Chapter

Electro Sensors Based on Quantum Dots and Their Applications in Diagnostic Medicine

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Abstract

Electrochemical biosensors currently account for an innovative platform capable of bringing simplicity, ease, and time reduction associated with drug screening, insect capture, DNA detection, and other analytes. Biosensors based on quantum dots are a new alternative unique properties of this nanomaterial to the world of diagnostic medicine and biochemical analysis, among others. In addition to the known optical properties of this nanoparticle, its use presents several advantages when combined with electrochemical detection systems associated with increased sensitivity and accuracy in detecting specific biomolecules, as well as the reduction of the analysis time of the material. This chapter describes in detail the advances and the various applications of these nanoparticles in the field of electrochemical sensors, as well as their advantages and difficulties today.

Keywords: biosensors, quantum dots, electrochemistry, nanoparticles, diagnostics

1. Introduction

Biosensors are typical devices that convert biological signals into electrical signals, usually with high specificity regardless of pH and temperature, and can be divided into several types of sensors [1].

Biological sensors are generally composed of two parts, the first by the natural elements such as enzymes, cells, DNA, antibodies, tissues, and others, and the other by transducers capable of converting interaction events between the biological parts into electrical, light signals, thermal, and others [2].

In addition to the diversity associated with the type of analyte detected by the biological part, biosensors also differ according to the principle of operation, which can be electrochemical, thermal, gravimetric, and optical, among others. For example, in an electrochemical biosensor, reactions are measured based on the current, voltage, or resistivity produced by the oxidation or reduction of molecules in the medium [3].

Quantum Dots (QDs) are classified as nanostructured semiconductors that are formed mostly by elements of periodic groups II–VI, III–V, and IV–VI. Due to their zero-dimensional nature and smaller size compared to their excitation Bohr radius, they exhibit various optical, electric, and magnetic properties, among others.

These unique characteristics make them highly valuable and applicable in several areas [4–6].

QDs attract attention for their optical properties, activities, and applications in the electrical field. Due to the controlled variation of the *Gap* between its valence and conduction bands, its electronic properties can be explored in several ways, such as in the evaluation of charge transport, photocatalysis, electrochemiluminescence, conversion of light into electrical energy, among others [7–9].

An important technique that unites QDs and electrosensory is electrochemiluminescence, which combines spectroscopy and electrochemistry, allowing the electronic excitation caused by light on the QD to generate currents measurable by equipment, which can be used as on/off switches on the surface of electrodes or in reactions that use molecules marked with these semiconductors [10].

Although mechanisms based on optical detection, such as Fluorescence Resonance Energy Transfer (FRET), fluorescence, and Chemiluminescent Resonance Energy Transfer (CRET), have already been widely studied, the use of quantum dots (QDs) in the field of photoelectrochemical sensors is relatively new. However, it has garnered significant attention due to its remarkable optoelectric properties and potential applications in various fields, including diagnostic medicine [11–13].

2. Electrochemical biosensors

Over time, the need for more precise technologies was necessary, making biosensors excellent alternative platforms, as they contain standards based on several points, such as high selectivity and sensitivity for detecting the specific analyte, even in small quantities. The fast response time, along with the reproducibility, linearity, and stability it offers, provides confidence in the measured value during the trial, thereby guaranteeing the superiority of this platform [14].

As in other platforms, biosensors have several classifications defined by how the biorecognition of the analyte occurs during the reaction. For example, enzymes are commonly used in various tests due to their catalytic properties, accelerating general biological processes. The principle of this type of biosensor is based on analyte metabolization processes, the transformation of the analyte into measurable by-products, inhibition of reactions, and the alteration of the initial enzymatic characteristics [15–17].

Currently, nanoparticles have been routinely used in electrochemical tests due to their ease of use and amplification of signals during the trial. Besides, nanoparticles have different behavior from sensors based on enzymes, with various advantages: immobilizing biomolecules, electrochemical catalysis, increasing electron transfer, and acting as reactants in solution [18, 19].

Most biosensors use platforms based on electrochemical transducers due to their low cost, ease of use, and portability. Reactions are easily measured through techniques such as current measurement (amperometry), charge accumulation (potentiometry), impedance differences (amperometry), or the union between conductive properties between the electrodes (conductometry) [20, 21].

One of the areas with great attention focused on the development of biosensors is related to the miniaturization of the architectures present in electrochemical platforms. This approach not only reduces noise but also enables the utilization of this platform in multiplexed assays, with the ability to detect multiple analytes [22].

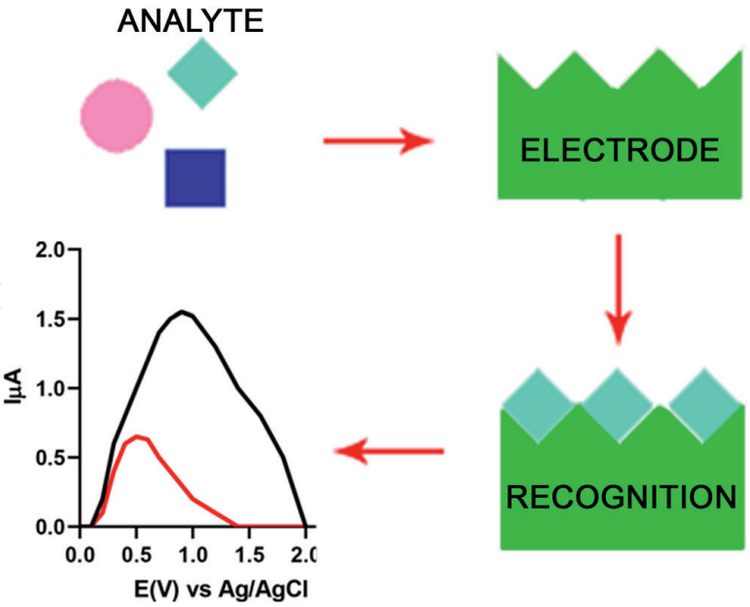

Figure 1.
A schematic of a biosensor with electrochemical transducer.

The selection of electrodes in electrochemical immunoassays brings several advantages related to their construction methods, such as the use of only one reaction substrate and the reduced size, allowing the use of smaller amounts of reagent (**Figure 1**). Furthermore, in addition to the potential for mass production, the utilization of biosensors based on quantum dots offers advantages such as reduced cost compared to conventional electrodes. Thses biosensors also provide the option of single-use, eliminating the need for cleaning processes that can negatively affect reproducibility and stability [23–25].

3. The electrochemistry of quantum dots

It is important to note that the influence of the core diameter, protective shell size, and functional groups on the QDs concerning their redox activity is not yet well understood. However, it is recognized that the quality of the nanomaterial plays a fundamental role in determining the photocurrent potential [26].

In the generation of current induced by light, some criteria are known to be significant in the process. For efficient electronic transfer, factors such as the distances and the nature of the connections between QD-electrode and QD-analyte are crucial. The redox rate can also be affected by the properties of the Quantum dots and their surface ligands. Moreover, the light induction can generate charge recombination events in the system, involving the electronic transfer [27].

Several investigations on the electrochemical behavior of QDs have been carried out using aqueous solutions as a basis or deposited on electrodes. Although there are few studies on the correlation between their structure and their redox potential, some works compare the optical performance concerning the electroche mical activity of these nanocrystals [28, 29].

Of the main challenges associated with the electrochemical behavior of these semiconductors, the main ones are related to the low solubility and the low diffusion coefficient, which makes the measurement of current intensity little distinguishable

from interference. Furthermore, the occurrence of electronic removal or injection within the particle, resulting from redox processes, often leads to chemical irreversibility. This chemical irreversibility can contribute to less reproducible measurements [30].

One study evaluated the correlation between the electrochemical band gap and the Luminous electronic spectrum. In quantum dots based on CdS, it is evident that these nanoparticles actively participate by fuctioning as both multiple electron donors and acceptors, owing to their confinement within the particle [28].

In order to gain a deeper understanding of the electrochemical properties of CdTe-based QDs, a comprehensive evaluation of multiple parameters was conducted. These parameters included particle size, solution pH, and surface stabilizing agents. The technique of cyclic voltammetry was employed to investigate these aspects. The results of the study revealed that the reduction and oxidation events observed in the QDs could be attributed to the positions of the energy bands, which were influenced by the quantum size effect [31].

The so-called traps are energy states formed by breaking the surface symmetry of the QDs that occur within the valence and conduction bands. These traps are closely linked to changes generated in the direction of the polarization potential, which affects the behavior of the QDs [32–34].

4. The use of quantum dots in electrodes

Electrochemical immunological sensors are strong candidates to be used as platforms in medical centers due to their great sensitivity and specificity associated with diagnostic tests. To increase these values, it is necessary to use signal amplification strategies in response to the analyte, mainly in immunosensors aimed at rapid detection [35].

The number of publications using QDs in electrosensors has increased exponentially since 2005. In addition, several publications relating nanoparticles of this type to modifications for the construction of immunosensors, comparisons of this material with bulky materials, immobilization platforms, and changes in electrodes and electrocatalysts were made during this period [35].

Quantum dots have been used in several signal amplification strategies to increase sensitivity in immunological electrochemical sensors due to their high surface-volume ratio. In addition to their biocompatibility when associating with other molecules, their unique reaction characteristics and surface modification capacity make this nanomaterial essential in these applications [35, 36].

QDs can also be used for marking various antibodies through conjugation methods involving the activation of esters through avidin-biotin-type bonds, among others. In addition, the electrodes can be directly modified with this nanomaterial and successively joined to molecules such as aptamers, antibodies, or antigens to recognize a specific target, where after the reaction, there will be a change in the electrochemical behavior [27, 37].

When electrodes are modified with nanostructures such as QDs, several functional groups allow greater accessibility of molecules, such as adsorption-type binding events, which occur on the surface of this electrode. In sequence, a fast electronic transfer is made due to the high conductivity of the material, in addition to the increase in the number of surface molecules associated with high surface area [38].

One of the most used techniques when working with metallic nanoparticles involves the use of acidic solutions capable of dissociating metallic cations so that it is possible to quantify the bound nanoparticles through voltammetric and amperometric techniques, to measure the number of ions, which are proportional to the number of nanoparticles and in turn of the analyte [35].

Nanoparticles can also function as carriers of electroactive species and be measured. As these nanoparticles would create two distinct electrochemical signals compared to single-metal nanoparticles such as AuNPs or AgNPs, they can be loaded with species of diverse chemical composition, allowing their use in multiplexed electro sensors [39].

As the immobilized layer, which normally connects the nanoparticles to the electrode, prevents the substances from reaching its surface, the electronic transfer reactions are attenuated, with a low current background. However, due to the photoactivation capacity of the QDs, the condition changes drastically after the correct excitation of the light spectrum and redox reactions become possible, creating easy-to-use, accessible, and portable sensor systems [40].

A common problem of the strategy that involves immobilizing the QDs on the electrodes is the production of unstable photocurrent (drift). One of the main reasons associated with this, including the poor connection between the QD-electrode, which ends up releasing the nanoparticles previously immobilized during the measurement of currents. In this case, coupling reagents capable of covalently joining the nanoparticles to the surface of the electrodes are used to guarantee the generation of stable photocurrents through the electronic conduction between both [41–43].

Another area for improvement in the direct connection of the QD-electrode is the so-called photo corrosion of the excited nanoparticles. In this case, the drift occurs because the QDs can act as capacitors; if, during the reduction and oxidation events of the system, there are no electron donors or acceptors in the solution, the nanoparticles are continuously reduced and oxidized by the electrode, generating a change in the photocurrent with the variation of time, affecting the stability of the reaction [44–46].

The incorporation of other nanoparticles into the electrode system along with QDs is an incredibly valuable approach to facilitate electronic transfer within the system. This alternative often involves the use of nanoparticles such as gold nanoparticles, carbon nanotubes, titanium dioxide, and graphene, which aid in enhancing the performance and efficiency of the QD-based electrol system. In addition to more, the use of these nanoparticles in the system helps to avoid charge recombination of the electronic carriers, ensuring greater sensitivity for the detection of redox species in the solution [47–50].

An alternative for modifying the electrode is the coating of ligands on the surface of the QDs for coupling to the electrode. In addition to these ligands adjusting the electrical properties, they make possible covalent and non-covalent connections depending on the strategy and the use of overlapping layers with the advantage of increasing the photocurrent magnitude [27, 51–53].

Generally, after light excitation and application of a specific potential, the electrons can tunnel from the electrode to the valence band of the QDs (**Figure 2**). Consequently, the conduction band's electrons interact with the solution's external electron acceptor molecules. In this case, the current increases proportionally with the concentration of acceptors on the surface. On the other hand, if the substances in the solution are electron donors, tunneling occurs in the opposite direction [54].

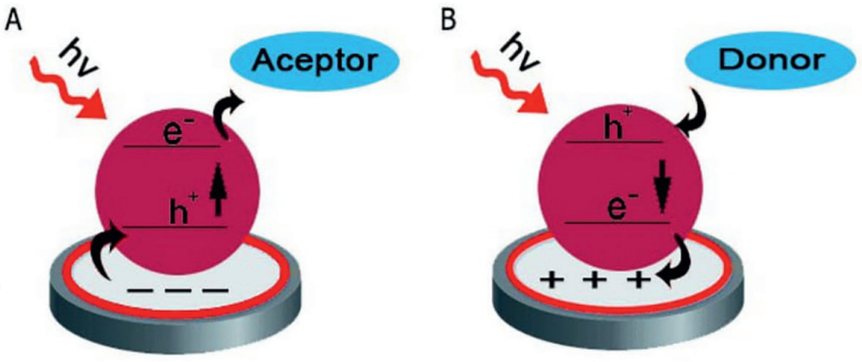

Figure 2.
Electron transfer process at a quantum dot-modified electrode after illumination: (A) reduction process generated by the electron acceptor and (B) oxidation process generated by the electron donor.

By comparing electrodes modified with QDs to unmodified electrodes, it becomes evident that the inclusion of nanoparticles offers an additional tool to regulate the reaction. The incidence of light directed to only a specific area allows the analysis of multiple regions within the same electrode. The analyte is only detected after the presence of light excitation. In this case, the resolution varies according to the acceptor molecule and the light system used, the name given to the strategy refers to the concept of light-addressable sensor systems [55–57].

When comparing theoretical and experimental models, it is possible to observe that both cite the implications associated with variations in the distance between the valence and conduction bands. The final formation of photocurrent is influenced by various factors, including the size of the nanoparticle, the distances between the electrode and the QDs, as well as the type of conductive properties of their ligands, the concentration of redox materials, and the light spectra. Thses parameters play crucial roles in determining the efficiency and characteristics of the generated photocurrent [41, 58, 59].

Another interesting concept of the QD-electrode system is its ability to recognize analytes without the need for labeling them with other secondary structures containing electroactive species. In this case, elements such as antibodies, aptamers, or DNA will be added on the surface of this, and only with the specific recognition of an analyte the charge of the system will be altered, characterizing the binding [60].

In addition to their role in coating the electrode surface, QDs can also serve as markers for molecules. They serve as electroactive structures that can be detected when the capture structure and the labeled analyte come into proximity, establishing a connection with the electrode. This system can also be amplified by increasing the number of molecules attached to the surface of nanoparticles [61].

Among the various ways of using QDs, electrochemiluminescence can detect a wide range of analytes in the solution. In this case, electrochemical reactions excite the nanoparticles, causing them to emit a certain fluorescence, which will be quantified concerning the amount of analyte recognized in the system [27].

Like many semiconductors, QDs can be excited through various means, including light spectra as well as chemical and electrochemical reactions. The emission of light from QDs can be controlled by applying potentials to the electrode, leading to sequential responses. One significant advantage of this approach is the ability to confine the reaction to a specific area without the need for external light sources. Additionally, the absence of a background associated with ambient light further enhances the precision and accuracy of the measurement conducted using QDs [62, 63].

Similar to the photoluminescence, the physical properties of QDs, such as the distance between the valence and conduction bands and the change in the applied electrochemical potential, can also be explored to refine the final result system. This capability allows for the utilization of QDs in a multiplexed format, enabling their application in several new fields [64, 65].

Despite the various advantages of electrochemiluminescence with QDs, when compared to substances such as luminol, the yield is much lower, for this some strategies are used, such as modifying the electrode with graphene, carbon nanotubes, and titanium oxide, in addition to the use of nanoparticles of gold to amplify the luminescent signal of the system [66–68].

Another limiting factor of systems using electrochemiluminescence involves light emission in visible spectra, requiring protection against external input of wavelengths [69, 70].

5. Use of electro sensors based on QD in the diagnostic area

Immunodiagnosis refers to techniques capable of detecting immunological analytes based on antibodies used in conjunction with other structures. The union of the high sensitivity and specificity of the antibodies makes the immunological tests widely used and, depending on the test, with relatively low cost, making these methodologies popular in a clinical environment [71].

As with any other platform, the selection of reagents, methodology, antigens, and antibodies used in immunological tests are extremely important, generating different limits of detection, sensitivity, reproducibility, and other parameters capable of affecting the performance of the test based on these precepts, several forms of detection have emerged over time for specific types of analytes [71].

For a long time, immunosensory platforms based on electrochemical signals have been used, bringing advantages such as speed, precision, and sensitivity to the tests [71, 72].

An indirect photoelectrochemical sensor employing enzymes was used to detect acetylcholine by monitoring variation in the photocurrent generated in relation to its concentration in the solution. The system consisted of the enzyme acetylcholinesterase covalently linked to CdS quantum dots connected to the electrode; the enzyme catalyzes the hydrolysis of acetylcholine, which releases acetate and thiocholine, the latter acting as an electron donor to the system, contributing to increasing the photocurrent peak amplitude [73].

In another work, using enzymes associated with QDs, sarcosine oxidase was used with electrodes containing CdSe/ZnS Quantum dots to determine the amount of free sarcosine in the solution. In this case, the catalysis of oxidation generated formaldehyde and glycine. However, oxygen was consumed during light excitation, causing changes in the photocurrent concerning the amount of analyte in the sample [74].

Several sensors use QDs on gold surfaces. In this case, their use for detecting the cytochrome C protein was first done with the binding of QDs CdSe/ZnS to the surface of the electrode with the help of specific linkers. During the tests, it was possible to observe the changes in the photocurrent with the oxidation and reduction states of the protein, resulting in different anode and cathode currents during the experiment [75].

Still on photoelectrochemical assays, an immunosensor capable of detecting the concentration of type G immunoglobulins was developed through the multilayer deposition of QD on the surface of Indium tin oxide electrodes. The photocurrent

variation was generated due to steric hindrances events by the formation of the immune complex [76].

Apart from traditional single-analysis methodologies, a novel approach was emoployed to develop a multiplex immunosensor capable of simultaneously detecting multiple biomarkers. This innovative strategy involved the utilization of PbS, ZnS, and CdS QDs. By employing square-wave anodic stripping voltammetry, it became feasible to detect and differentiate three different antibodies in the same sample [77].

Using the technique of dissolution of QDs in acid solutions, it was possible to develop an electro sensor based on QDs of CdSe/ZnS as a marker of phosphorylated bovine serum albumin. The nanoparticles were used for amplification of the electrical signal when conjugated to a specific secondary antibody, after acid dissolution, an electrochemical stripping analysis was performed making it possible to correlate between QD and antibody concentration [78].

Several types of QDs are useful in the construction of electro sensors to develop a Carcinoembryonic Antigen (CEA). One group used poly(5-formyl indole)/electrochemically-reduced graphene oxide nanocomposite (P5FIn/erGO) and Au nanoparticles (AuNPs) to facilitate the transport of ions during redox events. Moreover, the modification allows the increase of the primary antibody immobilization area, and finally, the gold nanoparticles amplify the system signal [79].

Assays of the "label-free" type have several advantages associated with nanoparticles. Therefore, an electrochemical immunosensor used graphene QDs with gold nanoparticles to detect and quantify Human Chorionic Gonadotropin (HCG) in human serum. The modification made the more sensitive assay increase the electronic flow, allowing the coupling of a greater number of proteins on its surface and greater reproducibility of the test [80].

In addition to electro sensors based on enzymes or antibodies, those based on DNA/RNA are of great use in the diagnostic area. A study involved the simultaneous detection of several proteins from aptamers immobilized on the gold surface of the electrode, and after incubation, different QDs of lead sulfide and cadmium telluride allowed selective detection and differentiation based on other voltammetric characteristics [36].

Still, magnetic nanoparticles based on ZnFe2O4/GQDs were used on DNA-based detection systems to mimic peroxidase-type activities. In this case, the capture DNA immobilized on the electrode surface served to capture the analyte. Susequently, in a sandwich system, the nanoparticles allowed this quantification through the reduction of electrical peaks [81].

In another example, a work proposed a glucose sensor without using enzymes. For this, it used CdTe QD-functionalized ZnO nanosheets with excellent photocatalytic activity, and the labeled capture DNA was immobilized on the associated modified electrode. The detection made by electrocatalysis of Pt/TiO2 NTA on glucose at low potential allows detection with very low interference [82].

A simple "label free" system was developed for the detection of hepatitis B virus through DNA using graphene QDs on the electrode, the method used an immobilized complementary DNA strand for the capture of HBV-DNA that, in the absence of this analyte, caused a low voltammetric value, referring to the low oxidation of potassium ferricyanide, but in the presence of complementary DNA, these values increased drastically, being able to diagnose the presence of the virus [83].

In diagnosing pathogenic bacteria, using electro sensors also proves to be a great alternative to conventional methods. Using graphene QDs on gold electrodes, a "label-free" type sensor was developed where specific antibodies were immobilized with

bovine serum albumin and ethanolamine. The quantification of the bacteria was done through amperometry, where after the addition of H_2O_2, the immunocomplex varied the oxidation levels with the growth of the concentration of *Yersinia enter*ocolitis [84].

In addition to common diagnoses, Living-cell detection has received attention associated with toxicity analysis and medical applications. One study used the photoelectrochemistry of graphene-CdS nanocomposites as a mechanism for amplifying the electronic transport process and increasing photocurrent, in addition to ensuring system stability and linear response with a low detection limit [85].

6. Conclusions

In recent years, there has been a rapid increase in research activity and interest in QDs. High quantum yield, stability, and stable electrochemical characteristics make these nanoparticles unique. The biosensors discussed in this work are electrical, utilizing reactive mediators that can be detected through various processes such as quantum tunneling generated by photoelectrochemistry, potential increase through changes in system charge, and electrochemiluminescent events. Applications of the distinctive electrochemical and photophysical features of QDs are expanding in many areas, offering fascinating prospects for the accurate and sensitive detection of various biochemical species. QDs functionalized with different biomolecules can provide distinct platforms for signal transduction for biomolecular detection and direct electron energy transfer for photoelectric interconversion processes. The development of QD-based electrochemical bioanalyses will continue to be driven by the demand for miniaturization, to develop faster, cheaper clinical diagnostic tests based on a lab on a chip application.

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