Wearable, Non-invasive, Nano-material based Glucose Sensing: A Review

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Abstract

Current glucose monitoring procedures for the rising numbers of diabetics worldwide are intrusive, uncomfortable, time-consuming and a provides a continual financial strain on families. Since, the non-invasive glucose monitoring technology gets over these drawbacks, recently a lot of research is being done in this particular area, and it represents a lucrative and interesting market for many businesses. Electrochemical sensors have drawn a lot of interest recently for the detection of certain bio-molecules due to their high sensitivity, selectivity, simplicity of fabrication, and speed of response. We provide an overview of nano-material based wearable, non-invasive (NI) glucose monitoring sensors. This review focuses on electrochemical capabilities and constraints of these nano-material based sensors. It also discusses the most recent developments in the use of nano-materials for the electrochemical detection of glucose, its challenges and future trends.

Keywords: Glucose monitoring, Electrochemical, Non-invasive, Nano-material, sensor, Bio-molecules.

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1. Introduction

Diabetes is a condition that manifests as aberrant insulin levels in the body, either as a result of inadequate insulin production by the pancreas or inadequate insulin uptake by body cells. By enabling cells to take glucose from the bloodstream and use it as fuel or store it for later use, the hormone insulin controls the amount of glucose in the body. However, if blood glucose levels fluctuate significantly over time, it can cause hypoglycemia or hyperglycemia, which can lead to serious health problems such as untreated tissue damage, stroke, renal failure, blindness, and heart disease, among other conditions. Diabetes Type-1 is brought on by insufficient insulin synthesis in the pancreas and is characterized by a sharp decline in blood glucose levels. Conversely, inadequate utilization of insulin results in elevated glucose levels are occurred in diabetes Type-2. Due to the lack of a treatment for either disease, diabetics will always require routine glucose testing [1]. Unfortunately, most diabetics find it unpleasant to test their blood glucose levels on a frequent basis because of in-vivo test of glucose. The electrochemical approach is used by conventional glucose monitoring systems. It requires drawing a little amount of blood from the body, either with the finger or by inserting a thin lancet under the skin (minimally-invasive technique). The first approach is referred to as self-monitoring blood glucose (SMBG), since it merely gives a momentary snapshot of the blood glucose level and does not need a doctor to use it. The second approach for glucose monitoring is minimally-invasive technique which provides the continuous glucose monitoring (CGM) [2].

However, both of them present hazards of possible infection and tissue injury with repeated usage, which leads to poor patient conformity for daily glucose measurement [3]. Therefore, researchers made lot of attempts to create non-invasive (NI) technique, which do not require the drawing of blood as in case of invasive methods. To minimize these problems , the creation of a truly non-invasive glucose testing gadget would be a game-changer, allowing individuals to safely check their blood sugar levels and, if necessary, receive prompt treatment. A sizable prospective market is also represented by it. According to the World Health Organization (WHO), there are approximately 700 million cases of diabetes globally, with that number potentially rising 450 million by 2045. In the United States alone, that number is

expected to rise to 39.7 million by 2030 and 60.6 million by 2060 [4-5].

Research has focused a lot on the creation of technology for glucose testing that does not have the invasiveness, pain, discomfort, or hazards associated with traditional approaches. Non-Invasive technologies don't require access to blood for measurement of glucose; instead it relies purely on other bodily fluids like tears, sweat, saliva, or urine [6-7]. The various techniques used in non-invasive glucose detection are optical, thermal, electrical, and electrochemical. In a broad sense, the term "optical" refers to any techniques developed to work in the infrared and optical regions of the spectrum, since, they rely on how light behaves as it passes through biological material, and its properties based on phenomenon of reflection, absorption, and scattering. Thermal techniques work in the far-infrared spectrum, because they detect physiological signals connected to the metabolic heat generated by the glucose molecule itself. Electric techniques make use of glucose's low-frequency dielectric characteristics by applying a moderate quantity of electromagnetic radiation, current, and ultrasound [1-7]. In an electrochemical sensor, an electrode serves as a transducer element when an analyte is present. Modern electrochemical sensors use a number of characteristics to detect different aspects in daily life, including physical, chemical, and biological parameters. Enzymes, bimetallic nano-particles, metal-oxide nano-composites, carbon nano-tubes, and conductive polymers are just a few of the sensing components used in electrochemical glucose sensors.

The term "nano-technology" refers to the process of modifying matter at a length scale between one and hundreds of nano meters, in order to produce useful materials, tools, and systems. Such a scale results in novel features and functions due to size. Scientists categorise nanomaterials according to how many of a material's dimensions exceed the nano-scale (100 nm) range. The nano-materials are classified as zero-dimensional (0D), one-dimensional (1D), two-dimensional nanomaterials (2D), and Three-dimensional (3D) nano-materials. In the case of zero-dimensional (0D) nano-materials, all dimensions are measured at the nano-scale (none of the dimensions are larger than 100 nm). Nano-particles (NPs) are the most prevalent type of 0D nano-material. One of the dimension is not present in one-dimensional nano-materials (1D), which exist at the nano-scale. nano-wires, nano-rods, and nano-tubes fall under this category. Two dimensions in two-dimensional nano-materials (2D) are larger than the nano-scale. Graphene, nan-ofilms, nano-layers, and nano-coatings all fall under this category, which has forms resembling plates. Materials that are three dimensional (3D) are not restricted to the nano-scale in any dimension. Bulk powders, NPs dispersions, nano-wire bundles, nano-tubes, and multi-nanolayer materials can all be found in this class. Appart from the above classification, numerous subgroups include metal NPs, ceramic NPs, and polymeric NPs. Since they are small and have a huge surface area, NPs exhibit unique physical and chemical properties. Based on their morphology, size, and chemical properties, NPs can be generally divided into a number of classes. Depending on the material's physicochemical composition. They include lipid-based NPs, metal NPs, ceramic NPs, semiconductor NPs, polymeric NPs, and NPs based on carbon. The advancement of nano-technology, also known as NPs technology, can provide unique features or modify a variety of applications, most notably sensor applications [8-9]. This paper provides the comprehensive review on work done in the area of nano-material based glucose sensing.

2. Nano-material based glucose sensing

Both optical [10-12] and electrochemical [13–15] techniques are commonly utilized in wearable glucose sensors. Since electrochemical sensors provide the characteristics of rapid reaction, high precision, and straightforward operation, they are used for design and development of wearable applications. Numerous non-invasive wearable sensors have been proposed by researchers in recent years for quick and real-time glucose monitoring from human bodily fluids. Sensing materials are an important component of the electrodes in electrochemical wearable glucose sensors. Due to their distinctive physical, electrical, and chemical characteristics when compared to bulk materials, nano-structured materials have recently attracted a lot of attention and have

been widely used in a range of wearable glucose sensing techniques [16-17]. The sensitivity of the sensor can be greatly increased by their larger specific surface area [18-19]. Enzymatic wearable glucose sensors have improved long-term stability and longer working lives due to good biocompatibility [20].

2.1 Various body fluid used in nano-material based glucose sensor:

Non-invasive glucose sensing technique uses the various body fluids like urine, sweat, saliva, tears, etc. Urine is one of the biological fluids that has undergone the most comprehensive analysis in clinical research. The discharge of excessively high levels of glucose in the urine is a symptom of a number of metabolic illnesses, diabetes mellitus being one of the most prevalent [21]. Normally, urine contains very little amount of glucose and other substances. When blood glucose levels are high, glucose overflows into the urine, giving it a sweet or fruity odour [22]. Since, it is a sign that diabetes is getting worse, high glucose levels in urine are regarded as a serious condition. The presence of more than 50-100 mg/dL (2.78-5.55 mM) of glucose is indicated by a positive urine test [23]. Even while blood and urine are the most frequently utilized biological fluids for diagnostic purposes, other fluids such as saliva, sweat, and tears have certain unique advantages and are being analyzed more and more. Saliva can be collected in its whole non-invasively without the use of specialized tools or skilled staff. The examination of saliva is more useful for youngsters and older persons, since, it requires less subject consent than the collection of blood [24]. Additionally, saliva analysis might offer a method for mass population screening that is both affordable and effective. The typical range of salivary glucose concentrations is 8 M to 0.21 mM [25-27]. Significantly lower than the range of 2 to 30 mM for blood glucose [28]. As a result, the majority of the tests mentioned use extremely advanced spectrophotometry to calculate glucose concentrations. These saliva glucose tests are becoming more widely used due to recent advancements in very sensitive materials [29].

Sweat is the most accessible non-invasive diagnostic method because it is naturally produced by humans and is therefore the easiest to sample [30]. Reverse iontophoresis is a technique that has been used to artificially pull tissue fluid via way of the skin. Electrodes for anode and cathode are placed on the surface of the skin, and reverse iontophoresis works by passing a small electrical current through the skin between them. Blood glucose levels and the amount of glucose present in physiological fluids are directly correlated [32],[31]. Although this procedure is non-invasive and accurate, it has certain drawbacks, including a 20-minute delay between fluid extraction and glucose testing. Due to extended reverse iontophoresis, the accuracy essential for gadgets (This liquid's glucose content is 1/1000 that of blood glucose.) may be negatively impacted [32].

Since, the 1950s, numerous studies have advocated using tear fluid to test for glucose instead of blood. Blood glucose levels in the normal, hyperglycemic, and hypoglycemic categories might be measured indirectly using tear glucose levels [33]. Tears are easier to access than blood or interstitial fluids, more accessible, and less prone to dilution than urine [34]. Tear fluid is kept at a tiny and remarkably steady volume (4μL). The production of the lacrimal gland and other accessory glands replenishes tears on a continuous basis at a rate of 0.5-2.2 L/min [35]. The measurement of glucose in tears using various techniques has received a lot of research attention. The detection technique must have a very low detection limit (since glucose levels in tear fluid are 50–100 times lower than blood levels), high selectivity over active interferents, and the capacity to quantitatively measure very small sample volumes in a brief amount of time is analytically very useful [32,36].

2.2 Nano-chemical Sensing

The use of glucose detection is crucial in the fields of biology, clinical medicine, and food processing. Accurate glucose testing is very useful for diabetics since it can help diagnose and manage diabetes mellitus [37-39]. The first and most widely used technique to measure blood glucose levels in clinical trials is the glucose oxidase (GOD) analytical method. But since the GOD being is an enzyme, it will shortly become inactive and denatured. As a result,

enzymatic electrodes have poor reproducibility and stability. This problem can be avoided by non-enzymatic glucose biosensors since glucose is directly catalytically oxidized on the surface of the electrode. [40-45]. Carbon nano-tubes (CNTs), nano-wires, mesoporous structures, and other nano-materials could be used as the substrate for these electrodes in order to increase specific surface areas and improve mass transport capabilities, and they could then be decorated with nanoparticles like Pt [46-47], Ni [48], Ag [49], and Cu [50].

Various approaches, including ceramic, sol-gel, and "wet" chemical processes, have been developed to create Ag doped TiO_2 nano-tubes in a variety of diameters. However, the preparation process revolves around drying, heating, or annealing at high temperatures. To introduce Ag NPs into the TiO_2 nano-tubes, a polyol method at low temperatures has been established. Glycerol and diethylene glycol were both utilized as a solvent and reducing agent in the polyol process. A solvent plus a reducing agent can aid in the formation of nano-structures during a process. It is possible to convert the Ag^+ ions in silver nitrate ($AgNO_3$) into metallic Ag. On the surface of TiO_2, the Ag nanoparticles were successfully deposited. Silver nanoparticles placed on TiO_2 nano-tubes will also significantly boost the specific surface area. For non-enzymatic glucose sensors, TiO_2 nano-tubes embellished with silver NPs offer a number of advantages. The polyol technique was used to successfully deposit Ag NPs on the surface of TiO_2. Scanning electron microscopy and nano-indentation were used for characterization (SEM). After stirring for 10 minutes, the electro-catalytic activity (DPV) of the Ag- TiO_2 electrode was evaluated using cyclic voltammetry (CVs) and differential pulse voltammetry. Ag-TiO_2/(500 C) was finally created after being totally submerged in this electrolyte under static conditions for 7 hours, rinsed with double-stilled water, and left to air-dry [51-53].

The development of commercial nano-chemical glucose biosensors has advanced significantly as a result of the maturing the use of synthetic electron acceptors, screen printing, semiconductor integration, and the domains of surface chemistry. To benefit from some of the highly desired characteristics of nano-materials, the significant advancement in biosensors and bioelectronics have been developed using nano-technology in recent years. For instance, numerous methods for creating nano-materials with different shapes and sizes have been developed, such as spherical particles [54-55], rods [56-57], cubes [58], etc. In the context of biosensors particularly, carbon-based nano-materials like graphene and carbon nano-tubes have greatly advanced the subject [59-64]. Such nano-structures are a crucial part of many detecting systems due to their structural, electrical, chemical, and mechanical capabilities. Nano-materials like carbon nano-tubes and gold NPs, which are similar in size and shape to redox enzymes, these nano structures may be employed to build an electrical connection between the electrode and the redox centre, which could lead to better electron transfer [65-68]. Researchers in the domains of biosensors and bioelectronics have recognized the work of the Willner group, which in short succession published two innovative techniques for nano-wiring redox enzymes, as being fundamental [69-70], provides a superb illustration of this kind of approach. Although glucose oxidase-based biosensors have received a great deal of investigation, the possibility of an enzyme's catalytic activity declining due to immobilization presents a considerable performance barrier for researchers in terms of sensors and long-term stability [71-72].

Some of the issues with enzymatic systems may be resolved by in the absence of the enzyme, glucose is directly electro-oxidized. But if the biosensor is going to be used in a very complicated matrix, a thorough investigation of the selectivity of the designed catalysts towards glucose is required [73-75]. The manufacture of Cu-Cu_2O, TiO_2 nano-tubes have NPs on their surface that act as transmitters for the direct electrocatalytic oxidation of glucose has been described as a non-enzymatic method [34]. Ti foils are anodized in two steps produced the TiO_2 nano-tubes, which were then coated with premade Cu and Cu_2O particles using an electro-deposition process. The glucose electro-oxidation not mediated by enzymes was then performed using the resulting hybrid electrode[76-77].

3. Conclusion

The electrode material has a significant impact on the electrochemical response of glucose sensors. Bimetallic electrodes, carbon-based electrodes, metals, and metallic compounds are typically employed as acceptable nano-materials for glucose sensing. Nano-materials are now highly helpful in improving electrochemical performance because of their superior qualities, such as a large surface area, distinctive structure, and increased number of active sites. As a result, numerous nano-structured inks are produced for a range of uses. Due to their excellent electrical conductivity, exceptional biocompatibility, and low cost, carbon-based nano-materials (CNTs, graphene, etc.) have generally been employed extensively in the production of sensing electrodes for wearable glucose sensors.

More novel nano-materials have recently been created and used to prepare the sensing electrodes for wearable glucose sensors. Future wearable glucose sensors need to focus on the following development trends in terms of sensing nano-materials.

- In order to significantly boost the sensitivity of the devices, a wide variety of sensing nano-materials with porous architectures, excellent electrical conductivity, and catalytic capabilities will be used in both enzymatic and non-enzymatic sensors.
- The mechanical properties of the sensing nano-materials should be enhanced to boost the reliability and flexibility of the sensors during everyday operations.
- Nano-materials that particularly recognize glucose may receive greater attention for enhancing selectivity due to the various interferences (such as lactate and salt) in wearable glucose sensors.

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