# Glucose monitoring through nanoparticles: differences between optical and electrochemical analysis

## Monitorización de glucosa mediante nanopartículas: diferencias entre análisis óptico y electroquímico

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**Abstract**

Constant glycemic monitoring is fundamental for adequate management of diabetes mellitus. Current methods for this surveillance have several limitations, especially the painful sampling and the inability to perform measurements when the patient sleeps. As a result, adherence to the monitoring is often low, impairing the assessment of treatment efficacy. In order to overcome this problem, newer products focus on continuous glucose measurement through the implementation of nanosensors and nanomaterials. Electrochemical and optical glucose sensors have evolved significantly with nanotechnology, addressing the inherent problems of older generation sensors. Despite the overall good performance of both systems, clinical application remains far from consolidated. Poisoning effects from oxidation intermediates, instability at physiological pH, low specificity for glucose, and high costs are only some of the problems researchers currently face regarding the development of implantable continuous glucose sensors. More research is needed, both for electrochemical and optical sensors, to gain enough clinical significance and applicability to fulfill patients' need for friendlier means of glucose monitoring. This review aims to define the molecular mechanisms of electrochemical and optical glucose nanosensors, and analyze the drawbacks, limitations, and challenges of each.

**Keywords:** Nanotechology, nanosensors, nanomaterials, glucose monitoring, diabetes.

**Resumen**

El control glucémico constante es fundamental para el manejo adecuado de la diabetes mellitus de interés en pacientes con insulinoterapia. Los métodos actuales para esta vigilancia tienen varias limitaciones, especialmente el doloroso muestreo y la imposibilidad de realizar mediciones cuando el paciente duerme. Como resultado, la adherencia al seguimiento suele ser baja, lo que perjudica la evaluación de la eficacia del tratamiento. Para superar este problema, los productos más nuevos se centran en la medición continua de glucosa mediante la implementación de nanosensores y nanomateriales. Los sensores

de glucosa electroquímicos y ópticos han evolucionado significativamente con la nanotecnología, abordando los problemas inherentes de los sensores de generaciones anteriores. A pesar del buen desempeño general de ambos sistemas, la aplicación clínica está lejos de consolidarse. Los efectos adversos de los intermedios de oxidación, la inestabilidad en el pH fisiológico, la baja especificidad para la glucosa y los altos costos son solo algunos de los problemas que enfrentan los investigadores actualmente con respecto al desarrollo de sensores de glucosa continuos implantables. Se necesita más investigación, tanto para sensores electroquímicos como ópticos, para obtener suficiente relevancia clínica y aplicabilidad para satisfacer la necesidad de los pacientes de medios más amigables para monitorear la glucosa. Esta revisión tiene como objetivo definir los mecanismos moleculares de los nanosensores de glucosa electroquímicos y ópticos, y analizar los inconvenientes, limitaciones y desafíos de cada uno.



**Palabras clave:** Nanotecnología, nanosensores, nanomateriales, monitorización de glucosa, diabetes mellitus.

## Introduction

Diabetes mellitus (DM) remains the leading cause of mortality and reduced life expectancy worldwide. Evidence shows that the overall burden of DM has steadily increased since 1990. The International Diabetes Federation (IDF) estimated that over 450 million adults lived with DM worldwide in 2017, a figure set to increase to over 700 million by 2045 if effective prevention measures are not taken[1]. Moreover, diabetic patients have a 2 to 3-fold increased all-cause mortality[2]. The presence of DM is strongly correlated with increased mortality from infections, CVD, stroke, cancer, and many others[3]. However, proper glycemic management has shown an important decrement in the overall morbimortality associated with DM[4]. Therefore, it is imperative to take early preventive measures to lengthen patients' life expectancy and significantly increase their quality of life. Constant glycemic control is fundamental for these goals[5].

At present, glucose monitoring requires patients to obtain a blood sample, typically via a finger prick; blood is then placed onto a sensor test strip, ultimately giving blood glucose concentration through an electronic device[6]. Most of these sensors are based on electrochemical enzymatic measurements, providing rapid and accurate measurements without needing laboratory intervention[7]. However, these methods have several limitations, especially the painful sampling and the inability to perform measurements when the patient sleeps[8]. In order to overcome this problem, newer products focus on continuous glucose measurement through the implementation of nanosensors and nanomaterials[9].

Glucose sensors are divided into two big families, electrochemical sensors and optical sensors. Electrochemical glucose sensors rely on the electro-oxidation of glucose, which is then transduced into a quantifiable electrical signal. Despite being the oldest method, it remains equally effective[10]. However, optical sensors offer a direct, real-time measure of glucose, which better pairs with the goal of continuously monitoring glucose. Non-enzymatic glucose sensors based on fluorescence and surface plasmons resonance (SPR) currently boast the most evidence[11]. This review aims to define the molecular mechanisms of electrochemical and optical glucose nanosensors, and analyze the drawbacks, limitations, and challenges of each.

## Electrochemical and optical sensors: molecular basis and evolution

Electrochemical glucose sensors were first introduced in 1962 by Leland C. Clark. They were based on three essential components: a biological recognition element, the electrochemical transducer, and the signal processing system. This particular model had a glucose oxidase (GOx) with a modified platinum (Pt) electrode[12]. The argument behind electrochemical glucose sensors is to convert glucose oxidation into a quantifiable electrical signal in the form of current or voltage to process and display it as a measurable unit in the electronic device. Another enzymatic system used in these devices was the glucose-1-dehydrogenase (GDH) and the oxidized form of pyrroloquinolinequinone (PPQ); however, the latter lacked specificity for glucose oxidation when compared to GOx. As a result, the GOx system has been historically preferred for this purpose[13].

Essentially, GOx catalyzes glucose oxidation by molecular $O_2$ with the subsequent production of gluconic acid and hydrogen peroxide ($H_2O_2$). Then, the Pt electrode comes into play by oxidizing the $H_2O_2$, producing an electron flow proportional to the amount of glucose in the sample[14]. Nonetheless, this first-generation system greatly depends on $O_2$ concentration. Thus, variations of $O_2$ in biological fluids can significantly modify the performance of first-generation devices[14]. This issue was addressed by replacing the $O_2$ with a non-physiological redox mediator able to transport electrons from the GOx to the sensing electrode, eliminating the $O_2$ prerequisite[15].

Afterwards, the need for a mediator was eliminated with the development of a direct electron transport system, the point at which gold nanoparticles and other nanomaterials were implemented to effectively stabilize GOx[16]. While this adjustment successfully overcame the oxygen issue, GOx instability was still a problem; moreover, given the complex processes needed to immobilize the GOx, chemical deformation became a problem during the manufacturing, storage, and use of these devices[17].

Recently, non-biological catalysts have gained significant attention for glucose detection because, theoretically, these models can overcome all the limitations of the 1st to 3rd generation glucose sensors. These non-enzymatic glucose sensor models are based on nanostructured metals, metal-oxides, metal-organic frameworks (MOF), and metal azolate frameworks (MAF)[18].

Later still, efforts were made to move towards non-biological models, as biological components require significant effort for stabilziation[10]. As a result, many researchers have focused on developing glucose detection assays that do not rely on enzymes for substrate recognition. Direct detection of glucose oxidation at the electrode has been extensively studied; however, slow reaction kinetics and the need for enormous applied potentials significantly decrease specificity[19]. In that matter, nanomaterials have been implemented to develop direct oxidation glucose sensors. Copper, copper oxide[20], silver[21], gold[22], nickel[23], and palladium[24] are just some of the nanomaterials that have been studied in this field. Finally, carbon nanomaterials were introduced in the form of carbon nanofibers or nanotubes, significantly increasing the sensitivity and decreasing the working potential of the modified electrodes[25].

Regarding the performance of direct glucose oxidation sensors, Meng et al.[26] showed that palladium nanoparticles system could work at pH 7.4 and in clinical samples diluted with a buffer. However, this kind of models will probably not see any utility in clinical settings without significant work to improve the functionality of these models in undiluted samples, like those routinely obtained by patients[10]. Moreover, at physiological pH, most of these sensors suffer from a poisoning effect due to interference from intermediates of the oxidation process. Additionally, most direct glucose sensors have low selectivity for glucose, thus, oxidizing other organic molecules resulting in unstable current responses and, decreasing the accuracy of glucose concentration measurements in real samples[27]. In conclusion, more research is needed to develop new nanomaterials that can non-enzymatically catalyze glucose oxidation free from poisoning effects and at a low cost.

On the other hand, optical sensors offer a more direct and real-time mechanism for glucose sensing. These methods rely on the change of intensity of the light upon binding of glucose molecules[11]. In that matter, fluorescence spectroscopy-based glucose sensors do not measure glucose concentration directly; rather, it measures the signal from a molecular recognition fluorophore after glucose binding occurs. The variations of fluorescence intensity of these fluorophores are directly proportional to glucose concentration[28]. Separately, SPR-based systems rely on glucose binding onto a plasmonic nanoparticle recognition compound which induces a variation in the angle of light reflectance. The variation of the angle of light reflectance is proportional to the concentration of glucose[29].

Fluorescence-based sensors (FBS) offer several advantages for continuous glucose monitoring. Firstly, FBS can optically interact with the sensors through the skin rather than depending on an implanted electrode system, minimizing the chances for infection or encapsulation of the device, which decreases the sensitivity for glucose, thus, compromising measurements accuracy[30]. The FBS approach often involves a “smart tattoo” because sensors need to be implanted into the patient’s skin. These implants are temporary and need replacement after a certain period. These sensors change their fluorescence properties in response to glucose; this signal is then translated by an optical sensor on the skin into a quantifiable unit, hence, eliminating the need for patients to take blood samples while allowing for continuous monitoring[31].



Several FBS are based on polymeric nanosensors with incorporated boronic acid derivatives for glucose recognition. For example, a nanosphere based on N-isopropylacrylamide with phenylboronic acid derivatives and two fluorophores was synthesized by Zenkl et al.[32]. In the absence of glucose, the nanospheres hold the fluorophores close together, allowing efficient resonance energy transfer (RET). Upon glucose binding to the boronic acid derivative, the polymer swells, distancing the fluorophores from each other. The latter decreases RET, augmenting donor fluorescence and reducing acceptor fluorescence, which is measured by the optic sensor. This model has been improved by using multiple boronic acid derivatives and increasing fluorophore concentration, resulting in faster response time and better signal interpretation within the physiological glucose range[33].

Likewise, Shen et al.[34] prepared fluorescent carbon dots functionalized with boronic acid derivatives by hydrothermal carbonization of phenylboronic acid. This model used UV light as the excitation source for non-enzymatic glucose detection. Glucose binds boronic acid groups, inducing fluorescence quenching of carbon dots emission, directly proportional to glucose concentrations. Further, to widen the linear range to a clinically relevant glucose range, other authors incorporated copolymer microgels into the carbon dots. The resulting hybrid microgels could modify their dimensions according to glucose concentration variations, inducing quenching of the fluorescence intensity accordingly. As a result, these models provide a direct and continuous measurement of glucose concentration within and over the clinically relevant range at physiological pH[35].

Furthermore, Mai et al.[36] recently developed a Zinc oxide (ZnO) nanotube (NT) modified circuit board substrate for optical glucose monitoring. The sensor could measure glucose concentration by relying on the photoluminescence quenching of ZnO NTs. The mechanism involves using UV light to photoexcite the electrons in the ZnO NTs to facilitate the emission of photon energies. In the presence of glucose, both ZnO NTs and UV

light act as catalysts for glucose oxidation, decreasing fluorescence intensity, which is proportional to glucose concentration. Despite the overall good performance of FBS, their practical application as implantable devices is, at best, questionable. Firstly, their dependency on UV light for photoexcitation is hazardous; moreover, most of these systems display low stability and lifetimes. Additionally, the variation in the illumination/excitation wavelengths results in inaccurate glucose measurements. Further investigation is needed to solve these issues[37].

SPR-based systems provide an alternative to overcome the elemental problems of the FBS-based systems, since they use visible light as a means for photoexcitation instead of UV light. Essentially, SPR systems are based on the principle of oscillation of electrons at the dielectric interface, which can detect glucose via the variation of the local refractive index before and after glucose binding. Yuan et al.[38] developed a SPR glucose sensor using a mixed-self-assembled monolayer modified with gold-coated optical fibers. After optimizing its selectivity for glucose by creating a sandwich structure, the sensor effectively measured glucose concentration within a clinically relevant range. However, the binding of glucose to gold nanostructures can lead to their aggregation, which can decrease the accuracy of glucose detection. Moreover, this method is expensive and suffers from the same poisoning effect from oxidation intermediates at physiological pH[39].



## Conclusions

Diabetes mellitus (DM) remains the leading cause of mortality and reduced life expectancy worldwide[40-46]. Traditional glucose monitoring is often painful and impractical for most patients, leading to low adherence or complete abandonment of the monitoring. This impairs the assessment of treatment efficacy. To overcome these obstacles, several attempts have been made to develop implantable devices that can continuously measure glucose without taking blood samples. Electrochemical and optical glucose sensors have evolved significantly with nanotechnology, addressing the inherent problems of the older generations' sensors. Despite the overall good performance of both systems, clinical application is still far from consolidated. Poisoning effects from oxidation intermediates, instability at physiological pH, low specificity for glucose, and high costs are only some of the problems researchers currently face regarding the development of implantable continuous glucose sensors. More research is needed, both for electrochemical and optical sensors, to gain enough clinical significance and applicability to fulfill patients' need for friendlier means of glucose monitoring.

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