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NANOMATERIALS IN VOLTAMMETRIC BIOSENSORS-RECENT ACHIEVEMENTS

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While we inhabit a macro-world, it is evident that our future will depend greatly on the tiniest of things. This is due to the fact that a majority of 21st-century sciences will be centered around materials with nanometer dimensions. Currently, we observe the significance of nanomaterials in facilitating the targeted delivery of active substances within the body. In the past two years, this has played a crucial role in combating the COVID-19 pandemic, with the assistance of vaccines containing graphene oxide nanoparticles that serve as carriers and enhancers for vaccine compounds. Furthermore, challenges related to drug delivery, such as poor water solubility and limited bioavailability, have already been overcome through the utilization of metal-based and carbon-based nanomaterials. Nanomedicine is poised to revolutionize the landscape of therapeutics and diagnostics. This brief review focuses on notable achievements in designing specific voltammetric biosensors using metallic nanoparticles and graphene-based nanomaterials. Metallic nanoparticles, particularly those based on silver and gold, along with graphene derivatives such as nanotubes, quantum dots, nanodiamonds, and fullerenes, exhibit remarkable physical and chemical properties. These include improved thermal stability, enhanced conductivity, and the ability to modify their surface area with various organic substrates. Notably, voltammetric sensors based on graphene nanostructures demonstrate high biocompatibility and superior selectivity in detecting important biological systems through voltammetry. The aim of this concise review is to highlight recent electrochemical advancements in nanosystems and present significant achievements of metallic nanoparticles and graphene-based nanomaterials as voltammetric biosensors.

Key words: metallic nanoparticles; graphene; carbon nanotubes; electrochemical biosensors, voltammetry

INTRODUCTION

Voltammetry is arguably the most valuable electrochemical technique for gaining insights into various aspects of electrode transformations in physiological and chemical systems, ranging from small ions to large lipophilic proteins and enzymes [1–3]. As voltammetry revolves around measuring the energy of electrons exchanged between specific analytes and an electronic conductor (the working electrode), it becomes evident that the nature of the working electrode plays a crucial role in this electrochemical technique. A limited selection of working electrodes, primarily composed of noble metals, mercury, or carbon materials, have been reported as suitable materials for the majority of voltammetric studies [1, 4–6]. The effective utilization of voltammetry for probing specific ions, drugs, or physiologically active systems at micromolar or lower concentrations often necessitates the modification of working electrode surfaces with materials possessing superior conductive and chemical properties compared to unmodified electrodes [7]. Over the past 20 years, extensive exploration has been carried out on various nanomaterials to enhance the surfaces of electronic conductors used in voltammetric experiments [8]. Among these, nanoparticles based on metals (such as Au, Ag, Pt), metal oxides (primarily Fe_2O_3, Al_2O_3, CuO, CoO, MoO_3, Bi_2O_3), and particularly those derived from different carbon materials (multiwalled and single-walled carbon nanotubes) have been widely employed in voltammetric systems. Their usage has significantly contributed to the successful application of voltammetry in the design of numerous voltammetric sensors for detecting important chemical and physiological compounds [1, 5]. This brief overview highlights some of the key achievements of nanomaterials in the development of voltammetric sensors in recent years.

RESULTS AND DISCUSSION

The concept of "nanotechnology," initially developed by Richard Feynman [9] (Nobel Prize laureate in 1965), has brought about revolutionary advancements in the fields of nanomedicine, pharmacy, chemistry, physics, high-tech industry, food industry, and numerous other related fields [8, 10–12]. Nowadays, nanomaterials have become ubiquitous in every aspect of our lives. Over the past 20 years, nanotechnology has made significant impacts in areas such as drug delivery, cancer therapy, drug synthesis, cellular phones and computer technology, development of new materials, high-precision electronics, and environmental analysis. Although nanoparticles (NPs) encompass a wide range of materials, they are commonly defined as "three-dimensional materials with at least one dimension in their structure measuring less than 100 nm" [11]. Numerous excellent books have been published in the last 15 years, covering important topics related to the synthesis, properties, functions, characterization, and applications of various NPs. Interested readers are advised to refer to some of these publications [13–20]. In general, the remarkable characteristics of nearly all nanoparticles (NPs) that render them highly suitable for implementation in electrochemical systems are attributed to their exceptional catalytic properties, larger surface area-to-volume ratio achieved by reducing their size, improved electronic conductivity, enhanced durability, and compatibility with various substrates. Additionally, many NPs, particularly those based on graphene, serve as favorable platforms for attaching functional groups, which is an important feature manifested in their reactivity towards specific substrates. While numerous recent excellent reviews cover different properties, synthesis protocols, characterization, and application of nanoparticles in electrochemical experiments [21–26], this overview focuses on highlighting only a selection of the most significant properties and achievements of certain types of nanoparticles utilized in voltammetric biosensing. Figure 1 illustrates a scheme showcasing some of the key NPs employed in electrochemistry, while Figure 2 depicts a modified working electrode with gold nanoparticles, suitable for voltammetric experiments.

The initial mention of metal nanoparticles in electrochemistry dates back more than 30 years [11]. Metal nanoparticles are highly attractive for modifying various electrode surfaces due to their easy and cost-effective preparation, as well as their notable electrocatalytic properties [11, 14, 26]. When attached to the working electrode, these nanoparticles significantly increase its active surface area due to their small size. Furthermore, the use of metallic nanoparticles commonly enhances the material's electrical conductivity, leading to an increased rate of electron exchange between the studied analytes and the modified electrodes [4–8, 14]. Among the metallic nanoparticles investigated in voltametric studies, silver and gold nanoparticles are the most well-known [14, 21]. This is primarily attributed to their relatively inexpensive and straightforward synthesis protocol, often involving chemical reduction from salt solutions using mild reductive substances such as citric acid [11, 14].

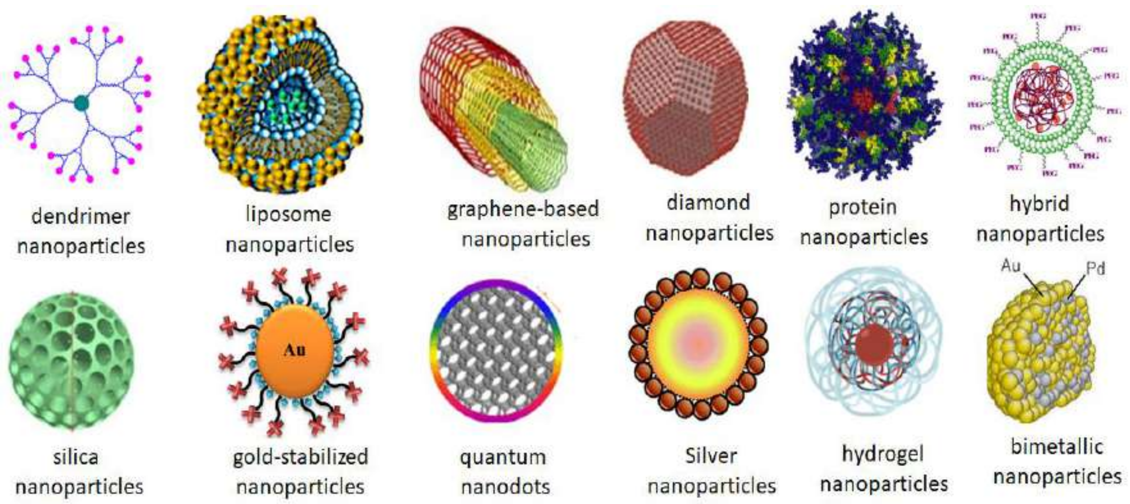

Figure 1. Schemes of some nanoforms mostly used in electrochemical experiments

Figure 2. Schematic representation of a working electrode, with active electrode surface modified with gold nanoparticles

Another advantage of utilizing silver and gold nanoparticles is their potential for stabilization and modification with various ligands and functional groups on their surfaces [26]. In the case of modifying working electrodes with silver nanoparticles, electrodeposition under controlled potential is also feasible and easily achievable, as reported in [14–17]. When silver nanoparticles are combined with graphene oxide, the reduction of silver nitrate from a water solution is commonly accomplished using hydrogen iodide as a reducing agent [27]. A chemical reduction protocol allows the production of silver nanoparticles with sizes ranging between 10 nm and 25 nm [28]. On the other hand, electrodeposition of silver nanoparticles typically results in larger particles with diameters ranging between 30 and 50 nm [27]. Unfortunately, aggregation of deposited silver nanoparticles into larger clusters often occurs and is difficult to avoid when using the electrodeposition method. The toxicity of silver nanoparticles is recognized as a significant drawback when applying these materials in experiments involving physiological systems. Gold nanoparticles are among the most extensively studied metallic nanomaterials for electrochemical detection of different analytes [29, 30]. The most common method for obtaining gold nanoparticles is through chemical reduction of chloroauric acid in water solutions using mild reducing agents such as sodium citrate, ascorbic acid, and sodium borohydride [11, 14]. An advantageous characteristic of gold nanoparticles is their ability to form covalent bonds with substrates containing thiol (-S-H) groups in their structure [14]. Numerous modification protocols involving "mercapto substrates" [31] have paved the way for the widespread use of thiol-modified gold nanoparticles in voltammetric sensing, particularly for the quantification of important biomolecules like DNA [32]. Other metallic and bimetallic nanoparticles derived from bismuth, platinum, copper, nickel, cobalt, titanium, palladium, mercury, and various other metals have also been extensively employed in various voltammetric studies [13–15]. In addition to metallic nanoparticles, metal-oxides and metal-sulfides nanoparticles have been extensively explored for voltammetric purposes over the last 10 years. Detailed information regarding their synthesis protocols, properties, functions, and applications can be found in comprehensive reports such as [14, 33–36]. Table 1 summarizes some of the most significant applications of metallic, metal-oxides, and metal-sulfides nanoparticles in voltammetric sensing of chemical and physiological systems, as published in recent years.

A significant turning point in experimental voltammetry occurred approximately 20 years ago, coinciding with the isolation of freestanding graphene [51]. The integration of this two-dimensional carbon material in electrochemical experiments marked the beginning of a new era in the development of voltammetric sensors for probing important chemical and physiological systems [52]. Due to its ability to be easily wrapped and rolled, graphene became a fundamental building block in the design of various carbon-based nanomaterials, including carbon single-walled and multi-walled nanotubes, fullerene, nanoplatelets, and other nanoforms [53]. Over the past 15 years, graphene has consistently demonstrated superior performance compared to existing electrode materials when used as a modifier for electrochemical sensors. Analysis of voltammetric sensors published since 2012 indicates that more than 30% of the works report the exploration of graphene-based nanomaterials (primarily single-walled and multi-walled carbon nanotubes) for the modification of electrode surfaces [51].

The extensive exploration of 3D graphene-based nanoforms in voltammetric biosensors can be attributed to their remarkable features, including their exceptional electrical conductivity, high chemical stability, and their ability to serve as platforms for attaching various substrates with specific functional groups onto their surfaces [54].

Table 1. Data about voltametric detection of different substrates with metal-based nanoparticles

Type of nanoparticles	Voltammetric Technique/ Working Electrode	Analyte	Detection limit of the analyte	Reference
Au-nanoparticles stabilized with dithiothreitol and dodecanethiol	DPV/Au electrode	epinephrine	0.06 μmol/L	[37]
various Au-nanoparticles	DPV and SWV/GCE/Au electrode	various polyphenols	in sub-micromolar range	[38]
Au-nanoparticles	CV/GCE	glutathione	0.7 pmol/L	[38]
Au-nanoparticles stabilized with various substrates	DPV, SWV and CV /GCE/Au electrode	DNA	sub-micromolar concentrations	[32]
various metallic nanoparticles	DPV, SWV and CV/GCE/Au electrode	hazardous polyphenols in water	sub-micromolar concentrations	[40]
Ag-nanoparticles/multiwalled nanotubes	DPV/GC electrode	glucose	0.01 mmol/L	[41]
Pt-Ag nanoflowers	DPV/GC electrode	hydrogen peroxide, glucose	0.02 mmol/L	[42]
various metallic and bimetallic nanoparticles	DPV, SWV and CV /GCE/Au/Pt electrode	Sb^{2+}, As^{5+}, Cd^{2+}, Cr^{6+}, Cu^{2+}, Pb^{2+}, Hg^{2+}, Ni^{2+}	mainly in sub-micromolar concentrations	[33]
Au-nanoparticles	DPV/GCE	glucose and hydrogen peroxide	for glucose 0.39 μmol/L for hydrogen peroxide 0.136 μmol/L	[43]
CuO nanowires	CV/copper foam	glucose	lower mmol/L range	[44]
Au-Pd/MoS_2	CV/GCE	glucose and hydrogen peroxide	for glucose 0.16 μmol/L for hydrogen peroxide 0.40 mmol/L	[45]
Pd-nanoparticles on Co-wrapped carbon nanotubes	CV/GCE	hydrazine	0.07 μmol/L	[46]
Au-nanoparticles stabilized with mercaptoundecanoic acid	CV/SWV/GCE	vitamin E	0.25 μmol/L	[47]
Au-nanoparticles stabilized with mercaptoundecanoic acid	CV and SWV/GCE	DNA	7. 5 μmol/L	[47]
Ag-nanoparticles at water-nitrobenzene interface	SWV and CV/GCE and PIGE	inorganic anions transferred across liquid-liquid interface	0.1 mmol/L	[48]
Ag/MoS_2 hybrid nanoparticles	CV/ITO	dopamine	lower mmol/L concentration range	[49]
Fe_3O_4 nanoparticles-polyvinyl chloride	CV/Sn electrode	glucose	8 μmol/L	[50]

* CV-cyclic voltammetry: SWV-square-wave voltammetry: DPV-differential pulse voltammetry:
** GCE-glassy carbon electrode: PIGE-paraffin impregnated graphite electrode: ITO-indium tin oxide electrode

To harness the extraordinary features of carbon nanotubes (CNTs) for the development of voltammetric sensors, they typically undergo initial functionalization with biocompatible molecules [55]. This functionalization step yields a biomodified nanointerface that serves as a crucial platform for designing specific voltammetric biosensors. Various organic or inorganic substrates are commonly employed for the functionalization of CNTs, resulting in improved properties such as enhanced chemical compatibility and increased water solubility [53–55]. "Covalent functionalization" primarily involves small molecules that induce changes in the π-electronic framework of graphene [56]. On the other hand, "noncovalent functionalization" of these nanomaterials involves interactions between graphene's structure and aptamers, enzymes, polymers, and other organic systems (as illustrated in Figure 3), typically achieved through van der Waals interactions [56].

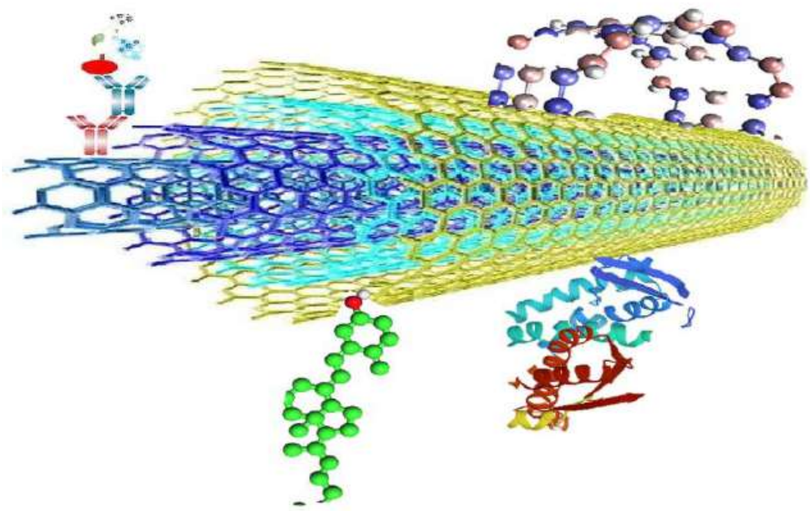

Figure 3. Scheme of a multiwalled carbon nanotubes that are functionalized with various organic molecules. The functionalization of carbon nanotubes with organic molecules is seen as a key step in achieving better selectivity of carbon nanomaterials.

Carbon nanoparticles, including graphene-made nanoparticles, have a propensity to induce changes in the electrical and chemical properties of non-modified electrodes. This often leads to significantly improved overall electrochemical performance of nano-modified electrodes for the detection of specific target molecules [56]. Over the past two decades, tens of thousands of papers have been published on electrochemical biosensors utilizing graphene-based nanoparticles in various forms, such as amperometric enzyme electrodes, voltammetric immunosensors, and nucleic acid voltammetric devices. In recent years, several comprehensive reviews have focused on graphene-based nanomaterials in the design of voltammetric biosensors suitable for quantifying diverse analytes, including DNA, dopamine, glucose, various hem-containing redox proteins, cytochromes, hormones, ascorbic acid, hydrogen peroxide, bilirubin, various pharmaceuticals, and other physiological systems. Interested readers are encouraged to refer to these works [52–61].

Enzyme-based electrochemical biosensors find extensive use in pharmacy, nanomedicine, food safety, and studies related to monitoring different substances relevant to environmental protection [53–56, 58].

Numerous voltammetric biosensors utilizing CNT-modified electrodes provide valuable insights into the activity of various redox enzymes [see reviews 58, 62, 63, and references therein]. Clinical biochemistry, being a major application area for biosensors, has witnessed a plethora of studies dedicated to the development of voltammetric biodevices for monitoring glucose, hemoglobin, urea, and other relevant physiological systems in whole blood [see reviews 58, 62–64, and references therein]. Additionally, over the past 10 years, there has been intensive exploration of graphene-based nanomaterials in designing reliable voltammetric biomarkers for medical diagnostics [65–67]. Table 2 provides information on some of the noteworthy recent achievements in the design of voltammetric biosensors using various graphene-based nanomaterials.

Table 2. Data about voltammetric detection of different substrates with graphene-based nanoparticles

Type of graphene-based nanoparticles	**Voltammetric Technique/ Working Electrode**	**Analyte**	**Detection limit of the analyte**	**Reference**
Multiwalled carbon nanotubes functionalized with cysteamine	CV/GCE	hemoglobin	0.03 μmol/L	[68]
Multiwalled carbon nanotubes immobilized on gelatin + glucose oxidase	CV/GCE	glucose	0.5 mmol/L	[69]
Multiwalled carbon nanotubes on poly(vinyl alcohol)+ alcohol dehydrogenase	CV/GCE	ethanol	0.16 μmol/L	[70]
multiwalled carbon nanotubes	CV/GCE	Cholesterol	0.5 μmol/L	[71]
multiwalled carbon nanotubes-metal oxide nanoparticles-7, 7, 8, 8-tetracyanoquinodimethane	CV/GCE	xanthine	0.2 μmol/L	[72]
composite of dendrimer-encapsulated Pt nanoparticles and carbon nanotubes	CV/GCE	Ascorbic acid, hydrogen peroxide	10 μmol/L 50 μmol/L	[73]
multi-copper enzyme co-adsorbed at carbon nanotube	CV/GCE	Hydrogen peroxide	lower micromolar range	[74]
dehydrogenase modified quantum dots-carbon (ZnS-CdS) nanotubes	CV/GCE	glucose	10 μmol/L	[75]
Hybrid of silver multiwalled carbon nanotubes/manganese dioxide.	CV/GCE	carcino-embryonic antigen	10 μg/L	[76]
Multiwalled carbon nanotubes	CV/GCE	paracetamol ibuprofen	1 μmol/L 1 μmol/L	[77]
carbon black nanoparticles	CV/GCE	hemoglobin	lower micromolar range	[78]
carbon black nanoparticles	CV/GCE	various hem-containing proteins	below 1 μmol/L	[79]
epoxy polymer and acetylene black nanoparticles	CV/GCE	Cytochrome P450	below 1 μmol/L	[80]

OUTLOOKS FOR THE FUTURE

It is increasingly evident that the remarkable properties of metallic nanoparticles and the exceptional chemical performances of graphene-based nanomaterials will play a pivotal role in shaping scientific advancements in medicine, chemistry, pharmacy, physics, new materials design, and environmental analysis throughout the 21st century [58]. During the last three years of the Covid-19 pandemic, it has become evident that the efficient functioning of vaccines relies on the support of graphene-based nanomaterials [81]. Furthermore, the delivery of many important drugs in medicine is closely linked to the unique properties of carbon nanotubes and fullerenes [82–86]. The remarkable electrochemical properties of graphene-based 3D nanomaterials have ushered in a new era of their widespread use in designing voltammetric biosensors for the detection of crucial biomolecules [58, 87]. As over 50 % of novel works on voltammetric biosensors incorporate the use of nanomaterials, we anticipate a rapid breakthrough in the more extensive application of voltammetry in commercially designed devices [88].

To enhance the sensitivity and selectivity of nanomaterials, the development of novel nanomaterials with functionalized surfaces, incorporating multiple substrates within a single nano-platform, is anticipated. This advancement will enable the simultaneous and selective determination of different biomolecules in real-time [89]. From this perspective, it is highly likely that the remarkable chemistry of nanomaterials will soon lead to the emergence of novel fields in electrochemical research that will impact various aspects of our daily lives, particularly by improving biochemical, pharmaceutical, and medical research in numerous ways [81, 83, 90–92].

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ПРИМЕНА НА НАНОМАТЕРИЈАЛИ ВО ВОЛТАМЕТРИСКИТЕ БИОСЕНЗОРИ – ПРЕГЛЕД НА НЕОДАМНЕШНИ ПОСТИГНУВАЊА

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Иако опстојуваме во макросвет, сепак, иднината на сите нас ќе зависи од работи што имаат мали димензии. Тоа е поради фактот што огромен дел од науката во 21 век е насочена кон проучување материјали со нанометарски димензии. Така, на пример, огромен дел од науката за наноматеријалите во овој период е насочена кон нивната способност за зголемување на ефикасноста на транспорт на активни супстанции во човечкото тело. Како што е познато, во минатите три години, овие наноматеријали имаа суштинска улога во борбата против пандемијата на ковид-19, при што голем дел од вакцините против ова заболување се базираа на наночестички што содржат графен оксид. Покрај тоа, голем број предизвици во медицината и фармацијата што се поврзани со биодостапноста на лековите и со нивната ниска растворливост во вода се надминати со употреба на различни наноматеријали базирани на метали или на јаглерод. Наномедицината, на пример, е гранка што ќе донесе револуционерни промени во дијагностичките и терапевтските третмани на пациентите. Во овој краток прегледен труд, главен фокус е ставен на некои од значајните постигнувања во дизајнирањето специфични волтаметриски биосензори што се базирани на метални наноматеријали и наноматеријали што содржат графен. Металните наночестички, посебно оние што содржат злато или сребро, во својот состав, заедно со наноматеријалите што се деривати на графен, како што се нанодијаманти, нанотуби и фулерени, покажуваат необични физички и хемиски својства. Така, на пример, овие наносистеми покажуваат зголемена термичка стабилност, подобрена топлинска и електрична спроводливост и имаат потенцијал за модификување на нивната површина со разни органски супстрати. Притоа, важно е да се нагласи дека волтаметриските сензори што се базирани на графенски наноматеријали покажуваат висок степен на биокомпатибилност и сензитивност кон важни биолошки системи чии својства се испитуваат со волтаметриски техники. Целта на овој краток прегледен труд е да ги прикаже некои од најновите електрохемиски придобивки од наноматеријалите и да ги претстави некои од значајните постигнувања на метални наночестички и наноматеријали базирани на графен во сферата на волтаметриските биосензори.

Клучни зборови: метални наночестички; графен; јаглеродни наноцевчиња; електрохемиски биосензори; волтаметрија