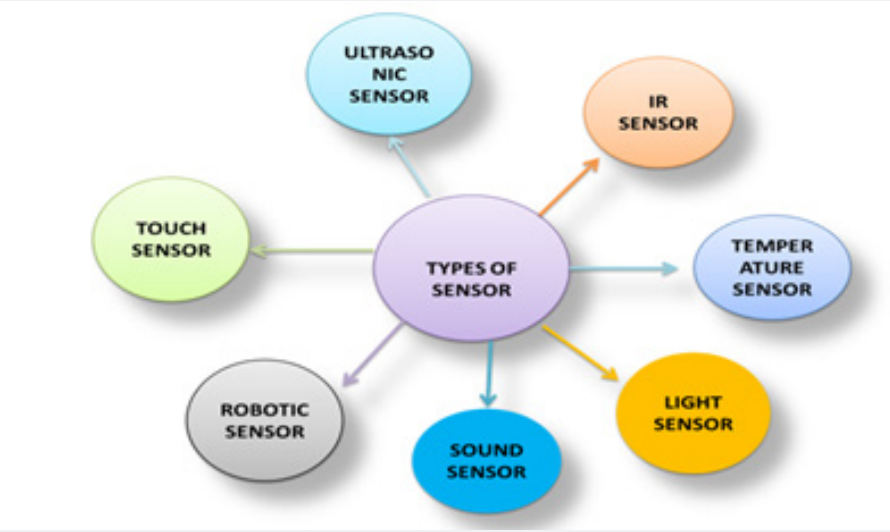

Figure 2: schematics view of types of sensors.

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Selective receptors and transduction processes in nano sensors can detect trace contaminants, enabling fast and accurate environmental assessments and cleanup. Nano sensors also monitor temperature, humidity, and radiation, helping to mitigate climate change and ensure environmental sustainability. Nano sensors are useful for scientific study and development due to their adaptability and scalability [12]. These gadgets let scientists investigate and manipulate nanoscale phenomena, revealing fundamental processes in physics, chemistry, biology, and materials science. Analyzing nanomaterials, nanocomposites, nanodevices, and nanostructures with nano sensors helps us understand complicated systems and processes. Finally, nano sensors are a transformative technology with broad applications in science, technology, and society. Nano sensors will progressively help solve global problems, drive innovation, and shape the future of numerous businesses and sectors as we advance nanotechnology and sensor development. Nano sensors can open new doors for scientific discovery, technical advancement, and social gain, leading to a more sustainable and affluent future [13].

Types of sensors

Both analog and digital sensors are utilized in a variety of industries, including automotive, aerospace, healthcare, environmental monitoring, consumer electronics, and industrial automation. Since they are both versatile and reliable, they are indispensable for the purpose of measuring and monitoring a wide variety of physical quantities and phenomena [14].

Classification of sensor

Transduction principles, which explain how sensors convert physical stimuli into measurable signals, often classify sensors. This taxonomy organizes sensor functions and applications across domains. In temperature and pressure measurements, resistive sensors detect resistance changes. Capacitive sensors detect proximity and touch via capacitance. Industrial automation uses electromagnetic induction-based proximity sensors. Light sensors use light properties for detection and imaging. When mechanically stressed, piezoelectric sensors create electric charges, enabling vibration sensing and acoustic measurements. This classification scheme helps professionals understand the different sensor landscapes and choose and integrate sensors for specific jobs and sectors [15,16].

Biosensor

Biosensors, a breakthrough combination of biology and technology, can detect a wide range of biological chemicals with extraordinary sensitivity and precision. A biosensor needs a transducer and a biological recognition element. The biological recognition element-an enzyme, antibody, nucleic acid, or entire cell interacts preferentially with the target analyte to start a biochemical reaction. The transducer converts this interaction's measurable signal into an electrical, optical, or other quantifiable output. Bio [16] sensors can detect everything from small molecules like glucose and cholesterol to huge macromolecules like proteins and nucleic acids. This makes them useful in healthcare, environmental monitoring, food safety, and biodefense. Glucometers, or glucose biosensors have transformed diabetes management by making blood glucose monitoring easy and frequent. Biosensor nomenclature reflects their different uses and designs. Immunological sensors, which use antibodies to detect antigens with great specificity, are essential for medical diagnostics and biosecurity [17].

Obtrudes use optical transduction to detect light signals, increasing sensitivity and multiplexing. Surface plasmon resonance makes resonant mirrors very good at finding biomolecular interactions, which is useful for drug discovery and biomolecular studies. Because they can detect environmental chemicals early, biosensors are also known as chemical canaries. Because of their miniaturization and integration, biochips provide high-throughput analysis and point-of-care testing. Biocomputers also combine biosensors with computing systems for real-time biological process monitoring and control. Biosensors are a wonderful combination of biology, chemistry, and engineering that provide sensitive and selective biological analyte detection instruments. Their various uses and expanding technology promote innovation in healthcare and environmental monitoring, offering improved detection and individualized diagnoses [18].

Since historical background

Since the 1950 Clark electrode breakthrough, biosensors have evolved greatly. Biosensor development has used a variety of biological components and novel technology to selectively and sensitively detect several analytes, building on Leland C. Clark Jr.'s landmark work. Medical diagnosis, environmental monitoring, food safety, and biotechnology have all benefited from this breakthrough. Biosensor technology has advanced greatly due to enzyme-based biosensors. Researchers have created sensitive, selective biosensors that can detect many analytes by immobilizing enzymes on sensor surfaces [19]. Enzyme-based biosensors, like glucose biosensors, have revolutionized diabetes management. By immobilizing glucose oxidase on the Clark electrode, researchers created an accurate blood glucose meter. This technology has simplified blood glucose monitoring for millions of people worldwide, improving diabetes management and health. Enzymes like urease have broadened biosensor applications beyond glucose monitoring. Urease-based biosensors can measure blood and urine urea levels, revealing kidney function and metabolic disorders. Biosensors are essential in clinical diagnosis and biomedical research due to their enzyme specificity and sensitivity. As biosensor technology has advanced, diverse generations of biosensors have evolved with different design principles and functions [20]. Direct interactions between biological responses and sensor surfaces enable rapid and sensitive detection in first-

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generation biosensors. These biosensors excel at point-of-care

testing and field applications that require speed and accuracy. First-generation biosensors may be unstable and susceptible to disturbance from complicated sample matrices. Second-generation biosensors add membranes or mediators for stability and selectivity. Advanced performance and reliability make these biosensors useful for environmental monitoring and food safety. Second- generation biosensors improve analyte detection by optimizing biological component-sensor surface contact. Recently developed third-generation biosensors use nanomaterials, microfluidics, and improved signal transduction methods [21]. These biosensors advance sensitivity, miniaturization, and multiplexing, enabling tailored medication, wearable devices, and real-time health monitoring. Third-generation biosensors will revolutionize healthcare by utilizing cutting- edge technologies and empowering patients to manage their health. Since the 1950 Clark electrode breakthrough, biosensor development has advanced. The field has advanced from oxygen electrodes to third-generation biosensors, thanks to innovation and cross-disciplinary collaboration. As biosensors improve, they could revolutionize healthcare, environmental monitoring and other industries by solving complicated problems faster, more accurately, and more easily [22]. Second-generation biosensors use mediators to improve sensitivity and efficiency.

These mediators boost biosensor performance by transferring electrons between the biological recognition element and transducer. Second-generation biosensors are trustworthy for accurate analyte detection due to improved interface stability and selectivity Figure 3. These biosensors are essential for clinical diagnostics, environmental monitoring, and food safety due to their improved capabilities. However, third-generation biosensors strive for autonomous and self-regulated analyte detection, a paradigm shift. Third-generation biosensors use biological interactions to activate sensor responses without mediators or other components. With this new technique, biological systems' sensitivity and specificity allow for more refined and robust biosensing [23]. Third-generation biosensors offer exceptional accuracy and dependability, promising to advance medical diagnosis, environmental monitoring, and more. By combining materials science, biochemistry, nanotechnology, and other sciences, researchers have advanced biosensing, improving healthcare, biotechnology, and environmental monitoring. As these interdisciplinary collaborations grow and technologies advance, biosensors may improve global health and quality of life [24].

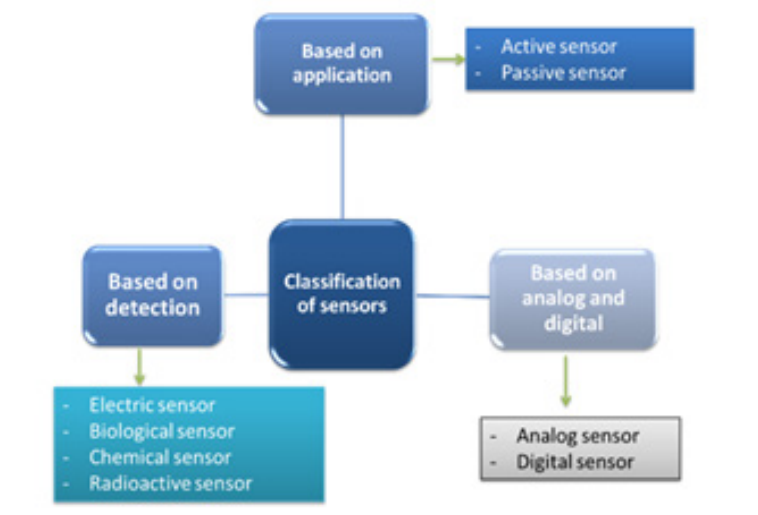

Figure 3: Schematic view of classification of sensors.

Working with a biosensor

Biosensor data integrity is crucial for medical diagnosis and environmental monitoring, as correct measurements determine decisions. Due to transducer qualities and signal characteristics, the conversion of biological events to electrical impulses is difficult. After biological events, transducers create weak electrical signals that are susceptible to interference and noise. Additionally, the signal often has a high baseline, making it difficult to detect target analyte changes. Signal processing methods like baseline subtraction overcome these issues. Subtracting a baseline signal isolates the signal of interest from background noise, boosting the signal-to-noise ratio and detection accuracy [25]. Signal processing is much more important for specificity and sensitivity in transducers that don't have a biocatalyst coating to speed up

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biological events and boost the target analytic signal during transmission. Signal processing techniques that extract useful information from the transducer output can improve biosensor performance without the need for biocatalyst coatings. Biosensor reactions filter electrical noise better than other biological processes due to their sluggish kinetics.

As the signal of interest evolves, noise variations become easier to detect. Using biosensor reaction kinetics, signal processing algorithms can distinguish signal changes from noise, improving measurement accuracy. Transducer output is usually analog after signal processing, requiring digitization for storage, analysis, and interpretation [26]. Digitization improves data manipulation precision and adaptability for microprocessor processing. The microprocessor can forward the signal, calibrate it to precise units, and execute quality control checks to verify data integrity. A repository stores data for usage or analysis after processing. The data repository may be local or cloud-based, depending on the application. Academics, healthcare professionals, and environmental scientists use this data to examine trends, find abnormalities, and draw conclusions from measurements. Biosensor signal processing pipelines convert electrical impulses into usable information, allowing biosensors to be used in healthcare and environmental monitoring. Researchers can improve biosensor performance and reliability using contemporary signal processing technologies, broadening their applications [27]. D-generation biosensors use mediators to improve sensitivity and efficiency. These mediators boost biosensor performance by transferring electrons between the biological recognition element and transducer. Second- generation biosensors are trustworthy for accurate analyte detection due to improved interface stability and selectivity. These biosensors are essential for clinical diagnostics, environmental monitoring, and food safety due to their improved capabilities. However, third-generation biosensors strive for autonomous and self-regulated analyte detection, a paradigm shift Figure 4.

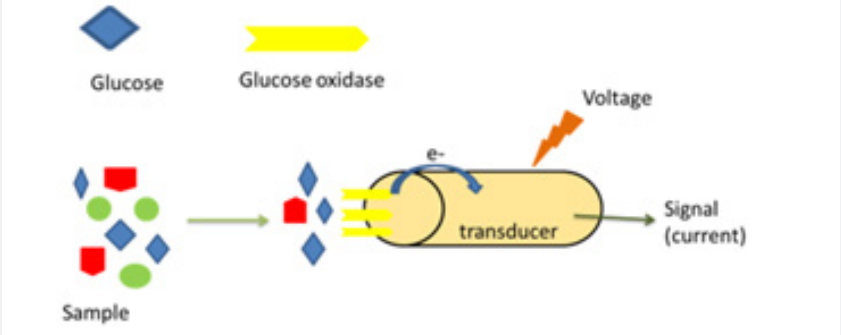

Figure 4: Representation of the working of biosensor.

Third- generation biosensors use biological interactions to activate sensor responses without mediators or other components. With this new technique, biological systems' sensitivity and specificity allow for more refined and robust biosensing [28]. Third-generation biosensors offer exceptional accuracy and dependability, promising to advance medical diagnosis, environmental monitoring, and more. Leland C. Clark Jr.'s pioneering work to the latest generations; multidisciplinary research and innovation have powered biosensor technology. By combining materials science, biochemistry, nanotechnology, and other sciences, researchers have advanced biosensing, improving healthcare, biotechnology, and environmental monitoring. As these interdisciplinary collaborations grow and technologies advance, may improve global health and quality of life [24].

Types of biosensors

These biosensors use enzyme selectivity and efficiency to catalyze reactions, allowing for fast detection and high sensitivity. They excel at clinical diagnostics, food safety monitoring, and environmental analysis. Immunosensors, on the other hand, use antibodies or antigens' high affinity and specificity to detect several targets, making them useful in medical diagnostics, disease detection, and drug screening. DNA biosensors accurately detect nucleic acid sequences in genetic analysis, disease diagnosis, and forensics [30]. Whole-cell biosensors detect substances using metabolic activity in living cells for environmental monitoring, bioremediation, and pharmaceutical research. Each biosensor has unique advantages and is suitable for specific applications and analytes, benefiting research and industry [31].

Glucose Based Biosensor

Continuous glucose monitoring (CGM) technologies have revolutionized diabetes management by allowing for real-time glucose readings. These devices monitor interstitial fluid glucose using various biosensors. Biosensors that use glucose oxidase (GOx), glucose-1-dehydrogenase (GDH), or hexokinase to measure

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aerometric enzyme electrodes are very popular. A major benefit of CGM systems is their ability to quickly detect glucose variations. Hypoglycemia and hyperglycemia, typical diabetic complications, must be managed quickly. By giving continuous glucose readings, CGM devices help patients and doctors make insulin dose, nutrition, and other diabetes management decisions [32]. Despite these benefits, CGM systems must overcome many hurdles to increase efficacy and dependability. Biofouling, calibration drift, selectivity, inflammatory reactions, sensor stability, and miniaturization are major difficulties. The buildup of biological material on a sensor, known as biofouling, can skew glucose values. After a while, the sensor's response deviates from its initial calibration, requiring frequent recalibration to maintain accuracy. Selectivity difficulties cause erroneous glucose readings when the sensor responds to other chemicals. Inflammation after sensor implantation can reduce performance and lifespan Figure 5.

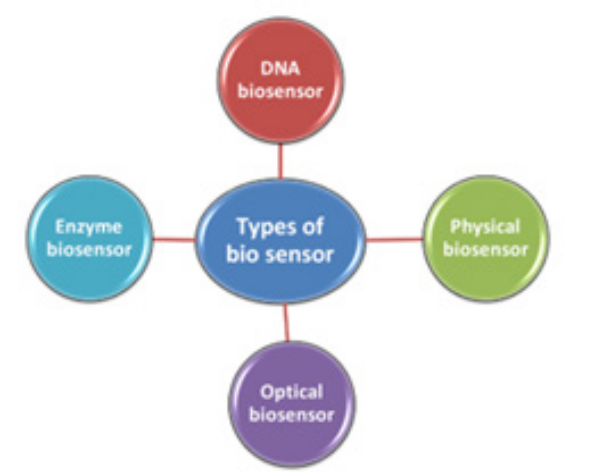

Figure 5: Schematic view types of biosensors.

Miniaturization is necessary for wearable and implantable CGM systems, while sensor stability is important for long-term glucose monitoring. We need innovative solutions and ongoing research to solve these problems. Novel coatings and materials reduce biofouling and improve sensor biocompatibility [33]. Advanced calibration methods and sensor designs can enhance precision and stability. Specific enzyme substrates or membrane technologies improve selectivity. Long-term sensor reliability requires limiting sensor implantation-related inflammation. Advances in microfabrication allow for smaller, more inconspicuous CGM devices, improving patient comfort and compliance. Clinical laboratories typically use the hexokinase test for spectrophotometric glucose measurement. Enzymatic glucose readings are accurate and dependable, and this assay validates CGM system performance. Continuous glucose monitoring technologies have improved diabetes management by providing real-time glucose dynamics and individualized treatment plans [34]. However, continued research and innovation are needed to overcome the remaining difficulties and improve CGM device performance and usability. Biosensors use enzyme selectivity and efficiency to catalyze reactions, allowing for fast detection and high sensitivity.

They excel at clinical diagnostics, food safety monitoring, and environmental analysis. Immunosensors, on the other hand, use antibodies or antigens' high affinity and specificity to detect several targets, making them useful in medical diagnostics, disease detection, and drug screening. DNA biosensors accurately detect nucleic acid sequences in genetic analysis, disease diagnosis, and forensics. Whole-cell biosensors detect substances using metabolic activity in living cells for environmental monitoring, bioremediation, and pharmaceutical research. Each biosensor has unique advantages and is suitable for specific applications and analytes, benefiting research and industry [35]. We use the enzyme families GO_x and GDH to construct glucose biosensors for blood glucose self-monitoring. Both enzyme families are required for glucose oxidation, although their redox potentials, cofactors, turnover rates, and glucose selectivity differ. Biosensors typically use GOx because it selects glucose better than GDH. GOx is also well-known for its ease of manufacture, affordability, and resistance to pH, ionic strength, and temperature changes. These properties make GOx-based biosensors suitable for laypeople without strict production or storage requirements. In GOx-based biosensors, molecular oxygen oxidizes D-glucose to gluconic acid and hydrogen peroxide via immobilized GOx. GOx's enzymatic activity requires FAD, a redox cofactor. FAD is the primary electron acceptor, and it converts to $FADH_2$ during the process. $FADH_2$ reacts with oxygen to form hydrogen peroxide. GOx-based biosensors use a platinum (Pt) anode for catalytic oxidation to detect hydrogen peroxide [36].

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Electrode counts electron transfers, which negatively correlate with blood glucose levels. This electrochemical technique measures glucose quickly and accurately. GDH-based aerometric biosensors, unlike GOx, are becoming popular due to their versatility and specificity. The GDH family includes GDH-NAD and GDH- pyro quinol in quinone. Unlike GOx, GDH enzyme activity is unaffected by dissolved oxygen. PQQ aids glucose oxidation by factoring the Quino protein GDH recognition element. GDH- based biosensors are stable, sensitive, and can work in oxygen-rich settings without interference.

There are three major approaches for electrochemical glucose sensing: measuring oxygen consumption, hydrogen peroxide formation, and diffusible or immobilized mediators to transport electrons from the enzyme to the electrode. Each approach has pros and cons, depending on sensor design, sensitivity, and application needs. Recent advances in GDH-based biosensors have expanded glucose monitoring technology [37]. These sensors may solve selectivity and environmental sensitivity difficulties in classic GOx-based systems. GDH-based biosensors are likely to help build next-generation glucose monitoring devices for diabetes treatment as research process [38].

Types of glucose-based biosensors

Glucose biosensors are classified into two types:

a) Enzymatic glucose biosensor

b) Non-enzymatic glucose biosensor global health and quality of life [29].

The enzymatic glucose biosensor

Due to its excellent glucose detection specificity and sensitivity, the immobilized GOx enzyme- based enzymatic glucose biosensor is popular. Immobilizing GOx makes the biosensor stable and accurate for glucose monitoring. Diabetic patients need accurate blood glucose self-monitoring (SMBG) readings for disease management. The enzyme-based biosensor catalyzes glucose oxidation to gluconolactone, creating hydrogen peroxide, which is electrochemically monitored to detect glucose content. Clinical and research contexts employ GOx-based biosensors extensively. They are widely used due to their ease of production, cost-effectiveness, and performance. Simple fabrication methods include electro polymerization, covalent cross-linking, and sol-gel entrapment allow enzyme integration onto electrode surfaces in these sensors [1].

For constant sensor performance throughout time and usage, stability is essential. The affordability of GOx-based biosensors allows for large-scale deployment in healthcare systems, enabling regular diabetic patient monitoring and rapid interventions. This is especially useful in resource-limited environments where financial restrictions may limit advanced diagnostic tools. In research applications, GOx-based sensors are dependable and cost-effective for researching glucose dynamics in biological and environmental environments. Another benefit of GOx biosensors is their durability. They work well under most conditions; however excessive pH, temperature, and detergents can affect enzyme function [39]. Although limited, the enzyme's stability in physiological pH ranges and common operational settings makes it a good choice for continuous glucose monitoring systems. The immobilized GOx enzyme-based glucose biosensor is essential for diabetes management and clinical and research applications due to its high specificity, sensitivity, stability, and cost. These sensors' research and enhancement could lead to more accurate, dependable, and accessible glucose monitoring solutions [40].

Non-enzymatic glucose sensor

To detect glucose, non-enzymatic glucose sensors conduct their operations directly employing the electrochemical oxidation of glucose as their principal mode of operation. When compared to enzymatic sensors, which are dependent on enzymes such as glucose oxidase (GOx) to catalyze the oxidation of glucose, this technique is a significant departure Figure 6. Nanostructured materials, such as Au-Ni alloy, have been developed as substrate electrodes for both enzymatic and non-enzymatic glucose sensors because of recent breakthroughs in the field. Several illuminating findings have been uncovered because of the comparative performance evaluations of various sensors. According to several studies, enzymatic glucose sensors, in comparison to their non-enzymatic equivalents, often demonstrate greater analytical performance [4,41]. To be more specific, it was discovered that the sensitivity of the enzymatic sensor was 1.4 times higher than that of the sensor that did not use enzymes. In addition, the enzymatic sensor displayed a much lower detection limit, which was 20.1 times lower than the detection limit of the non-enzymatic sensor. When it comes to reliable glucose monitoring, this better sensitivity and lower detection limit are necessary. This is especially true in the case of complex biological samples, where precision detection at low concentrations is necessary. The immobilization of enzymes onto the electrode surface in a steady manner is one of the most important variables that contribute to the enhanced performance of enzymatic sensors [42].

This immobilization not only improves the selectivity and stability of the sensor, but it also increases the efficiency of the catalytic process. Enzymes have a unique interaction with glucose molecules, which reduces the chance of interference from other compounds that are typically found in biological samples. Because of this, enzymatic sensors often have a high degree of selectivity, which guarantees that the glucose measurement is correct even when there are possible species that interfere with it, such as ascorbic acid (AA) and uric acid (UA). Additionally, the sustained immobilization of enzymes is a factor that contributes to the expanded linear range of enzymatic sensors. Furthermore, this indicates that they can properly measure glucose concentrations within a wider range, which is essential for applications that need monitoring of glucose levels in a variety of physiological and pathological states [43].

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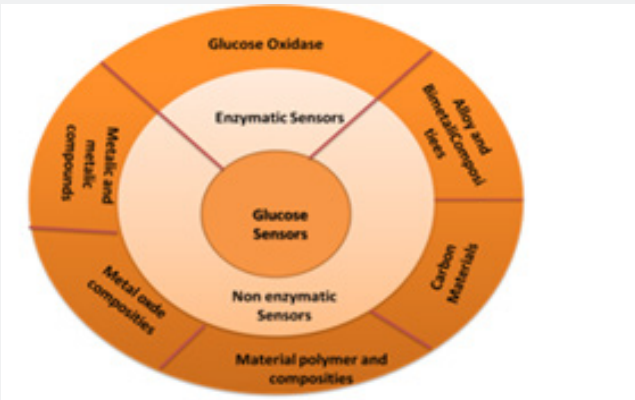

Figure 6: Schematic view of types of Glucose sensor.

As a result of the improved stability of the immobilized enzyme, the sensor has a longer operating lifespan, which in turn reduces the number of times it needs to be recalibrated or replaced. On the other hand, non-enzymatic glucose sensors, even though they eliminate the requirement for enzymes and have the potential to reduce production costs, frequently confront difficulties in terms of selectivity and sensitivity. Utilizing the direct electrochemical interaction that occurs between the glucose molecules and the electrode surface, these sensors can detect glucose. Even though nanostructured materials such as Au-Ni alloys improve the surface area of the electrodes and the catalytic capabilities of the electrodes, they are still unable to achieve the same level of performance as enzyme sensors. There are several substantial obstacles, including interference from other electroactive species and the larger overpotentials that are necessary for glucose oxidation. Nanotechnology and material science are conducting continuing research to investigate ways to improve the performance of non-enzymatic glucose sensors [44].

This study is being conducted despite the hurdles that have been presented. These sensors have the potential to improve their selectivity, sensitivity, and stability, which might potentially bridge the performance gap with enzymatic sensors. This could be accomplished through the development of composite nanomaterials, as well as through innovations in electrode materials and surface modifications. It is possible that non-enzymatic glucose sensors will become increasingly practical for a variety of applications as these improvements continue. These sensors will provide alternatives for glucose monitoring that are robust and cost-effective [45].

Brief History of Glucose Biosensor

Clark and Lyons played a key role in laying the groundwork for the first generation of glucose sensors during the 1950s and 1960s. 6. Their methods involved immobilizing a thin layer of glucose oxidase (GOx) enzyme over an oxygen electrode, using a semipermeable dialysis membrane. Additionally, they employed an electrochemical methodology to ascertain the oxygen consumption of the enzyme-catalyzed process [46]. A negative voltage was applied to the platinum cathode to perform a reductive detection of the oxygen consumption [47]. The method was enhanced by Updike and Hicks by employing an additional oxygen working electrode (without enzyme) and measuring the differential current between two working electrodes. This was done to consider fluctuations in the oxygen background in samples. After that, Guilbault and Lubrano proposed an additional enzyme electrode for the measurement of blood glucose that was based on aerometric monitoring of hydrogen peroxide as a product [48].

The first-generation glucose sensors have several drawbacks, including their excessively high applied potential for oxygen reduction or H2O2 oxidation, as well as their strong dependence on the oxygen that is present in the surrounding environment. Both the high negative and positive potentials have the potential to cause potentially harmful interference reactions of electroactive chemicals (such as ascorbate, urate, and paracetamol) in the bloodstream if there is no size- selective membrane present. First developed in the 1980s, the mediator-based glucose sensors of the second generation were initially brought into existence [49]. The redox active molecules known as mediators are extremely small and soluble. They can carry out redox reactions in a short amount of time and transport electrons between the redox center located at the active site of an enzyme and the electrode surface. Ferrocyanide, ferrocene derivatives, organic salts, and quinones are all examples of chemical compounds that can act as mediators. To gain an understanding of the mechanism behind the second-generation biosensors, the following equations could be utilized [50].

It is important to note that M(ox) and M(red) represent the reduced and oxidized versions of the mediator, respectively. In equation (5), mediators have assumed the role of O_2 molecules as the electron shuttle to facilitate a reaction with the redox active center of the enzyme. M(red) undergoes re-oxidation at potentials that are relatively low, and a current is generated when it meets the

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working electrode in equation (6). Incorporating mediators in lieu of the bulk glucose sensor allows for a reduction in interference from other molecules and eliminates the requirement for oxygen in the glucose sensing process [51]. In 1987, Medi Sense Inc. introduced the first personal glucose meter, which was made possible by the high specificity and reliability of glucose sensors that were of the second generation. After then, other companies such as Roche Diagnostics, Life Scan, Abbott, and Bayer released a variety of glucose sensors that had smaller sample loading volumes and more advanced capabilities Figure 7. However, the fundamental concept that underpins the design of glucose sensors has remained substantially unchanged.

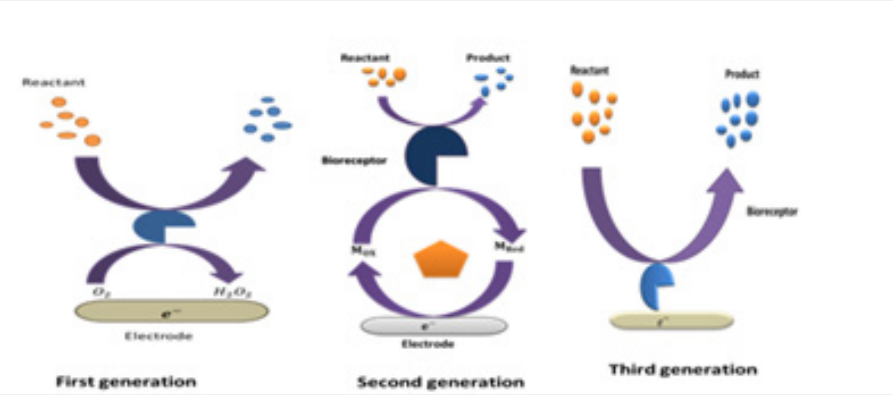

Figure 7: Schematic view of different generations of Glucose biosensor.

Even though the commercialization of several home-use, disposable devices based on screen-printed strips has successfully demonstrated the viability of second-generation glucose biosensors, the fact that most mediators are soluble results in short operation times and results that cannot be reproduced [52]. Furthermore, the potential biotoxicity of mediators prevents the second- generation biosensor from being used for in vivo detection of glucose levels. Over time, the goal of glucose sensing is to eliminate the requirement for a mediator or even an enzyme. This would result in a reduction in the complexity and expense of the manufacturing process, while simultaneously increasing the lifespan of the glucose sensor. The third-generation glucose sensor makes it feasible for direct electron transfer to occur between the redox center of the enzyme and the electrode. This results in extremely high sensitivity and repeatability, and it does not require the use of mediators. It is possible that the system could be run at a low voltage because it is close to the physiological enzyme redox potential of 0.44 degrees. The mechanism of the third- generation glucose biosensors can be described using the responses that are listed below [53]:

glucose

$$glu\cos e + GOx(FAD) \rightarrow gluconic\ acid\ + GOx(FADH_2).....(7)$$

$$GOx(FADH_2) + 2e^2 \rightarrow GOx(FAD) + 2H^+.....(8)$$

Because of the substantially lower operating potential, the interferential reactions of electroactive species are significantly reduced. This is a significant improvement. The third-generation glucose sensor is a great choice for monitoring blood sugar levels in living organisms because of its long-lasting nature and its compatibility with biological systems. An important disadvantage of this glucose sensor is that, in comparison to glucose sensors of the first and second generations, it has a linear range that is substantially lower [54]. Because of this, the implanted glucose monitors that are currently available on the market continue to use the same fundamental design as the ones that were used in the first generation. Additional work needs to be done to improve the performance of the third generation of glucose sensors to meet the criterion for commercialization [55].

Advantages of Glucose Sensing without Enzyme

Enzymatic glucose biosensors have dominated the glucose sensor market for over two decades, yet they confront numerous major obstacles to their development. Stability is a major challenge with enzyme-based biosensors. Protein enzymes are particularly sensitive to environmental variables. The enzyme most typically used in these biosensors, glucose oxidase (GOx), can only work at temperatures below 44°C and has a pH range of 2 to 8. Additionally, GOx needs precise ambient humidity to function. Sodium n-dodecyl sulfate at low pH and hexadecyl trimethyl ammonium bromide at high pH quickly inactivate GOx. GOx's chemical and thermal instability limit continuous monitoring applications, such as in the body or fermentation processes, where sterilization and stability are critical [4]. Several complex fabrication methods have been devised

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to stabilize enzymatic glucose biosensors. These include electro polymerization of the enzyme in a polymer matrix, covalent cross-linking on a pre-treated electrode surface, sol-gel entrapment, and electrochemical wiring of GOx to facilitate polymer chains [56]. These approaches increase short- term stability and enable single-use disposable sensors, but they do not solve enzyme-based sensors' long-term stability difficulties. The vulnerability of enzyme-based electrodes to severe temperatures and chemicals during manufacturing, storage, and use is a major negative. Cost-effective, long-lasting glucose biosensors are needed due to the increased prevalence of diabetes in underdeveloped countries. These locations require more robust and permanent alternatives to enzymatic glucose biosensors due to their high manufacturing costs and short shelf life. These challenges have sparked intensive research into non-enzymatic glucose biosensors. Non-enzymatic sensors are more resistant to extreme environmental conditions and cheaper to create because they do not use biological catalysts [57]. Nanotechnology and material science have enabled sensitive and stable non-enzymatic glucose sensors. Enzymatic sensors have limits, but these technologies promise to make glucose monitoring more dependable and accessible for a wider audience. Enzyme less glucose biosensors are promise for continuous glucose monitoring in various and demanding environments due to their stability, lower production costs, and extended shelf life [1]. As this science advances, glucose biosensors will become more practical and accessible worldwide.

Mechanisms of Non-Enzymatic Electrooxidation of Glucose

Non-enzymatic glucose biosensors use electrocatalysts to oxidize glucose. These electrocatalysts include metals, metal oxides, alloys, complexes, and carbon. In glucose oxidation, transition metal- containing enzymes are very effective. The active chemisorption model and the Incipient Hydrous Oxide Adatom Mediator (IHOAM) model have been proposed to explain glucose electrooxidation in electrocatalysts containing transition metals such as Au, Pt, Pd, $Co3O_4$, CuO, and RuO_2, as well as various alloys and complexes [4]. Pletcher's active chemisorption model says that glucose molecules stick to the electrocatalyst that is made of transition metals in a concentrated phase to turn glucose into oxygen. Following this, hemiacetalic hydrogen is extracted. Adsorption creates d- electron and d-orbital links between the adsorbate and transition metal substrate. The elimination of hydrogen during analyte chemisorption is thought to determine this model's rate. Evenly spaced adsorption sites on the electrocatalyst may boost glucose oxidation kinetics. In contrast, Burke's IHOAM model emphasizes hydroxyl radicals in electrocatalysis. In this idea, "active" metal surface atoms go through pre-monolayer oxidation, which creates an early layer of hydrous oxide with OH ads [57]. This layer speeds glucose electrooxidation and slows reduction. Lattice coordination and stability energy are low.

Pre-monolayer oxidation is more prevalent at lower potentials, especially on polycrystalline surfaces with discontinuous grain boundaries and edges. According to the IHOAM model, hydrous species form on the electrode surface, and then glucose molecules chemisorb, starting electrocatalytic oxidation. At very low potential, the hydrous pre-monolayer regenerates the metal surface. At a specific voltage, oxygen species oxidize the "active" metal again, repeating the glucose oxidation cycle. Both models reveal glucose oxidation electrocatalytic pathways using different electrode materials. According to the IHOAM model, noble metal-based materials have better electrocatalytic activity. Electrocatalysis needs hydroxyl groups because the starting hydrous pre-monolayer changes the oxidation state of the metal hydroxide. Nickel and copper-based electrodes are no exception [3]. Finally, the IHOAM model and the active chemisorption model help describe how transition metal-based glucose oxidation electrocatalysts work. These models improve non-enzymatic glucose biosensors, which may solve glucose monitoring and diabetes management problems. Research into electrocatalytic material mechanisms and optimization will advance glucose sensing and biosensor technology [58].

Nanomaterials Used for Electrocatalytic Glucose Sensing

Electrocatalytic glucose sensing has improved sensitivity, selectivity, and performance with nanomaterials. Excellent catalytic characteristics make metal and metal oxide nanoparticles like gold (Au), platinum (Pt), nickel (Ni), and copper (Cu) popular. Pt-based alloys like Pt-Pb and Pt- Ru are active and selective, and nanoporous Pt structures reduce interference. Alkaline solutions make Ni and Cu nanoparticles cost-efficient and effective, although physiological circumstances are difficult. Carbon-based nanomaterials like CNTs, graphene, and CNFs have large surface area and conductivity, enabling direct electron transport [33,59]. Single-walled and multi-walled CNTs are sensitive, although species like ascorbic acid (AA) and uric acid (UA) can interfere. Metal nanoparticles improve the performance of graphene and CNFs, which have high conductivity and surface area. Metal-organic frameworks (MOFs) and nanocomposites combine metal, metal oxide, and carbon-based strengths. Pt/NiO and Cu/NiO nanocomposites outperform their components. By using distinct shell and core materials, core-shell systems improve stability and performance. Nanomaterials make non-enzymatic glucose sensors more sensitive, reduce interference, and

enable glucose oxidation under varied situations, making glucose monitoring solutions more effective and trustworthy [60].

Transition metals

Transition metals, recognized for their ability to adopt different oxidation states and absorb other species on their surfaces, play a primary role in this process, making electrocatalysts extremely important. This adaptability greatly facilitates the ability to

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generate and activate intermediates during chemical processes, which is of critical importance. The presence of nanostructured metallic compounds enhances the performance of these materials as electrocatalysts, showcasing their distinctive physical, chemical, optical, and electrical properties [61]. Some of the best things about this material are that it has a high surface-to-volume ratio, high-index facets, a large specific surface area, great electrical conductivity, optical properties that can be changed, and great electrocatalytic activity. These qualities are primarily responsible for the relatively large proportion of surface atoms with free valences in comparison to the total number of atoms. These attributes are primarily due to the improvement in mass transfer characteristics and catalytic effectiveness [62]. The process of generating and improving nanostructures made of transition metals for use in a variety of catalytic applications has received substantial attention over the past few years.

Because of their increased surface characteristics and reactivity, these nanostructures have demonstrated a great deal of promise in the field of electrocatalytic biosensing, particularly in the field of non-enzymatic glucose oxidation applications [63]. Transition metals such as gold (Au), platinum (Pt), and palladium (Pd) have garnered significant attention due to their exceptional catalytic properties. Additionally, this domain has recognized copper (Cu) and nickel (Ni) as effective electrocatalysts. For instance, gold nanoparticles have outstanding catalytic characteristics because of their high surface area and their capacity to assist electron transfer processes. Nanoparticles accomplish this. Due to its exceptional conductivity and high level of stability, platinum remains a standard material in the field of electrocatalysis. Palladium, with its one-of-a-kind electrical capabilities, offers a more efficient and cost-effective alternative to platinum in a variety of catalytic processes [64]. Copper and nickel, on the other hand, are highly appreciated since they are inexpensive and possess a high catalytic activity, which makes them appealing for use in applications that are on a large scale. Nanostructured forms of different nanomaterials, like nanoparticles, nanowires, nanorods, and nanosheets, often make the electrocatalytic activity of the nanomaterial in question higher. In comparison to their bulk counterparts, these forms have a larger surface area and a greater number of active sites via which chemical reactions might initiate. Furthermore, the synthesis and modification of these nanomaterials make it possible to tune their electrical and structural properties, which in turn allows for the optimization of their performance for certain catalytic applications [65].

The discovery of nanostructures made of transition metals has opened new options in the science of electrocatalysis, particularly in the areas of biosensing and energy conversion. The exceptional characteristics of these nanoparticles, such as a high surface-to-volume ratio, good conductivity, and the ability to tune their optical and electrical properties, make them extremely efficient catalysts. As research continues to advance, we anticipate expanding the potential applications of these materials in various industries like medical diagnostics, environmental monitoring, and renewable energy. This will likely drive more innovation and technical progress [66].

Gold

Many studies have shown that gold nanoparticles, which are sometimes referred to as Au NPs, perform remarkably well in the process of glucose biosensing that is electrochemical and does not include enzymes. The construction of a biosensor made possible by Kurniawan et al. through the application of gold nanoparticles (AuNPs) on top of a thin gold electrode. This biosensor functioned remarkably well in a solution of 0.1M NaOH, displaying a detection limit of 0.5mM, a sensitivity of 160mAcm^2, and a linear detection range that extended up to 8mM. In addition, the biosensor had a performance limit of 0.5mM. This kind of deposition, which is carried out in a layer-by-layer fashion, increases the surface area and ensures that nanoparticles are distributed uniformly throughout the material, which eventually leads to an improvement in sensor performance [67]. By utilizing a self-assembling strategy, Jena and her colleagues were able successfully insert gold nanoparticles across a soul-gel three-dimensional silicate network. This accomplished. This forward-thinking design was crucial in the development of an enzyme-free aerometric glucose biosensor.

Phosphate buffer solution (PBS) with a pH of 9.2 is the environment in which it functions at 0.16V. Alternately, the electrode that modified with Au NPs was able to detect 50nM, had a sensitivity of 179mA mM^{-3} cm^{-2}, and had a linear range that extended up to 8mM. All these characteristics were seen in the electrode. Sol-gel creates a three- dimensional silicate network. This network stabilizes nanoparticles and increases glucose molecule interaction surface area [68]. This improves the sensor's sensitivity and lowers the detection limit. Ma and his colleagues created an enzyme-free glucose sensor by directly electroplating gold nanoparticles on indium tin oxide. Another major advance has been made. The Au NPs-modified ITO electrode broke down glucose in 0.01M NaOH and 0.05M PBS at pH 7.4. These solutions were 7.4ph. Direct electrodeposition and here nanoparticles on indium tetra oxide (ITO), making the sensor more durable and long lasting. This arrangement has strong electrocatalytic potential because of the ITO substrate's high conductivity and Au NPs' high surface area. They help transfer electrons during glucose oxidation. Gold nanoparticles' biosensing potential showed these non-enzymatic glucose sensors' outstanding performance. Adding Au NPs to sensors refines their sensitivity, detection limits, and linear detection ranges. Layer-by-layer deposition, self-assembly on a three-dimensional silicate network or direct electrodeposition can do this [68]. These qualities make glucose sensors a reliable and effective medical diagnosis alternative to enzymatic sensors. Non-enzymatic glucose sensors' endurance and efficiency enable continuous research and development, which could lead to biosensing breakthroughs for various analytes and applications. Ma and colleagues created a biosensor that could detect 0.004–5mM in 0.01M NaOH and 0.05–5mM in PBS

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at 0.2V. The electrode had 183.5mAcm^2 sensitivity and 0.005mM LOD in 0.01M NaOH. In clinical diagnostics, high sensitivity and a wide detection range are needed for accurate glucose monitoring for diabetes treatment. Another unique method was Zhao et al.'s green chemistry-based gold nanostructured film for enzyme-free glucose measurement. This biosensor, tested in pH 7.4 PBS, showed a linear range of 57.5mM to 30mM with detection limits of 0.72mM and 3.6mM at 0.3volts and 20.15volts [69].

Gold nanostructure production using green chemistry is more environmentally friendly and increases sensor biocompatibility for biomedical applications. To achieve voltametric and aerometric glucose perception, Cherenkov and Chung developed an electrode that was constructed out of gold nanowire arrays. The aerometric detection method functioned remarkably well in 0.1M NaOH, displaying a calibration range of 10mM and a sensitivity of 309mAmM^{2}cm^2 when running at 20.4volts. This was accomplished by exhibiting a calibration range of 10mM. According to the voltametric sensing method, the linear range was twenty millimoles, the sensitivity was forty- nine milliamperes per millimeter squared, and the detection limit was thirty millimoles [70].

Since it possesses dual functionality, the gold nanowire array electrode makes it possible for glucose sensing applications to be both flexible and sensitive, in addition to offering a wide detection range. Through the utilization of Au NP self-assembly on freestanding graphene paper, Xiao and his colleagues have made important advancements in the field of flexible electronics. A flexible electrode has been developed because of their efforts. Using electricity to find glucose and H_2O_2 in PBS solution at pH 7.4, this nanostructured composite electrode functioned effectively [71]. Gold nanoparticles (Au NPs) and graphene paper, known for its enormous surface area and conductivity, improve biosensor performance. This composite electrode is sensitive, stable, and bendable. It also encourages wearable biosensors and portable diagnostics.

The development of enzyme-free glucose biosensors shows the importance of gold nanostructures for sensor performance. Au NPs can be deposited in many ways for electrocatalysis. They can be placed one layer at a time, self-assembled, directly on an electrode, or coupled with flexible materials like graphene in electrocatalysis. Practical applications require improved detection limits, sensitivity, and linear detection ranges, especially in medical diagnostics, where glucose monitoring is crucial. Zhao et al. [72] biocompatible chemical synthesis process follows the increased emphasis on green technology in medical and environmental protection [72]. These nanostructured electrodes can detect biomolecules and environmental contaminants in addition to glucose sensing due to their flexibility and durability. To non-enzymatic biosensing, nanostructured materials made of gold represent a significant advancement. These materials are intriguing components for the future generation of biosensors because of their exceptionally high sensitivity, their vast detection ranges, and the one-of-a-kind fabrication methods that they employ. They have the capacity to tackle a wide variety of analytical problems that are present in the sectors of environmental monitoring and healthcare [73].

Platinum

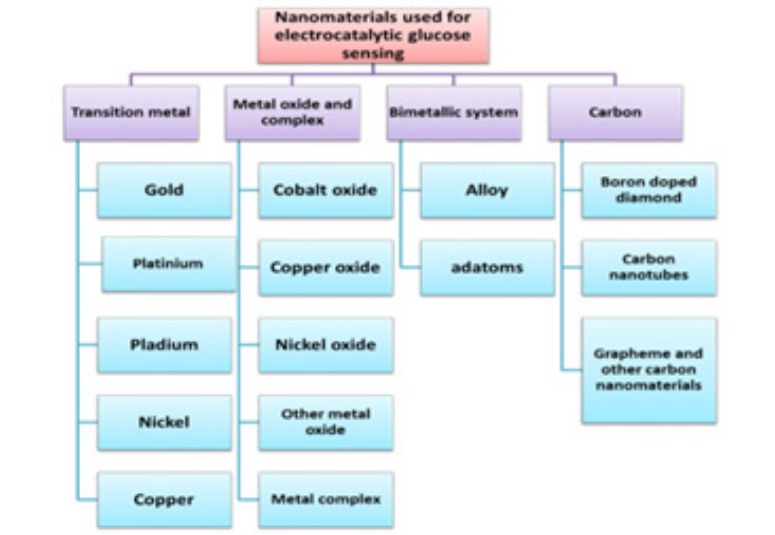

Figure 8: Schematic view of nanomaterials used.

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Platinum is noted for its catalytic activity with glucose and hydrogen peroxide, among others. Thus, it can be an electrocatalyst and biosensor. Unfortunately, the flat platinum electrode has many drawbacks that prevent its use in enzyme-free biosensors. Physiological species, especially chloride anions, can poison Pt surfaces. Chloride ions have a strong affinity for platinum, inhibiting active sites and preventing analytes from reaching the electrode. The electrode's biosensing and catalytic performance are greatly reduced by this poisoning [74]. Since chloride ions abound in every physiological environment, this is a constant worry. The second factor reducing Pt electrode electrocatalytic performance is blood chemisorption of several organic molecules. In medicine, Pt may bind to amino acids such ascorbic acid (AA), uric acid (UA), creatinine, and adrenaline. These compounds generate a chemisorbed layer that takes up active sites and changes the electrode surface, reducing catalytic activity Figure 8. This fouling effect is especially significant in biological samples with many organic components. Additionally, biosensors that use PT electrodes do not possess selectivity [75].

Because of the sluggish electron transfer and reaction speeds, the current responses of the target molecules are not very significant. Because of the slow electron transit, signal-to-noise ratios are reduced, which makes it more difficult to differentiate the signals of the target analyte from those of other electroactive species. The decreased selectivity of platinum- based biosensors results in decreased dependability and precision, which in turn renders them less practical. Surface area and biosensor sensitivity both decreased because of the flat topology of the Pt disc electrode [76]. However, electrode sensitivity decreases since catalytic active sites have a relatively small surface area. Researchers have tried a variety of approaches to enhance biosensors that are based on platinum. It is possible to change the surface of platinum by using nanostructured materials such as nanoparticles, nanowires, or nanoclusters.

These nanostructures increase the surface area of the electrodes as well as the number of active sites, which ultimately leads to an increase in sensitivity and catalytic efficiency. Combining platinum with other conductive materials, such as graphene or carbon nanotubes, are examples of composite materials that have the potential to enhance the sensitivity and selectivity of biosensors. It is possible to functionalize platinum surfaces by applying protective coatings or selective layers to prevent organic and chloride ion fouling. It is possible to prevent interference from species by using self-assembled monolayers (SAMs) or polymer coatings; nonetheless, the target analyte can still make its way to the surface of pure platinum [77]. Additionally, the kinetics of electron transfer and the biosensor's current responsiveness are improved by these functional layers. Platinum exhibits effective catalytic properties for the detection of glucose and hydrogen peroxide; nevertheless, its application in non-enzymatic biosensors is restricted due to the presence of surface poisoning, organic fouling, low selectivity, and a restricted surface area. Innovative nanotechnology and surface modification techniques could potentially contribute to the production of Pt-based biosensors that are more effective and dependable [78]. When it comes to non-enzymatic glucose sensing, nanostructured platinum materials can overcome the drawbacks that are associated with bulk platinum electrodes. Because of its exceptional sensitivity and resilience to interference, nanoporous platinum has captured the attention of the scientific community. The increased roughness factor of the electrode surface results in an increase in both the effective surface area and the catalytic activity [68].

Using nanoporous platinum electrodes, Park et al. [2] became the first to pioneer non-enzymatic glucose sensing. Compared to ascorbic acid (AA) and acetamido phenol, the porous Pt electrode had a higher level of responsiveness to glucose current signals, as demonstrated by their extensive research. The nanoscale dimensions of the Pt structure, which enhance the active surface area of glucose oxidation, make slow reactions more sensitive. This is because the Pt structure is tiny [79]. In addition, the nanoporous design resists fouling, which ensures that the electrode continues to function well even when exposed to high concentrations of chloride ions. A high sensitivity of $9.6 mAmM^{-1}cm^{-2}$ was established by the biosensor in the research conducted by Park et al. [2], and it had a linear range that extended up to 10mM. Following the groundbreaking work that was done, other investigations have produced nanoporous platinum electrodes for the sensitive detection of glucose without the use of enzymes. Nanoporous platinum has excellent surface properties, which means that these electrodes function better than other electrodes. The stability and reproducibility of nanoporous platinum electrodes make them an excellent choice for use in biosensing environments [80]. There has been a significant amount of research conducted on nanoparticles, nanotubules, and nanoporous platinum.

The glucose sensitivity and selectivity are both improved because of the tiny size and high surface area of platinum nanoparticles, which provide many catalytic active sites. Using electrodepositions, highly ordered platinum nanotubule arrays have been constructed for the detection of glucose without the use of enzymes. With a range of 2-14mM at $0.1 mAmM^{-3}cm^{-2}$, the nanotubule arrays demonstrate remarkable performance, enabling them to detect glucose concentrations as low as 0.1mM in PBS (pH 7.4). Additionally, they have a wide range of detection abilities [81].

It is necessary for nanotubules to be highly structured to achieve both a consistent distribution of catalytic sites and efficient electron transport. Another innovative concept was the utilization of three- dimensional dendritic platinum nanostructures on electrodes for enzyme-free electrocatalytic glucose biosensing. Increasing the amount of catalytic activity, these three-dimensional dendritic structures have a large surface area and many active sites. With a pH of 7.4, the electrodes had

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a linear range that extended from 1 to 20mM, were sensitive to 12.1mA mM^{-3} cm^{-2}, and had the ability to detect as little as 1.2mM within their range of operation [82]. Dendritic structure enhances biosensor sensitivity, stability, and endurance, making it suitable for long-term use in applications that are based in the real world. These advancements provide evidence that nanostructured platinum materials have the potential to enhance glucose sensors that do not rely on enzyme interaction. By improving surface area, electron transfer kinetics, and stability, these nanostructured materials provide a solution to the problems that are associated with broad platinum electrodes [83].

Due to the ease with which nanoporous, nanoparticle, nanotubule, and dendritic nanostructures may be assembled, the characteristics of the sensors can be adapted to meet the requirements of certain applications. Nanostructured platinum materials have finally brought about a transformation in the non-enzymatic glucose sensing process. These cutting-edge nanoparticles offer great sensitivity, selectivity, and dependable performance, which allows them to circumvent the issues that are associated with bulk Pt electrodes. Glucose monitoring devices become more dependable and effective because of this. It is possible that biosensing devices for other biochemical analytes besides glucose could be developed because of research and innovation in this field [84].

Palladium

Palladium (Pd) and its hybrids with carbon nanomaterials are receiving attention as non-enzymatic biosensing electrocatalysts. This is since they have a high electrocatalytic activity and are relatively inexpensive. These compounds are intriguing alternatives to platinum catalysts for the purpose of developing biosensors that are inexpensive. A porous tubular Pd nanostructure was produced by Bai et al. for the purpose of glucose sensing. The template for this structure was CdS-modified alumina. The screen-printed porous tubular Pd electrode (SPE) had a detection limit of 0.08mM and came with a signal-to-noise ratio of three [85]. It was capable of measuring between 0.1 to 58mM. Using an aerometric method, this sensor measured glucose at 0.6V (vs. Ag/AgC) in PBS with a pH of 8.1 or higher. Increased sensitivity and detection limits are achieved because of the porous structure's high surface area, which enhances the interaction between the electrode and glucose. As part of their efforts to improve the area, Meng and his colleagues developed a hybrid nanomaterial that consists of Pd nanoparticles and SWCNTs.

In PBS with a pH of 7.4, this hybrid showed a high degree of sensitivity to the non-enzymatic oxidation of glucose. The glassy carbon electrodes (GCE) that were modified with Pd/SWCNTs were particularly effective at neutralizing poisons, even when there was a significant amount of chloride ions present [86]. The significance of this lies in the fact that chloride ions are prevalent in physiological conditions and have the potential to influence the performance of sensors. A high sensitivity of 160 mA mM^{-3} cm^{-2} was observed at a voltage of -0.35V vs SCE. Additionally, the hybrid material-modified electrode exhibited a low detection limit of 0.2 ± 0.05mM and a good linear range of 0.5-17mM across the range of concentrations.

The time it took to react was three seconds. The efficiency of biosensors is improved by SWCNTs because they increase the rate of electron transfer and the surface area. A composite material consisting of functionalized carbon nanotubes (FCNTs) and platinum nanoparticles (Pd NPs) was developed by Chen et al., and it can detect glucose without the use of enzymes. This customized electrode possessed anti-interference and anti-poisoning properties that were of the highest quality [87]. At a voltage of +0.4V (in comparison to SCE), the modified Pd NPs/FCNTs electrode was able to measure aerometric glucose in 0.1MNaOH.

The linear range of the sensor was from 0 to 46 mM, and its sensitivity was around 11.4 mA cm^2. CNT functionalization increases the number of active sites and improves the dispersion of Pd nanoparticles, which in turn improves the electrocatalytic activity and stability of the sensor. Another work was published by Wang and his colleagues, in which they discussed a graphene oxide hybrid with well-dispersed Pd NPs that has the potential to be used for glucose measurement without the utilization of enzymes. On the other hand, the biosensor was able to detect 0.2–10 mM in a 0.1 M NaOH solution at +0.4 V against SCE with a reaction time of two seconds. Conductive graphene oxide has a huge surface area [88]. Electrode catalytic activity is uniform due to evenly distributed Pd nanoparticles. In situ Pd NPs/Graphene Nanohybrid with Navion-functionalized Glucose Biosensor by Lu et al.

With a low detection limit of 1μM in 0.1M NaOH solution at +0.4V (vs. SCE), the sensor measures glucose from 10μM to 5mM. Perfluorinated ion-exchange resin Navion helps glucose molecules reach catalytic sites and rejects interfering species, boosting sensor selectivity. The breakthroughs in Pd-based hybrid materials propose non-enzymatic glucose sensing. Pd improves electrocatalytic activity, stability, fouling, and interference resistance with CNTs and graphene [89]. As a result of their high surface area and conductivity, these hybrid materials have the potential to detect glucose in medical diagnostics and continuous glucose monitoring devices in a quick and sensitive manner. Finally, hybrid nanomaterials based on Pd improve enzyme-free glucose sensing. The high sensitivity, broad linear ranges, quick reaction times, and anti-poisoning properties of these sensors are beneficial to applications in the fields of healthcare and analysis. The investigation and improvement of hybrid materials could lead to improvements in biosensors [90].

Nickel

Nickel (Ni) electrodes react differently from Au, Pt, and Pd electrodes. Thus, they have been used in many studies for glucose oxidation without enzymes. Nickel-based electrodes use nickel (III) oxyhydroxide as a catalyst. The redox pair $Ni(OH)_2$ and Nio

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OH are crucial to glucose oxidation. This occurs due to the surface bond change reaction. The oxidation of nickel hydroxide (Ni $(OH)_2$) to nickel oxide (Nio OH) releases water and one electron when hydroxide ions (OH^-) are present. After Nio OH oxidizes glucose and reverts to Ni (OH), the redox cycle is complete. Nickel electrodes cannot conduct electrons directly between glucose and the metal surface, unlike gold, platinum, and palladium electrodes. Fleischmann found that Ni (III) oxyhydroxide oxidizes glucose [91]. Ni-based electrodes perform better and last longer due to steady and constant catalytic Ni $(OH)_2$/Nio OH redox cycling. This mechanism is suitable for glucose sensing since it performs reliably in alkaline conditions. The steady and active Ni $(OH)_2$/Nio OH redox pair makes this method valuable. Researchers have incorporated nanostructures and composites to nickel electrodes to boost their electrocatalytic activity and glucose detection sensitivity. These advances make nickel-based electrodes a promising low-cost, high-performance option for non-enzymatic glucose sensors [92].

Wang and colleagues successfully produced highly ordered nickel nanowire arrays (Ni NWAs) for non-enzymatic glucose sensing. The Ni NWA electrodes exhibit a high sensitivity of 1043 mA mM^{-1} cm^{-2} and a low detection limit of 0.1mM. A wide linear range of 0.5mM to 7.0mM helps them detect glucose.

The highly structured nanowire structure boosts sensitivity by increasing surface area and electron transport. Electro spun Ni nanoparticle-loaded carbon fiber paste electrodes by Liu et al. provide non-enzymatic glucose biosensing. The biosensor has a linear 2mM0-2.5mM range and 1mM detection limit [93]. Electrospinning creates a porous, conductive network that makes glucose molecules accessible to Ni nanoparticles, enhancing sensor sensitivity and detection limits. SMWNTs covered by Ni NPs are used for enzyme-free glucose monitoring. Ni NPs/SMWNTs hybrid biosensors had a linear range from 1mM to 1mM and a 500nM detection limit after 3 seconds. This hybrid material creates a sensitive and stable glucose sensor by combining SMWNTs' strong conductivity and vast surface area with Ni nanoparticles improved catalytic capabilities.

Stable and anti-interference, the modified nanohybrid electrode was useful [94]. Numerous investigations demonstrate high sensitivity (mA mM^{-1} cm^{-2}) of Ni-based nanomaterials for non-enzymatic glucose oxidation. A study discovered that Ni nanoflakes on Ti substrates were most sensitive at 7.32mA cm^2. Nanoflakes' high surface area and catalytic activity enable glucose oxidation, boosting performance. Although beneficial, Ni nanomaterial-based non-enzymatic glucose sensors have considerable limitations. Most issue is their inability to detect glucose in physiological pH solutions. Hydroxyl ions in the electrolyte create Nio OH electrocatalyst. These ions are common in alkaline but rare in physiological or neutral pH. The dependency limits biological sample use of Ni-based glucose sensors. Although chloride ions do not dirty Ni-based electrodes, selectivity is low [95].

Electroactive species in biological samples may impact glucose detection, causing mistakes. Researchers are improving glucose selectivity by changing electrode surfaces or adding materials. Due to their sensitivity and longevity, Ni-based nanoparticles are promising for non-enzymatic glucose sensing. We must overcome physiological pH and selectivity to detect glucose. Research and development are addressing these issues to provide reliable, accurate, and affordable glucose sensors for clinical and personal health monitoring. Ni-based electrodes have been extensively explored for non-enzymatic glucose oxidation, achieving sensitivity of mA mM^{-1} cm^{-2}. Fleischmann found that Ni-based electrodes catalyze well after Nio OH production [96].

This oxide layer allows glucose, and other small organic compounds oxidize at similar potentials. In alkaline liquids, Ni electrodes oxidize small organic molecules at +0.5V. Nio OH's strong reactivity oxidizes numerous substrates. Ni-based electrodes oxidize ethanol faster than glucose. Ni electrodes can start activities beyond glucose sensing because they easily oxidize ethanol. Oxidizing multiple small organic molecules at the same voltage is useful and difficult. Ni-based electrodes are useful for alcohol detection, fuel cells, and glucose biosensing due to their broad catalytic potential. But this broad oxidizing potential contradicts glucose specificity. In biological samples, ethanol and other small organic molecules can affect glucose measurements [97].

Ni-based electrodes are sensitive and efficient at oxidizing glucose, but selectivity is still a research focus. Selectivity can be improved by favoring glucose molecules on the electrode surface or adding components that distinguish glucose from other oxidizable substances. These methods reduce interference from other species and improve the specificity and practicality of Ni-based non-enzymatic glucose sensors. Ni-based electrodes have high sensitivity and broad non-enzymatic glucose oxidation catalytic activity [98]. Ni-based sensors can oxidize tiny organic compounds like ethanol at the same voltage, demonstrating their adaptability and difficulties. We must address selectivity to produce dependable and accurate glucose biosensors that function in complex biological contexts. In this area, research and innovation may help Ni-based glucose sensors overcome these obstacles and improve performance [99].

Copper

Copper (Cu)-based electrodes behave in a manner that is comparable to that of their nickel (Ni) counterparts when it comes to the electrooxidation of glucose. However, the electron transfer channel between Cu (II)/(III) is not as evident as it is for Ni-based electrodes, even though the redox pair of Cu (III)/Cu (II) is highly significant for accelerating the reaction. Notwithstanding

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this, non-enzymatic nanostructured copper-based glucose sensors have been receiving a growing amount of interest over the past few years. The capacity of electrodes modified with copper nanoparticles (Cu NPs) and copper nanobelts (Cu NBs) to detect glucose in a nonenzymatic manner was the subject of a comprehensive investigation conducted by Huang et al. Additionally, they investigated the movement of electrons through copper foil [64]. Cu NB electrodes were shown to have significantly greater reduction and oxidation reactions in PBS buffer than Cu foil and Cu NP electrodes. This discovery was made because of the reasons stated above. Additionally, in an electrolyte containing 50mM NaOH, the aerometric response of Cu NB electrodes was significantly higher than that of Cu NP electrodes. A glucose sensor based on copper nanotubes displayed an impressive sensitivity of 77.8 milliampere-meter squared [100]. With a concentration range of 10mM to 1.13mM, we found that there was a linear

connection between the glucose concentration and the oxidation current. Kang and Male investigated how Cu NPs combined with MWCNTs and SWCNTs affected glucose oxidation without enzymes. The modified glassy carbon electrode (GCE) with Cu NPs and MWCNTs demonstrated high sensitivity (17.76 mA mM^{-3} cm^{-2}), low LOD (0.21mM), and short reaction time (5seconds). A linear glucose detection range of 0.7mM to 3.5mM was shown. Alternatively, the Cu NPs/SWCNTs-modified GCE showed 250nM reaction time, 10seconds LOD, and 256.3mA mM^{-1} cm^{-2} sensitivity. The current response was linear with glucose concentration up to 500mM [101]. Another enzyme-free glucose biosensor comparison using Ni and Cu nanoparticles. The table shows that Ni and Cu nanoparticle-modified electrodes are used for alkaline solution glucose detection. Although these electrodes were sensitive to mA mM^{-3} cm^{-2}, their linear range was limited and aerometric detection required high potentials (e.g., 0.6V), making it difficult to avoid undesirable reactions. Because of their high sensitivity and rapid response times, electrodes based on copper have the potential to be suitable for glucose sensing that does not include enzymes [102]. To circumvent restrictions such as linear range and high operating potential, copper-based sensors for glucose monitoring are currently being put through the development process. Through a better understanding of electron transfer pathways and the optimization of electrode materials and topologies, the performance and utility of Cu-based non-enzymatic glucose sensors should ultimately be improved [103].

Complexes & Metal Oxides

Cobalt oxide

Prior to the groundbreaking research carried out by Ding et al., a considerable amount of attention had not been dedicated to the utilization of cobalt oxide for the aim of non-enzymatic electrochemical biosensing. Significant progress was made because of the investigation that Ding, and his colleagues carried out into the capacity of electro spun cobalt oxide nanofibers (Co_3O_4 NFs) to aid in the process of glucose breakdown [104]. Their ability to perform sensitive and selective glucose detection was made possible by the employment of Navion-modified glassy carbon electrodes (GCE) and nanofibers made of Co_3O_4 material. Because of this, the utilization of cobalt oxide glucose sensing became viable. Ding believes Co_3O_4 nanofibers' electrocatalytic activity in alkaline solutions is due to their transition into CoO_2. This transition helps CoO_2 oxidize glucose better. This research revealed cobalt oxide's electrochemical characteristics, enabling its use in enzyme-free glucose detection. Cobalt oxide glucose electrodes improved electrochemical biosensing [82]. Electrocatalytic applications benefit from cobalt oxide's conductivity, stability, and catalytic activity. Ding and colleagues showed that cobalt oxide nanofibers could detect glucose selectively, opening new biosensing platforms. Electrochemical biosensing with cobalt oxide has a variety of applications beyond glucose detection [105]. Researchers are conducting more research to enhance the sensitivity, selectivity, and compatibility of cobalt oxide-based electrodes with a variety of electrolytes and operating conditions. These advancements will lead to advanced biosensing technologies for healthcare, environmental, and industrial applications [106].

$$2CoO_2 + C_6H_{12}O_6\left(glu\cos e\right) \rightarrow 2CoOOH + C_6H_{10}O_6\left(gluconolactone\right).....(7)$$

Studies on cobalt oxide-based materials for non-enzymatic glucose sensing have advanced biosensor technology and excellent performance metrics. Following Ding et al.'s pioneering work on Co3O4 nanofibers (NFs), Kung et al. synthesized acicular cobalt oxide nanorods (CoO NRs) for glucose detection. This research showed that CoO NR-modified electrodes could selectively detect glucose without a Navion membrane, which stops molecules having negative charges from getting in the way [107]. The CoO NRs-based glucose sensor outperformed Ding's electrode with a sensitivity of 571.8mA mM^{-1} cm^{-2} and a low LOD of 0.058mM.

Its larger linear range of 3.5mM and lower detecting potential of 0.5V made it more practicable for glucose sensing. Another notable development in cobalt oxide-based glucose sensors was Dong et al.'s freestanding electrode of 3D graphene and Co_3O_4 nanowires. This biosensor outperformed Kung's CoO NRs-modified electrode with a sensitivity of 3.39mA mM^{-1} cm^{-2} and a LOD of 25nM. The 3D graphene/Co3O4 nanowire electrode had a linear range of 80mM, which was lower than Ding and Kung's biosensors [108]. However, the combination of 3D graphene and Co_3O_4 nanowires improves conductivity, surface area, and stability, making it ideal for glucose sensing. Dong's group introduced a graphene-cobalt oxide needle electrode to expand cobalt oxide-based electrode applications. This needle electrode detected glucose in micro-droplets at linear values of 50-300mM. This novel method could enable rapid and accurate glucose monitoring in clinical settings using microfluidic systems or point-of-care diagnostics. These investigations demonstrate cobalt oxide-based materials' versatility and potential for non-enzymatic glucose sensing. Exploration and modification of these materials could

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lead to better biosensing platforms with improved sensitivity, selectivity, and reliability for glucose monitoring in healthcare, biomedical research, and beyond [109].

Copper oxide

In recent years, copper oxide (CuO) has emerged as a highly promising material for non-enzymatic glucose biosensing. Because of its good electrochemical characteristics and catalytic activity, it has attracted significant research attention, making it an attractive candidate for this application [64]. The electrochemical oxidation of glucose on a copper oxide electrode closely resembles the process on a bare copper electrode. Zhuang and colleagues' study demonstrated the potential of CuO nanowire-modified Cu electrodes for non-enzymatic glucose sensing. The improved catalytic CuO nanowires demonstrated their improved catalytic activity by displaying a substantially lower overpotential for glucose oxidation in their biosensors compared to electrodes made of bare copper. Ranging from 0.4mM to 2mM, a low limit of detection (LOD) of 49nM (s = 3), and a sensitivity of 490 mA mM^{-1} cm^{-2} at an applied voltage of 0.33V (against Ag/AgCl), this biosensor displayed remarkable performance features [110].

For glucose sensing without enzymes, Wang et al. & Zhang et al. both talked about modified CuO/Cu nanowire composite electrodes and CuO nanowires. We conducted both studies in the same manner. When it came to glucose detection, Wang's electrode revealed a speedy response time of two seconds and a low detection limit of forty-five nanometers, but Zhang's biosensor demonstrated a broad linear range that extended from 0.1 to twelve millimoles. The findings of these investigations collectively demonstrate the adaptability and efficiency of CuO-based electrodes for glucose sensing applications. Using flower-like CuxO modified Cu electrodes, Li investigated the possibility of developing an enzyme-free biosensor.

This sensor had a high sensitivity of 1.62 milliamperes per millimoles per centimeter over a linear concentration range of up to 4 millimoles. This shows that copper oxide nanostructures have a lot of potential for glucose electrocatalysis [111]. Researchers have also investigated CuO nanofibers and CuO nanospheres for glucose electrocatalysis, in addition to nanowires. However, CuO nanowire-augmented electrodes seem to outperform other structures in biosensing operations. Based on these observations, it appears that the one- dimensional morphology of nanowires provides several distinct benefits. These advantages include a high surface area-to-volume ratio and greater catalytic activity, both of which lead to improved sensitivity and selectivity in glucose detection [112]. We coupled Cu_2O nanoparticles (NPs) with multiwalled carbon nanotubes (MWCNTs) to further enhance the sensitivity of copper oxide-based biosensors. Jiang reported that a CuO NPs modified MWCNTs array electrode had an extraordinarily high sensitivity of 2.596 mA mM^{-1} cm^{-2} over a concentration range that extended up to 1.2mM, with a limit of detection (LOD) of 0.2mM within the experiment. This electrode also displayed a rapid response time of within one second upon the injection of 0.1mM glucose, which highlights its potential for applications that include monitoring glucose levels in real time. The research on copper oxide-based biosensors for non-enzymatic glucose detection has revealed copper oxide nanowires as particularly effective sensing materials [113]. In conclusion, the research has produced findings that are encouraging. Further optimization of electrode designs and compositions, along with research into novel nanomaterial combinations, could lead to increased sensitivity, selectivity, and practical usability of copper oxide-based biosensors in glucose monitoring and related biomedical applications. This has the potential to be accomplished [114].

Nickel oxide

Providing the foundation for the electrochemical oxidation of glucose on a NiO-modified electrode is the redox pair of Ni $(OH)_2$/Nio OH that is created by NiO. This pair is identical to the one that is generated by a Ni-based electrode [91]. Several studies have highlighted the promising electrochemical properties and performance of biosensors that are based on nickel oxide (NiO). Recent research has witnessed a surge in the exploration of nickel oxide (NiO) nanoparticles for non-enzymatic glucose sensing. Mu and his colleagues investigated the electrochemical characteristics and analytical performance of carbon paste electrodes (CPE) treated with nano-NiO [115]. Within a span of five seconds, their biosensor demonstrated quick response kinetics, exhibiting a sensitivity of 43.9nA mM^{-1} cm^{-2} and a low limit of detection (LOD) of 0.16mM simultaneously. The concentration range of the calibration plot, which went from 1 to 110mM, was chosen to show how flexible and useful NiO nanoparticles could be in glucose sensing applications [116].

Differently, Samiur and Zhang both wrote about how they made glucose biosensors out of nanocomposite materials made of nickel oxide and multiwalled carbon nanotubes (MWCNTs). These biosensors eliminated the requirement for enzyme components. Furthermore, we discovered that MWCNTs considerably increased the reactivity of NiO for glucose oxidation, ultimately leading to an improvement in sensor performance. Zhang's biosensor had a high sensitivity of 1.77mAmM^{-3}cm^{-2} and a linear range of up to 7mM. Its limit of detection (LOD) was set at 2mM. Samiur's electrode, on the other hand, had a more extensive linear range that extended from 0.2mM to 20mM, and it had a lower limit of detection (LOD) of 0.16mM. Over the course of these experiments, it has become clear that NiO nanoparticles have the potential to serve as efficient sensing materials for glucose detection without the use of enzymes [116].

Not only does the incorporation of carbon nanotubes or other nanocomposite structures into NiO result in an increase in NiO's catalytic activity, but it also results in an improvement in the sensor's sensitivity, selectivity, and stability. Furthermore, the

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ability of nickel oxide-based biosensors to detect glucose across a broad concentration range demonstrates their adaptability. This means that they are suitable for a wide range of applications in biomedicine and clinical medicine. The development of biosensors based on nickel oxide (NiO) is meeting the growing demand for accurate, quick, and cost-effective glucose monitoring technologies. Continued research efforts focused on refining electrode design, material composition, and fabrication procedures in the field of glucose sensing and other relevant biomedical fields will further enhance the performance of NiO-based biosensors and their practical applications [117]. Exploring novel strategies such as surface functionalization, nano structuring, and interface engineering can further enhance the electrocatalytic properties and biocompatibility of NiO nanoparticles. This will facilitate the creation of next-generation glucose biosensors with enhanced performance and practical applications. The recent developments in biosensors based on NiO nanoparticles represent significant progress towards the creation of glucose sensing platforms that are very sensitive and dependable. These platforms have the potential to transform the field of biomedical diagnostics as well as customized healthcare [118].

Other metal oxides

Researchers have developed a wide variety of glucose sensors with improved performance characteristics because of studying nanostructured metal oxides for non-enzymatic biosensing. These sensors are particularly promising. Chen et al. showed an aerometric glucose sensor that doesn't use enzymes. It is based on MnO_2 and multiwalled carbon nanotubes (MWCNT). To achieve effective glucose oxidation, this sensor makes use of the catalytic activity of MnO_2 nanoparticles as well as the conductivity of MWCNTs. Si et al. similarly reported the synthesis of a nanocomposite, composed of hierarchically ordered Mn_3O_4 and three-dimensional (3D) graphene. They utilized this nanocomposite for catalytic glucose metabolism and biosensing. This cutting-edge nanocomposite structure provides a high surface area and makes it easier for electrons to travel quickly, both of which contribute to increased sensor performance. Zinc oxide, generally known as ZnO, has presented itself as a potentially useful material for the non-enzymatic biosensing of glucose [119]. Dar et al. and Baby et al. introduced ZnO nanorods and ZnO nanoparticles modified with MWCNTs for glucose detection, respectively. These ZnO-based biosensors exhibit enhanced electrocatalytic activity towards glucose oxidation, enabling glucose detection that is both sensitive and selective without the need for enzyme components.

Researchers have also discovered that ruthenium dioxide (RuO_2) can detect phenolic compounds and glucose without the need for enzymes. Glucose sensors can improve their sensitivity and selectivity by using modified electrodes that incorporate RuO2 nanoparticles, which in turn enables precise and dependable glucose monitoring in a variety of applications. Cao et al. have utilized iron oxide (Fe2O3) nanowire arrays to develop glucose sensors that do not rely on enzyme intervention. These Fe2O3-based biosensors have exceptional electrocatalytic characteristics and high sensitivity to glucose oxidation, making them suitable for glucose sensing applications in biomedical and environmental monitoring. Silver oxide (Ag_2O) nanostructures have demonstrated potential as useful materials for the development of non-enzymatic glucose biosensors [33]. Fang et al. described Ag_2O nanoballs grown on a copper substrate as a novel glucose sensor that exhibited improved electrocatalytic activity in alkaline solutions. This was in comparison to previous Ag_2O nanostructures, such as nanoflowers and nano spindles. When it comes to non-enzymatic glucose biosensing, the exploitation of nanostructured metal oxides offers a multitude of benefits, including excellent sensitivity, selectivity, and stability. The presence of these materials results in huge surface areas, which in turn makes electrochemical reactions more efficient and enables accurate detection of glucose even at low concentrations. We will continue research activities focused on refining the synthesis processes, morphology, and surface chemistry of nanostructured metal oxides to further improve the performance and usability of non-enzymatic glucose biosensors in a variety of domains, including healthcare and environmental monitoring [120].

Metal complexes

Metal complexes, especially those combining cobalt and iron, are popular due to their electrocatalytic characteristics, notably in small-molecule oxidation. Such complexes, such as metal hexacyanoferrates and Metallo phthalocyanines, are effective in electrochemical applications like glucose detection. Hexacyanoferrates are coordination compounds with metal centers and cyanide ligands. Due to redox reactions, ferricyanides and ferrocyanides are electrocatalytic. Electrodes undergo modification in glucose sensing to oxidize glucose, thereby producing a current proportional to glucose levels. Wang showed that metal hexacyanoferrates make good glucose sensors. Wang created a sensor with a low limit of detection (LOD) of 1.25mM at 3 seconds and a broad linear range from 5mM to 2.5mM by altering a glassy carbon electrode (GCE) with metal hexacyanoferrate [121]. This sensor showed good sensitivity and reliability, demonstrating metal hexacyanoferrates' non-enzymatic glucose-detecting capability. Metallo phthalocyanines (MPcs) are another promising electrocatalytic metal complex. Metal ions are at the heart of phthalocyanine ligands, which are large aromatic macrocycles like porphyrins. We can modify MPcs with substituents to enhance their electrocatalysis and solubility. Researchers have extensively explored Cobalt phthalocyanine (CoPc) and its derivatives for glucose oxidation catalysis. Barrera et al. conducted a comparison of the electrocatalytic activity of substituted cobalt phthalocyanines. They studied Cobalt phthalocyanine (CoPc), hexadecafluorophthalocyanine ($CoF_{16}Pc$), octaethylhexyloxyphthalocyanine (CoOEHPc), tetraaminophthalocyanine (CoTAPc), and

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tetrasulfophthalocyanine. The unsubstituted CoPc has the highest glucose oxidation electrocatalytic activity [122].

The unsubstituted CoPc has great electrical and structural properties that let glucose molecules interact and transfer electrons, which leads to better performance. Ozcan et al. created a glucose biosensor that doesn't use enzymes. It uses overoxidized polypyrene nanofibers that have been treated with CoTSPc. This biosensor performed well in alkaline solutions with a wide linear detection range of 0.25–20mM, a low LOD of 0.1mM at 3seconds, and great repeatability with a 2.7% RSD. The biosensor was stable and resistant to interference, making it ideal for glucose monitoring. These metal complexes electro catalyze glucose oxidation in alkaline solutions in a multistep manner. When the metal complex oxidizes, an active oxidized species emerges. This active species oxidizes glucose and generates an electrical signal. The metal complex's electrical characteristics, oxidized species stability, and electron transport ability determine this process's efficiency. Non-enzymatic glucose sensors based on metal complexes have various benefits over enzymatic ones. Concerns about stability and a shorter life span for glucose oxidase (GOx)-based enzyme sensors can be caused by enzyme denaturation and degradation [123]. Metal-complex-based sensors are more stable and can withstand significant pH and temperature changes. They also measure glucose more accurately due to less biomolecule interference.

Metal complexes such as metal hexacyanoferrates and Metallo phthalocyanines are great for non-enzymatic glucose sensors because they have strong electrocatalytic activity. Researchers from Barrera et al. and Ozcan et al. found that these complexes, especially CoPc and CoTSPc, are very good at detecting glucose oxidation in alkaline solutions and have a wide range of sensitivity. They are also very stable. They demonstrate the potential of metal complex-based electrochemical sensors for clinical diagnostics and continuous glucose monitoring [124].

Bimetallic Systems

Bimetallic compounds' unique electrical characteristics and enhanced catalytic activity make them promising candidates for high-performance electrocatalysts. These materials use two metals that synergistically improve electrocatalysis. The main bimetallic electrocatalysts include alloys, adatoms, and metal (oxide)-metal oxide composites. Each type of glucose is electrooxidized differently, making it suitable for non-enzymatic glucose monitoring. A homogenous atomic combination of two metals creates bimetallic alloys. These combinations can improve catalytic characteristics over individual metals. Due to better electron transport and more active sites, platinum alloys containing palladium, gold, or nickel have exhibited exceptional glucose oxidation activity [81]. These alloys can improve stability and toxin resistance, which are essential for sensor longevity. Adatoms are formed by depositing one metal layer onto another. This bimetallic arrangement can drastically alter base metal surface characteristics, improving catalytic activity. Adatoms can build new active sites and change the electrical environment to improve glucose adsorption and activation.

For instance, gold adatoms on a platinum surface can minimize the poisoning effect of glucose oxidation intermediates, sustaining catalytic performance over time. Metal-oxide composites combine the benefits of metal and oxide [33]. Some composites have catalytic capabilities that their components do not. Metal oxide provides a supporting matrix that improves metal particle dispersion, surface area, and metal-oxide synergy. The glucose oxidation catalytic performance can improve significantly. Nickel oxide composites with cobalt or copper are stable and have strong electrocatalytic activity in the oxidation of glucose. This is because the metals are conductive, and the metal oxides are catalytic. Because of their synergistic effects, bimetallic systems significantly reduce glucose oxidation interference and poisoning on single- metal electrodes. In bimetallic systems, two metals help remove toxic species and increase tolerance to interfering chemicals, making glucose sensing more reliable and selective.

In physiological pH solutions, the complex network of biological fluids may introduce interfering species, making this critical. Current research focuses on developing and optimizing bimetallic materials for non-enzymatic glucose sensing. Different ways of making things, like co- precipitation, electrochemical deposition, and chemical vapor deposition, let you finetune the composition and shape of bimetallic catalysts. These advances have enabled the development of bimetallic catalysts with tailored physiological glucose sensing characteristics [61]. Researchers have found that bimetallic nanoparticles made of platinum and palladium have better glucose oxidation activity and stability than monometallic ones. Gold-copper bimetallic nanostructures improve glucose detection sensitivity and selectivity. The ability to fine-tune the electrical and catalytic properties of bimetallic materials makes them appropriate for next-generation non-enzymatic glucose sensors. Bimetallic catalysts for non-enzymatic glucose sensing are promising. Alloys, adatoms, and composites of metal (oxide) and metal oxide improve catalytic activity, stability, and interference resistance. The current research and development on this subject should produce sensitive, selective, and dependable glucose sensors for diabetes treatment and other biological applications [125].

Alloys

Recently developed alloy nanomaterials show potential for non-enzymatic glucose biosensors. Pt- based alloy nanoparticles are very effective at electrooxidizing small organic compounds. Pt-Pb, Pt-Ru, Pt-Ir, Pt-Ni, Pt-Pd, Au-Pt, Au-Ag, Au-Ru, Au-Cu, and Ni-Cu alloy systems have been extensively explored for non-enzymatic glucose biosensing. Catalytic characteristics are very good in Pt-based alloys. Sun et al. found that Pt_2Pb alloy optimized glucose oxidation is better than another Pt, Pb, Au, Pd, and Rh combinations. Pt_2Pb's ability to catalyze glucose

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oxidation at negative potentials reduced interference from typical interfering substances like ascorbic acid (AA), uric acid (UA), and acetaminophen (AP), improving sensitivity and selectivity. Pt_2Pb electrodes are susceptible to surface chloride ion poisoning, which makes them less efficient. Wang et al. modified a Ti electrode with a Pt-Pb nanoporous network to improve chloride ion poisoning resistance.

The modified electrode has excellent anti-interference capabilities and could measure glucose perimetrically at 280mM (vs. Ag/AgCl in PBS solution, pH 7.4). This change made the Pt-Pb alloy-based non-enzymatic glucose sensor more practicable [33]. Bai et al. created PtPb nanowires for enzyme-free glucose detection, reaching 11.25mAmM-1cm- 2 sensitivity, 1 mM linear range, and 8mM detection limit (σ =3). The hybrid material with PtPb alloy nanoparticles on multi-walled carbon nanotubes is another notable development. A higher sensitivity of 18mA mM-1cm-2 was attained with this nanocomposite electrode, although its linear range was restricted to 5mM. PtRu (1:1)/MWCNTs/IL modified GCE has the highest glucose oxidation electrocatalytic activity in neutral pH medium, according to Xiao et al. This biosensor has a sensitivity of 10.7mA mM-1cm-2, a 50mM LOD, and a linear range of 15mM. By supporting

PtRu alloy nanoparticles on CNTs, Li and colleagues improved the sensitivity of this configuration to 28.26mAmM^{-1}cm^{-2} and a reduced LOD of 0.25mM. Ni-Cu alloy research has also achieved important results. Yeo's research on Cu-based alloys of Ni, Fe, and Mn found that pre-adsorption of glucose molecules on Mn sites gave Mn_5Cu_{95} a high anodic response to glucose in 0.1 M NaOH. However, Jafarian et al. noted that Cu alloyed nanomaterials failed to catalyze glucose oxidation under physiological settings, limiting their blood glucose monitoring applications [1]. Researchers use novel composite materials to tackle Cu alloyed nanomaterial biosensing issues. Recently discovered 3D Aunanoporous Cu (Au@NPC) core-shell composite material shows potential. This material had a significant glucose oxidation peak in 0.1 M PBS (pH 7.4) and a linear response at 3-8mM. Despite this accomplishment, other Au-Cu nanoparticle alloy modified carbon electrodes have performed poorly in neutral pH solutions, indicating continued work to optimize these materials for physiological glucose sensing.

These alloy nanoparticles demonstrate the necessity of understanding and manipulating metal interactions to improve electrocatalytic activity. Pt-based alloys like Pt_2Pb and PtRu have strong catalytic activity and increased selectivity and sensitivity, making them promise. Chloride ion poisoning still plagues these materials, requiring further research and innovation. The addition of carbon-based supports like MWCNTs and nanoporous structures has improved alloy nanomaterial performance. These methods increase surface area, electron transfer rates, and glucose oxidation sites, improving sensor performance. Overall, alloy nanomaterials lead non-enzymatic glucose sensor research [126]. Pt-based alloys have excellent catalytic characteristics; however, chloride ion toxicity and narrow linear ranges must be addressed. Carbon support and innovative composite materials may overcome these challenges, enabling highly sensitive, selective, and reliable non-enzymatic glucose biosensors for clinical and biological applications [127].

Adatoms

Adatoms, which are sub-monolayers of metals like Pb, Bi, Hg, and Tl, are formed on Au and Pt electrodes by under-potential deposition in acidic solutions. This intentional alteration can increase glucose oxidation's anodic current responsiveness in alkaline solutions by one to two orders of magnitude. These adatoms increase electrode sensitivity and decrease poisoning adverse effects, especially on Pt electrodes. Pletcher noted that metal adatoms, such as Pb, affect Au and Pt electrode catalysis. Pb adatoms partially covering the electrode surface can boost long-term catalytic activity and minimize harmful species [1,128]. Pb atoms interact with two Pt sites.

Localizing the active sites prevents poison from spreading throughout the electrode surface, improving stability and performance. Adatoms aren't just for Pb. Researchers have also studied Ag and Hg for their benefits in glucose oxidation on Au electrodes. Aoun et al. investigated how glucose can be electrocatalytically oxidized on single-crystalline gold electrodes that have Cu, Ag, Ru, Pt, Pd, and Cd atoms added to them. The most effective catalysts were Au electrodes with a third layer of Ag atoms. These electrodes also had the biggest negative shift in the glucose oxidation overpotential. This improvement enabled glucose to be easily oxidized at 20.5V (vs. Ag/AgCl), where most interferential species are inactive. This large shift enhanced glucose oxidation efficiency and reduced interference from other chemicals, improving biosensor selectivity and reliability. Further research has confirmed that in alkaline solutions, Hg adatoms increase glucose oxidation current on Au electrodes. Putting Hg atoms on the surface of the Au electrode increased the amount of OH-2 that was absorbed, which made the oxidation current response stronger. This shows that Hg adatoms improve glucose molecule-electrode surface contact, boosting electrocatalytic activity. Adatoms provide benefits beyond catalytic activity and toxicity reduction. By carefully selecting and installing metal adatoms, researchers can customize electrochemical properties to the desired performance [129]. On Pt electrodes, Pb adatoms can prevent intermediates from poisoning active sites, allowing for long-term catalytic activity. Au electrodes containing Ag atoms are also highly catalytic. The Au surface's unique Ag atom arrangement generates an electrical environment that allows glucose oxidation at lower overpotentials. This reduces electroactive species interference, increasing glucose oxidation efficiency and electrode selectivity. Adatoms can improve glucose sensor performance and make electrodes more durable. Adatoms extend electrode lifespans by preventing poisoning species and retaining catalytic activity, making them better

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for continuous monitoring. Strategically utilizing adatoms can improve the electrocatalytic performance of Au and Pt electrodes for glucose oxidation. Researchers can improve non-enzymatic glucose sensitivity, selectivity, and stability by carefully selecting and depositing metals like Pb, Ag, and Hg. These advancements enhance the reliability and efficiency of glucose monitoring systems, while also advancing electrocatalysis for application in other crucial chemical reactions. Exploration and optimization of adatom-based changes may further improve electrochemical sensors and catalysts [130].

Composites

In recent years, research on non-enzymatic glucose sensing employing metal (oxide) or metal oxide nanocomposites has increased. These materials' electrocatalytic characteristics improve over their metal or metal oxide counterparts due to synergistic effects. Nanocomposites like Ag/NiO, Pt/NiO, Cu/NiO, Cu/ZnO, Cu/CuO, Pd/CuO, TiO_2/CuO, and CdO/NiO have been shown to be better at sensing glucose. Ag/NiO, popular nano compost, enhances glucose sensitivity. The sensor with silver (Ag) and nickel oxide (NiO) in the form of nanofibers had a better linear range, lower LOD, and higher sensitivity than the sensor with Ag and NiO nanofibers that were porous. Ag/NiO nanofibers showed improved electrochemical activity at 0.1V and 0.6V, making them efficient glucose detectors. The nanocomposite structure's increased surface area and electron transfer kinetics help glucose molecules oxidize, improving performance. Pt/NiO nanofibers show improved sensitivity and LOD. Platinum (Pt) and NiO nanofibers had higher sensitivity and lower detection limits at 0.6V, demonstrating their efficacy [131]. Platinum is a very good catalyst, and when it is mixed with NiO, the nanocomposite has more active sites and better conductivity, which makes it better at sensing glucose. In non-enzymatic glucose sensing, Cu/NiO nanocomposites have potential.

Copper (Cu) is a cheap, catalytic material that reacts well with NiO to generate a nanocomposite with increased electrocatalytic activity. Cu/NiO nanofibers offer better glucose detection sensitivity and linear range than their components. The synergistic impact of Cu and NiO boosts sensor electrochemical performance. Also notable is the Cu/ZnO nanocomposite. When coupled with copper, zinc oxide (ZnO) generates a nanocomposite that improves glucose sensing. ZnO has strong electron mobility and chemical stability. The Cu/ZnO nanocomposite is a better glucose sensor because it is more sensitive and selective. Copper has a high catalytic activity, and ZnO is good at transporting electrons. Researchers have explored both Cu/CuO and Pd/CuO nanocomposites for glucose sensing. Copper and CuO, or Pd and CuO nanocomposites, have increased electrocatalytic activity [132]. Compared to the separate parts, the nanocomposite structure is better at sensing glucose because it has a larger surface area and faster electron transfer. TiO2/CuO nanocomposites exhibited similar glucose sensing enhancements. Titanium dioxide (TiO_2), a semiconductor with photocatalytic properties, makes a nanocomposite with better electrochemical performance when it is mixed with copper oxide (CuO). The TiO_2/CuO nanocomposite enhances glucose detection with increased surface area and active sites, resulting in a more sensitive and lower detection limit sensor. The glucose sensing performance of CdO/NiO nanocomposites has also improved. Combining CdO and NiO, which have high catalytic characteristics, forms a nanocomposite with improved electrocatalytic activity. At 0.6 V, NiO- CdO nanofibers detected non-enzymatic glucose, 6.5 times better than pure NiO. The linear range was higher, and the LOD was lower, indicating that CdO and NiO produce a nanocomposite with improved glucose sensing. In conclusion, nanocomposite metal-metal oxide architectures improve non-enzymatic glucose sensors [133]. These nanocomposites use metal-metal oxide synergy to increase sensitivity, linear range, and detection limit. These sensors function better due to the nanocomposite structure's increased surface area, electron transfer kinetics, and active spots. We expect further study to generate more advanced nanocomposites, thereby improving non-enzymatic glucose sensing systems [134].

Carbon

Carbon-based biosensor substrates are popular due to their electrical conductivity and electrochemical inertia. In the 1990s, industrialized screen-printed enzymatic electrodes transformed personal glucose monitoring. The glassy carbon electrode (GCE), carbon paste electrode (CPE), and boron-doped diamond (BDD) are the most used electrodes for electrochemical research and biosensor development. In 1985, Vasilyev et al. discovered that bare GCE had a very weak anodic current response to glucose due to its electrochemical inactivity [135]. To improve glucose sensing, GCE modifications or alternative materials were required. However, researchers widely use CPE due to its easy preparation, low cost, and renewable surface. Because of these qualities, CPE is attractive for electrochemical applications like biosensing. Recently, BDD electrodes have gained popularity in electrocatalysis. BDD is a good electrode substrate for changing the surface and electrochemical biosensing because it has a low capacitance current, a very inert surface, a high fouling resistance, and a wide potential window.

Because of their characteristics, BDD electrodes are robust and dependable for glucose and other analyte detection. The rapid evolution of nanotechnology over the past decade has produced graphene, fullerene, carbon nanotubes (CNTs), carbon nanofibers, and doped diamond-like materials. After extensive research, these materials show potential as enzymatic and non-enzymatic electrochemical biosensors [136]. Nanostructured carbon materials are intriguing because of their high conductivity, huge surface area, easy functionalization, and biocompatibility. These traits boost electrochemical glucose biosensor performance. One layer of carbon atoms in a two-dimensional honeycomb lattice is graphene. Its electrical conductivity, mechanical strength, and

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huge surface area make it ideal for biosensing. Graphene's wide surface area allows enzyme immobilization or catalytic component attachment, boosting glucose sensor sensitivity and efficiency. Researchers have also extensively researched the biosensing uses of CNTs. CNTs are ideal for electrochemical sensors due to their electrical, mechanical, and chemical characteristics [33]. Most biosensors use CNTs as inert supporting materials for catalytic components like enzymes and electrocatalysts, despite some research claiming direct electrochemical activity.

In sensor systems, CNTs increase electron transfer rates and target-analyte interaction surface areas. Researchers are also investigating electrochemical glucose sensing using carbon nanofibers and doped diamond-like materials. Doped diamond-like materials, such as BDD, are strong, chemically inert, and have a wide potential window. Carbon nanofibers have a high surface area and conductivity. New research shows that nanostructured BDD, CNTs, graphene, and other carbon nanomaterials make non-enzymatic electrochemical glucose biosensors better. These advances are driven by nanostructured carbon materials' better electrical characteristics, vast surface areas, and chemical stability [122]. Chemical groups or catalytic particles can also functionalize them to customize sensor characteristics for analytical needs. Because graphene has a lot of surface area and can move electrons around easily, it has been used to make sensitive and selective glucose sensors that don't use enzymes. CNT-based glucose sensors have higher detection limits and linear ranges due to increased electron transfer rates and surface area. Finally, nanostructured carbon materials have improved non-enzymatic electrochemical glucose biosensor performance. These materials are ideal for improved glucose sensors because of their high conductivity, broad surface area, simplicity of functionalization, and biocompatibility. Future research should lead to more sensitive, selective, and dependable glucose detection devices [137].

Boron Doped Diamond

Some investigations have shown direct glucose oxidation on unaltered boron-doped diamond (BDD) electrodes, despite most literature claiming they lack electrochemical activity and sensitivity to glucose. Lee et al.'s 2005 observation was crucial. This treatment changed the BDD electrode's surface characteristics, increasing its electrochemical activity. The hydrogen-annealed BDD electrode's glucose oxidation peak was 0.65V (vs. Ag/AgCl) in an alkaline solution, like polyamine oxidation. This discovery was crucial since it disproved the idea that BDD electrodes needed modification to respond to glucose oxidation. Hydrogen annealing may have altered surface structure or functions to increase glucose oxidation [138].

The equation shows that glucose is oxidized by hydroxide ions to create gluconic acid, water, and electrons. Electrochemical sensing measures anodic current from electrons created during oxidation. Starting with glucose adsorption on the BDD electrode, the mechanism has several phases. Alkaline solution hydroxide ions work with adsorbed glucose to oxidize it. The hydrogen flame annealing procedure may increase active site density or change surface electronic characteristics of the BDD surface, enhancing glucose adsorption and oxidation. BDD electrodes can now be used for non-enzymatic glucose sensing thanks to this discovery. The ability to directly oxidize glucose on bare BDD electrodes simplifies sensor design by eliminating the requirement for extra modification procedures that might complicate fabrication and impact stability and repeatability. BDD electrodes are interesting for electrochemical applications due to their robustness, chemical inertness, and wide potential window. Further study has examined ways to boost BDD electrode electrochemical activity. Surface doping, heteroatoms, and BDD with other nanostructured materials have been researched to improve glucose sensitivity and selectivity [139]. These strategies optimize BDD surface characteristics for electron transport and glucose adsorption. Lee et al.'s discovery of direct glucose oxidation on hydrogen-annealed BDD electrodes questioned previous assumptions and showed BDD's potential for non-enzymatic glucose sensing. This discovery shows that BDD electrodes can attain high electrochemical activity with proper surface treatment, enabling the construction of robust and efficient glucose sensors. BDD electrodes for glucose sensing and other electrochemical applications will require continuing surface modification research and knowledge of the principles.

Using M and M' adsorption sites, BDD electrodes break down glucose. Polyamine oxidation involves oxygen adsorption, anodic oxygen transfer, and an intermediate oxidized organic molecule. The nanocrystalline BDD electrode that Zhao et al. used to find glucose in sodium hydroxide solution without enzymes worked well. It was sensitive, had a low detection limit, was selective, and had a large linear range. Luo et al. made a boron-doped diamond nanoforest (BDDNF) that can detect glucose without enzymes. It has a clear current response and is more sensitive than planar BDD. The BDDNF electrode showed well-defined glucose, ascorbic acid (AA), and uric acid (UA) peaks at 0.1, 0.3, and 0.6V. Despite these improvements, glucose sensors in these investigations had a linear range of 10 mM, restricting their practical use. Compared to metal-modified BDD electrodes, their sensitivity is lower. For instance, nickel nanoparticle- modified BDD had a sensitivity of 101.9mA mM^{-1} cm^{-2}, while BDDNF could only reach 8.1mA. Even with these problems, nanocrystalline and nanostructured BDD electrodes might make glucose biosensors more sensitive and be able to detect higher amounts of glucose [140].

Carbon Nanotubes

Researchers have studied carbon nanotubes (CNTs) over the past ten years for their potential to enhance first- and second-generation glucose biosensors. Their unique electrical, mechanical, and structural features make them suitable biosensor performance improvers. Early glucose sensors employed CNTs to assist other electrocatalysts. Third-generation glucose sensors, which directly transfer glucose oxidase electrons, now use them. Researchers are investigating multi-walled carbon nanotubes (MWCNTs) and single-walled carbon nanotubes (SWCNTs)

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are used for glucose detection, in addition to their enzymatic applications. Ye et al. developed the first non-enzymatic glucose sensor using well-aligned MWCNTs grown on tantalum. This sensor has a linear range of 11mM in 0.1MNaOH and strong glucose oxidation sensitivity at a low overpotential of +0.2V (vs. Ag/AgCl). This MWCNTs-based sensor was very good at detecting poisons because it kept the glucose current response constant even when chloride ion levels were high. However, ascorbic acid (AA) and uric acid (UA), whose oxidation potential overlapped with glucose, interfered with the sensor's glucose detection. Also, Wang et al. constructed a non-enzymatic glucose biosensor using SWCNTs [135].

They used Nacion to make large-area, freestanding SWCNT films on glass. At 0.5 V (vs. Ag/AgCl), the SWCNT film electrode directly oxidized glucose in alkaline solution. Even with 0.2 M chloride ions, the glucose sensor responded in less than 10 seconds, demonstrating its chloride ion resistance. The SWCNT-based biosensor outperformed the MWCNT-based electrode with a sensitivity of 248.6 mA mM^{-1} cm^{-2}, delivering significantly higher sensitivity. SWCNT film electrodes had a small linear range of 2.16mM, which hampered their use for glucose monitoring in varied circumstances. The SWCNT-based sensor's high sensitivity is due to its unique electrical features, which enable electron transfer and provide a broad surface area for glucose adsorption and oxidation. Nacion helps here the SWCNT sheet to the glass substrate and improves sensor stability and reproducibility. Even with these advancements, the sensor's short linear range necessitates more research to widen it and increase selectivity against interfering species. To overcome these issues, researchers are investigating ways to functionalize CNTs with metal nanoparticles, including other nanostructured materials, and optimize CNT alignment and density. These methods improve CNT-based glucose sensitivity, selectivity, and linear range for glucose monitoring applications. MWCNTs and SWCNTs offer potential for non-enzymatic glucose sensing, but each has pros and cons. We expect CNT-based sensor research and improvement to yield highly sensitive, selective, and reliable glucose biosensors for clinical diagnostics and personal glucose monitoring [141].

Graphene and Other Carbon Nanomaterials

Since Novoselov et al. discovered graphene in 2004, a single-atom-thick sheet of sp2 hybridized carbon has garnered major scientific attention. Researchers have extensively researched this material due to its great mechanical strength, specific surface area, and electrical properties. Its features allow it to be used in enzymatic glucose biosensors. However, graphene-based non-enzymatic glucose biosensors are newer. Mallesha et al. say that an FGGE (functionalized graphene-modified graphite electrode) can measure glucose in alkaline solutions without the need for enzymes. It had a linear range of 0.5-7.5mM and a detection limit of 10μM for glucose oxidation at +400mV (vs. SCE). Its sensitivity was 28.4mA mM^{-3} cm^{-2}.

Researchers have investigated other graphene-based hybrid materials besides FGGE for non-enzymatic glucose biosensors. Carbon nanofibers (CNFs), another exciting family of carbon nanomaterials with many applications in chemistry and biosensing, complement graphene's extraordinary features. CNFs have well-organized graphite layers piled into cylindrical shapes without a hollow center [59]. The edge-plane exposure of graphene layers on CNFs increases their surface area and conductivity. CNFs work in non-enzymatic glucose biosensors, according to recent investigations. Rathod et al. examined CNFs/Pt nanoparticles (NPs) for glucose oxidation electrocatalysis at physiological pH. This work showed that CNFs/Pt NPs composites can improve glucose sensors. Liu et al. created a CNFs/NiNPs non-enzymatic glucose biosensor. The biosensor had a wide linear range of 2μM to 2.5mM and a high sensitivity of 420.4 mA mM^{-1} cm^2. This shows that CNFs have a lot of potential in biosensing. For real-life glucose monitoring, CNFs with metal nanoparticles like Pt and Ni make the electrocatalytic properties better, leading to high sensitivity and a large linear range. As a trend in nanomaterial research, CNF-based biosensors use the unique properties of carbon nanostructures to make high-performance glucose sensors that don't use enzymes. Current research and development promise to improve sensor performance, making them suitable for clinical and personal glucose monitoring [142].

Conclusion and Prospects

Nanomaterial-based non-enzymatic glucose biosensors have grown in popularity due to nanotechnology's unique benefits. Nanostructured materials have solved many problems with non-enzymatic glucose sensors. A PtPb nanoparticle alloy and a nanoporous Pt electrode have been shown to efficiently reduce chloride ion surface poisoning, a major problem with Pt electrodes. A few nanostructured catalysts can also lower the overpotential needed to oxidize glucose, reducing blood electroactive molecules' influence. Nanomaterials have greatly improved non-enzymatic glucose sensor sensitivity. Nanomaterial-enhanced sensors have sensitivities higher than 100mA mM^{-3} cm^{-2}.

This is higher than bulk electrode-based non-enzymatic sensors and many enzymatic glucose biosensors, which usually have sensitivities lower than 10mA mM^{-3} cm^{-2}. In complex biological contexts, accurate glucose monitoring necessitates this increased sensitivity. Unfortunately, many non-enzymatic glucose biosensors cannot catalyze glucose oxidation under physiological conditions, limiting their use in human blood. Despite their great sensitivity, Ni, Cu, metal oxide, and carbon nanomaterial electrodes are very limited. The best nanomaterials for non-enzymatic glucose sensors are nanoporous Pt electrodes and Pt-based alloy-modified electrodes. These materials resist chloride ions and other surface fouling, and they catalyze glucose oxidation in neutral pH solutions, making them ideal for physiological use. The cost of production hinders the commercialization of these advanced non-enzymatic glucose sensors. Precious metals and

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intricate nanostructures increase production costs, limiting adoption.

However, nanomaterial- based non-enzymatic glucose sensors have applications beyond blood glucose monitoring. These sensors could find widespread use in bioreactors or fermentation facilities that require continuous monitoring of glucose levels, oxygen, and pH. Some non-enzymatic glucose catalysts may not be suited for blood glucose monitoring, but they may work in glucose fuel cells. These fuel cells don't need physiological conditions and can use nanostructured electrocatalysts to totally oxidize glucose to CO_2 and H_2O at low potentials, improving energy conversion efficiency. In contrast, enzymatic systems only oxidize glucose to gluconolactone. Nanostructured materials' unique features and nanotechnology's extensive potential suggest that the glucose biosensor sector will soon undergo transformational changes. The exploration and integration of new nanomaterials will revolutionize glucose monitoring, as well as other biotechnology and energy applications.

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