Laís S. Porto¹ / Daniela N. Silva¹ / Ana Elisa F. de Oliveira¹ / Arnaldo C. Pereira¹ / Keyller B. Borges¹

Carbon nanomaterials: synthesis and applications to development of electrochemical sensors in determination of drugs and compounds of clinical interest

¹ Departamento de Ciências Naturais, Universidade Federal de São João del-Rei (UFSJ), Campus Dom Bosco, Praça Dom Helvécio 74, Fábricas 36301-160, São João del-Rei, MG, Brazil, E-mail: arnaldocsp@yahoo.com.br, keyller@ufsj.edu.br. <https://orcid.org/0000-0003-1067-1919>.

Abstract:

It is notorious that researches related to electrochemical sensors increased significantly due the promising characteristics that these devices present such as the possibility of obtaining information, with minimum manipulation of the studied system, in real time, and with low environmental impact. This article covers the carbon nanomaterials, presenting important aspects such as main properties, synthesis methods, and the application of these materials in the development of electrochemical sensors for the analysis of drugs and compounds of clinical interest. In this context, drug analysis is extremely important for quality control, to ensure that the medicine fulfills its role effectively without possible complications that could compromise the patient's health and quality of life. In addition, analytical methods capable of determining compounds of clinical interest in biological fluids are extremely important for the indication of effective diagnoses. Thus, the versatility, selectivity, and portability of the electroanalytical techniques make the electrochemical sensors a favorite tool for the determination of drugs and compounds of clinical interest. It will be possible to follow in the present work that carbon nanomaterials have excellent thermal and electrical conductivity, strong adsorption capacity, high electrocatalytic effect, high biocompatibility, and high surface area. The possibility of formation of different composite materials based on carbonaceous nanomaterials that makes these materials promising for the development of analytical sensors, contributing to rapid, sensitive, and low-cost analyses can also be highlighted.

Keywords: carbon nanomaterials, carbon nanotubes, electrochemical sensors, fullerene, graphene

DOI: 10.1515/revac-2019-0017

Received: September 26, 2019; **Accepted:** December 11, 2019

1 Introduction

Drugs have a medical purpose: for relief or treatment and used to alter or exploit physiological systems for the person in whom they are administered. Drug analysis is essential for quality control, which consists of a set of measures aimed at ensuring, at all times, the production of medicines and other products, which meet the standards of identity as content and purity among others (ANVISA,). In this sense, the analysis of pharmaceutical compounds and of interest to clinical analysis is highly relevant, mainly to the health area. The analysis of compounds of clinical interest makes it possible to indicate a more accurate and effective diagnosis. Both investigations require sensitive, effective, and reliable analytical methods to ensure the quality of the drug and the good health of the patient.

Several analytical methods were used for the quantification of drugs and compounds of clinical interest, with special emphasis on spectroscopic and chromatographic techniques (Ferey et al., 2018; Østergaard, 2018). The literature shows that most of the methodology drugs for drug determination are based on chromatographic techniques. These techniques are well established and accepted by regulatory organizations; however, they have some disadvantages related to the relatively high cost, time of analysis, and pretreatment steps (Sena et al., 2007; Alam et al. 2017a; 2017b). However, electroanalytical methods, especially those employing electrochemical sensors, showed to be promising to complement the existing traditional techniques because of their versatility, portability, and possibility of miniaturization of the system, without compromising their sensitivity

Arnaldo C. Pereira, Keyller B. Borges are the corresponding authors.

© 2019 Walter de Gruyter GmbH, Berlin/Boston.

and selectivity. The electrochemical sensors make use of low-cost instruments when compared to the instrumentation required for chromatographic and spectrophotometric analyses, besides the low detection limit and less use of reagents (Pandey et al., 2020).

Electrochemical sensors are devices that allow collecting and transforming chemical information, such as electron transfer or proton release, into an analytically useful signal such as a current or potential variation. Researches related to electrochemical sensors increased significantly because of the promising characteristics that these devices present such as the possibility of obtaining information, with minimum manipulation of the studied system, in real time, and with low environmental impact, besides the possibility of modification of the surface of the base sensor with chemically active species. These modifications can improve some characteristics such as sensitivity, selectivity, and stability (Baig, Sajid & Saleh, 2019).

The efficiency of the electrochemical sensors is directly related to the interaction of the recognizing material (modifier) with the analyte, and with the ability of the element to convert the energies of the chemical signal, generated because of this interaction, in a measurable signal. Then, the choice of the electrode material is very important, as it must have appropriate electrochemical characteristics and should be suitable for the modifier immobilization on the electrode surface. Among the materials, platinum, gold, glassy carbon, carbon paste, and pyrolytic graphite were frequently used (Oliveira et al., 2013; Hun et al., 2017; Yildiz et al., 2017; Lenik & Nieszporek, 2018).

After choosing the electrode, the modifying layer should be chosen according to the interest for sensor application. Over the recent years, nanostructured materials had growing tremendous attention for numerous applications in different areas such as computing, electronics, energy generation and storage, analyses of fundamental biological research, clinical diagnostics, food safety, environmental monitoring, medicine, development of new materials, and to improve the efficiency of conventional materials (Li et al., 2019).

One significant property that makes nanoparticles different from other materials is the fact that nanomaterials have a massive surface area. Because of their very high surface area, nanoparticles are extremely reactive compared to their larger form. Thus, the excellent physicochemical properties of this materials, high adsorption, reactive capacity, and surface-to-volume ratio, not present in the bulk materials, made the use of nanomaterials in the development of analytical methods increase in the last few decades (Walcarius, 2012).

Therefore, electrochemical and biosensor platforms integrated with nanostructured materials were employed as powerful analytical devices owing to numerous advantages such as rapid response, high performance, cost effective, high sensitivity and selectivity by signal amplification not only via the catalytic activity and high conductivity but also by facilitating the immobilization of chemical and biological reagents on the sensor surface (Kimmel et al., 2012; Maduraiveeran & Jin, 2017).

Among the various materials that can be classified into the nanomaterial class, carbon nanomaterials may be the most representative in view of their unique combinations of physical and chemical properties. Recently, Li et al. (2019) wrote a review about the development of carbon-based functional nanomaterials describing all the versatility, functionalities, and their potential application in diverse fields. In this review, the authors demonstrated that carbon-based nanomaterials exhibit distinct physical and chemical properties such as chemical stability, good thermal and electric conductivity, could improve optical properties, besides displaying great potential for applications in material preparation, environmental science, energy storage, pharmaceutical analyses, and medical science. All these factors made carbon nanomaterials attract great attention since they were first reported (Li et al., 2019).

Regarding the development of electrochemical sensors, the use of carbon nanomaterials also gained attention, and they are continuously described in the literature because of the advantages that these materials present, such as the relatively low cost, wide potential response window, physical and chemical characteristics, and variations in conductivity. The adsorption of easily detectable target molecules and electrocatalytic activity for various redox reactions contributes to the development of sensors with low detection limit and high sensitivity (Trojanowicz, 2006; Yang et al. 2010; 2015a; 2015b; Maduraiveeran & Jin, 2017).

Thus, considering the different carbon nanostructures that were widely used in the construction of electrochemical sensors and biosensors, this review highlighted recent advances and applications of chemically modified electrodes with carbon nanomaterials for analysis and detection of drugs and compounds of clinical interest that are extremely important for the indication of effective diagnoses and for quality control analyses, in order to protect human health. The present work focused on three of the most important representatives of the carbon nanomaterial class, graphene, carbon nanotubes (CNTs), and fullerene, because of the good results that these materials provided in the development of electrochemical sensors. Furthermore, a brief review about the synthesis process and the principal properties of these carbon nanomaterials will be presented throughout this review.

2 Carbon nanomaterials

Nowadays, the use of different materials in the actions of our day-to-day life, such as driving a car, lighting a lamp, making calls on the cell phone, or watching a TV program became so commonplace and well established that we do not question what our life would be like if these materials were not developed. In general, any substance or mixture of substances, which have properties that make them useful for application in the development of devices, products, and machines, may be classified as materials. In the last years of the 20th century, the emergence of a new class of materials enabled a true scientific and technological revolution, leading to the consolidation of a whole area of knowledge: Nanoscience and Nanotechnology (N & N). This area of knowledge studies materials made up of particles in the order of nanometers, which are now recognized as nanomaterials (Song et al., 2019).

N & N became, by far, the fastest growing area in materials science today, pushing the boundaries of research, reaching industries, and rapidly reaching the general public. The effect of its development can already be seen in the products of our daily life that have had their aspects and properties renewed and improved, from computer chips and cell phones, to beauty products. The great N & N essence consists in the fact that the properties of materials depend not only on their composition and structure but also on their critical size. In this way, when the particles of this material differ below the critical size (in this case on the order of a few nanometers), the properties of the material form the properties observed for it on a macroscopic scale, thus, enabling the preparation of new materials only with the control of the size and shape of its particles (Gogotsi & Presser, 2014).

Among the new materials developed with the advancement of N & N, carbon nanomaterials deserve to be highlighted because they are considered highly versatile. Carbon nanomaterials presented thermal, electrical, chemical, and mechanical characteristics, besides the richness and diversity of carbon, which is the chemical element that considered the symbol of life and is present in thousands of compounds (Schroeder et al., 2019).

The discovery of fullerenes, followed by CNTs and the recent isolation and characterization of graphene in 2004 (Novoselov et al., 2004) provided new possibilities in the chemistry and physics of carbon and made interest in carbon nanomaterials grow still more. Figure 1 presents a short timeline containing information about the year of discovery and the main awards of work related to carbon nanostructures.

Figure 1: Timeline of carbon nanomaterials.

2.1 Graphene

Graphene (Figure 2A) is the carbon allotrope of the nanomaterials family that was isolated most recently. Before being isolated, graphene was considered a purely theoretical material only to explain the formation of other allotropic forms of carbon, such as graphite, CNTs, and fullerene (Figure 2) (Syama & Mohanan, 2019).

Figure 2: Schematic representation.

(A) graphene (2D material) used as a precursor for the construction of carbon materials of other dimensionalities, such as (B) fullerene, (C) CNTs, and (D) graphite.

The term graphene came into being in 1962, a year in which this material was actually observed for the first time by German chemists Ulrich Hofmann and Hanns-Peter Boehm (Boehm et al., 1962), who named it graphene because of the graphite junction with the suffix-ene related to the double bonds existing.

However, it was only four decades later in 2004 that graphene was isolated and first characterized by researchers Geim and Novoselov of the University of Manchester, through the mechanical exfoliation of graphene sheets in individual layers of small plates of pyrolytic graphite (Novoselov et al., 2004).

Novoselov, Geim, and coworkers increasingly improved the efficiency of the material obtained, improving its conductivity, and thinning it to the thickness of an atom (Geim & Novoselov, 2007). To the researchers' surprise, the ultrafine material presented not only a structure of flat monolayer of carbon atoms connected by means of a hexagonal organization but also excellent thermal and electrical conductivity, good mechanical resistance, being light, flexible, and presenting a large specific surface area.

All the excellent physical, chemical, mechanical, optical, and electrical properties that graphene presents make it one of the most promising and revolutionary nanomaterials today. However, all the prominence achieved by this material only became possible due to its two-dimensional structure and atomic organization, which is responsible and directly related to the properties that it presents.

Graphene is formed by carbon atoms with sp^2 hybridization in a conjugated π bond system, arranged in monolayers in a two-dimensional structure. The bond length between the carbon atoms in the graphene structure is approximately 1.42 Å. Each atom has an orbital p , oriented perpendicular to the molecular plane, which overlaps forming valence and conduction bands, which provide the phenomenon of planar conduction (Soldano, Mahmood & Dujardin, 2010; Ghany, Elsherif & Handal, 2017).

Some characteristics turn the graphene into a particular material, for example, the electrons of graphene monolayer can move at a velocity of up to 10^6 m s⁻¹, which turns this material into an excellent electrical conductor (up to 2×10^4 S cm⁻¹). It possesses an electronic mobility up to 100 times larger than that of silicon ($\sim 2 \times 10^5$ cm² V⁻¹ s⁻¹) and thermal conductivity at room temperature up to 5000 W m⁻¹ K⁻¹ (compared to 400 W m⁻¹ K⁻¹). Graphene also shows a very high surface area (~ 2600 m² g⁻¹), higher than those observed for materials such as graphite (10 m² g⁻¹) and CNTs (1300 m² g⁻¹) (Soldano, Mahmood & Dujardin, 2010; Syama & Mohanan, 2019).

However, the electronic properties of graphene change with the number of layers and with the relative position of atoms in adjacent layers determined by the order of stacking. Therefore, graphene should not be considered as a single material, but rather as a family of compounds that can be formed by a single layer of atoms (monoatomic sheet), to materials formed by two, three, four, etc. Graphene sheets are stacked in an organized way. Thus, the electronic structure of the graphene presents different couplings with the increase in the number of layers up to the limit of 10–20 layers (3D limit) when the material is considered graphite (Geim & Novoselov, 2007).

All these remarkable features and properties turn graphene into a promising material for applications ranging from polymer-composite materials for transistors, electrodes for electrochemical storage, supercapacitors, electrode material in lithium-ion batteries, photo application electrochemical sensors, and the development of electrochemical sensors and biosensors.

In recent years, several graphene-based sensors and biosensors, or graphene-related materials, such as graphene oxide and reduced graphene oxide, were reported in the literature for analyses of compounds from

environmental sources. Some examples are the detection of metal ions such as Pb^{2+} and Cd^{2+} , analyses of pesticides, as well as food analyses, clinical applications, such as in the detection of glucose, ascorbic acid, uric acid, and drugs (Justino et al., 2017).

Graphene is extremely sensitive to the changes in the environment to which it is inserted because of its high surface area and specific electronic properties. In this way, any molecular perturbation is easily detected, making this material contribute to the development of sensors that are enhanced and highly sensitive electrochemicals (Xiao-Mei et al., 2011).

In addition, graphene can form composites with other materials such as polymers, nanoparticles, and biomolecules, such as DNA and enzymes, by physical adsorption or chemical bonding. As a result, by combining the thermal, electrical, and mechanical properties of graphene with the properties and functions of several other components, new materials and innovative analytical systems can be created, providing new opportunities for the sustainable progress of chemical analyses.

2.2 Carbon nanotubes

CNTs are nanomaterials formed from one or more graphene sheets rolled cylindrically from their own axis, forming tubular structures with a diameter in the nanometer and length range that can range from micrometers to centimeters. The first evidence of the tubular nature of some nano-sized carbon filaments was reported in a Russian article in 1952 (Radushkevich & Lukyanovich, 1952). However, this article is not widely known or cited because of the difficulties of access by Western scientists to the Russian publications at that time because of the Cold War (Monthioux & Kuznetsov, 2006).

In 1978, Wiles and Abrahamson also observed graphite fibers rolled in layers with a hollow center (Wiles & Abrahamson, 1978). However, it was only in 1991, in the work developed by Iijima that these fibers became known as carbon nanotubes (CNT) (Iijima, 1991). Therefore, even if there are previous reports, the scientific community considers Iijima's work to be the first description of the CNT, since a complete structural study was carried out for the first time.

Nowadays, the term "carbon nanotubes" corresponds to a family of compounds that may have different characteristics from each other. Conceptually, CNTs can be divided into two groups: single-walled carbon nanotubes (SWCNTs) (Figure 3A) and multiple-walled carbon nanotubes (MWCNTs) (Figure 3B). SWCNTs are made up of only one sheet of graphene and have a diameter ranging from 1 to 5 nm. However, the synthesis methods currently employed to produce only a small fraction of SWCNT increase its cost and make it difficult to be applied on a large scale. MWCNTs are formed by a set of two or more concentrically coiled graphene sheets, which may have diameters of 10–50 nm (Schroeder et al., 2019; Song et al., 2019).

Figure 3: Structures of CNTs.
(A) SWCNT; (B) MWCNT.

In order to form the nanotubes, a sheet of graphene is rolled up so that two sites of its hexagonal network, crystallographically equivalent, coincide. Depending on the way the graphene sheet wraps around, CNTs may have different geometries and properties. In this way, the electrical properties of the CNTs depend on how the hexagons are oriented along the axis of the tube (Terrones, 2003).

In general, the electronic properties of MWCNTs are similar to those observed in SWCNTs because of weak coupling between concentric carbon cylinders. Some studies describe that the electronic transport in these materials occurs in a ballistic way, that is, without spreading, allowing excellent electrical conduction through large extensions of nanotubes (Asadian, Ghalkhani & Shahrokhian, 2019).

CNTs have several attractive and promising properties for various applications because of their structure. The strength of the $\text{Csp}^2\text{--Csp}^2$ bond gives CNTs high chemical and mechanical resistance. However, even presenting one of the most robust structures known, this material denotes high flexibility and can be tensioned and bent, without destroying its structure. In addition, CNTs have a tensile strength, tensile than steel, and excellent thermal and electrical conductivity (Terrones, 2003).

All these properties together in a single class of material consider the CNTs as one of the components most used in the development of N & N. These materials have a potential application in several systems, products, and devices such as, electron emitters for televisions; in composites with polymers, ceramics and metals, diodes, transistors, photovoltaic devices, computer memories, and development of electrochemical sensors and biosensors.

CNTs were employed in the development of highly sensitive electrochemical sensors to determine the most diverse analytes such as gases, toxins, DNA fragments, various biomolecules, drugs, among many others. High electron transfer velocity, high surface area, and the presence of functional groups are characteristics that make the CNTs a desirable material for the development of sensors, which can be modified with several types of species (enzymes, genetic, metal complexes, among others). These modifications can further improve the electron transfer between analyte and electrode, improving response in a short time.

2.3 Fullerene

Another example of a carbon allotrope at nanoscale is the fullerenes. Unlike the other allotropes, the fullerenes are in the molecular form, being considered spheroidal nanometric molecules constituted only by carbon atoms. Since 1966, theoretical calculations demonstrated the possibility of the existence of “cages” formed only by carbon atoms. However, only in 1985 was the existence of fullerenes proven in the work done by Harold W. Kroto, Robert F. Curl, and Richard E. Smalley (Kroto et al., 1985).

The discovery of fullerenes was a result of Kroto's interest in the quantum mechanics study of certain carbon chains (polyynes, $\dots\text{C}\equiv\text{C}-\text{C}\equiv\text{C}\dots$) and of attempting to reproduce interstellar conditions to prove the existence of these large chains of carbon in space. With the help of Curl and Smalley, Kroto performed an experiment in which a graphite plate was subjected to a pulsed high-frequency laser forming agglomerates, which were later analyzed by mass spectrometry (Ariga, Minami & Shrestha, 2016; Silveira et al., 2018).

At the end of this experiment, the formation of molecules with 60 carbon atoms was observed, leading researchers to wonder what molecular structure could give such stability to these molecules. After some suggestions, Kroto had the idea of organizing the atoms in the same form of the geodesic domes idealized by the architect Richard Buckminster Fuller, in which hexagonal faces construct a spherical structure due to the combination with pentagons. In this way, the structure of the C_{60} was defined as a polyhedron of 32 faces, being 20 hexagonal and 12 pentagonal, and was baptized as buckminsterfullerene in honor of the American architect (Silveira et al., 2018).

Currently, other stable forms of fullerene were already isolated as, for example, C_{20} , C_{70} , C_{78} , and C_{84} . However, in all these forms, C_{60} fullerene is the most abundant and most stable, with π bonds between the six-membered rings and single bonds between the five-membered rings as shown in Figure 4.

Figure 4: Schematic representation (2D and 3D) of the fullerene structure C_{60} .

Through all the studies that were already done on fullerene, one of the most admirable discoveries is the ability of the C_{60} molecule to receive from one to six electrons, even though it is already rich in electrons, forming corresponding anions. This fact is only possible because the non-binding LUMO molecular orbitals of the C_{60} molecule are at a very low energy level. Other interesting properties that the fullerenes present are good chemical stability, large surface area, high mechanical resistance, and the ability to become a superconductor when combined with alkali metals. These properties make this material promising for several types of applications, such as photovoltaic (Li, Qi & Wang, 2013a, Li et al., 2013b), biomedical applications, transport of antivirals (Bosi et al., 2003), chemotherapeutics, antibiotics, and the development of sensors (Ariga, Minami & Shrestha, 2016).

3 Synthesis of carbon nanomaterials

3.1 Synthesis of graphene by mechanical and chemical exfoliation

As previously mentioned, graphite is composed of several layers of graphene sheets bonded by Vander Waals forces. Consequently, graphene can be produced from the graphite after the breakage of these bonds, which can be accomplished by two main methods: mechanical exfoliation or chemical exfoliation.

Mechanical exfoliation is the method that allowed the isolation of graphene for the first time and is used until today. In this method, an adhesive tape is used repeatedly to perform exfoliation of high-purity graphite. Next, some captured flakes are transferred to the surface of a silicon/silicon oxide disk, and it is possible to verify the existence of graphene by an atomic microscope (Novoselov et al., 2004). This approach presents good reliability and provides graphene samples that are practically free of defects. However, its main drawback is that it does not allow the production of graphene on a large scale.

Chemical exfoliation, or chemical reduction, involves the conversion of graphite to graphene by the introduction of functional groups containing oxygen, by reacting graphite with strong oxidizing agents such as sulfuric acid or nitric acid. This reaction forms graphite oxide, which is chemically reduced to graphene using reducing compounds such as hydrazine or sodium borohydride. The chemical exfoliation from graphite to graphene is possible because of the addition of groups such as OH and COOH that by chemical oxidation reduces the forces of Van der Waals, responsible for keeping the graphene sheets in the structure of the graphite, and the separation takes place (Figure 5). The main advantage of this method is the possibility of obtaining graphene with good uniformity and excellent yield, when compared to the mechanical methods, allowing its use to obtain graphene on a large scale (Gilje et al., 2007; Zhang et al., 2010; Oliveira et al., 2018).

Figure 5: Schematic representation of the reduced graphene oxide production by the mechanical or chemical exfoliation method.

3.2 Synthesis of graphene and carbon nanotube by chemical vapor deposition

It is possible to obtain thin films of various materials, such as ceramics, metal, or semiconductors on the surface of different substrates using chemical vapor deposition (CVD). For the preparation of graphene by this method, pyrolysis of precursor compounds, such as hydrocarbons, occurs on the surface of metal catalysts at high temperatures up to the formation of the graphite structure from the previously dissociated carbon atoms (Son & Ham, 2017). Thus, by thermal decomposition of hydrocarbons, or segregation of carbon atoms on the surface of metallic catalysts, such as Ni, Pt, Ru, Ir, for example, followed by a cooling process, carbon species precipitate on the surface of the metal leading to nucleation and growth to form the graphene. The number of the graphene layers formed depends directly on the cooling rate (Zhao & Gou, 2018). This method is schematized in Figure 6.

Figure 6: Schematic representation of the graphene production by CVD.

CVD is also one of the most widely used methods for the synthesis of CNTs because it enables large-scale production and is relatively inexpensive. Thus, in the synthesis of CNTs by CVD, carbon precursors (hydrocarbons, alcohols, etc.) are also used in atmospherically controlled kilns with a temperature high enough to provide the energy required to perform the decomposition of the hydrocarbons and form CNTs on the surface of a metal catalyst. The role of the catalyst is fundamental in obtaining the CNTs, as it will guarantee the process of nucleation and growth of the bundles of nanotubes. The advancement of characterization techniques (mainly electron microscopy techniques) enabled a better understanding of the growth stages of CNTs and, consequently, better control of the homogeneity of the prepared samples, as well as the control in the production of SWCNTs or MWCNTs (Shah & Tali, 2016).

3.3 Synthesis of fullerene by electric arc discharge

Even with the discovery of fullerenes in 1985, the development of a method for the synthesis of C₆₀ in macroscopic quantities occurred only in 1990 with the work done by Krätschmer and collaborators, making it possible to obtain sufficient quantities so that the chemical properties of fullerenes could begin to be explored (Krätschmer et al., 1990). The method developed by Krätschmer and collaborators was very similar to the electric arc discharge method, which was also used by Iijima during the first synthesis of CNT (Iijima, 1991).

The arc-discharge method consists of applying a potential difference between two graphite electrodes at a sufficiently small distance within a steel chamber in an inert atmosphere (usually Ar or He) and at low pressure, so that an electric arc between the electrodes is formed, ionizing the surrounding gas, and generating a plasma between the electrodes (Figure 7). Thus, as the electrons are accelerated against the anode, collision occurs with carbon atoms from the surface of the electrode transferring enough energy to pull them out, so that carbon atoms pass through the plasma and lose kinetic energy due to collisions with the gas atoms of the inert atmosphere. This procedure allows the formation of new graphite chains on the surface of the other electrode (cathode) (Ariga, Minami & Shrestha, 2016). The electric arc discharge method is still one of the most widely used methods for the synthesis of fullerene.

Figure 7: Schematic representation of the fullerene production by electric arc discharge method.

3.4 Synthesis of carbon nanotube and fullerene by laser ablation

The laser ablation method is used both for the synthesis of CNTs and for the synthesis of fullerenes. In this method, a solid graphite stick is used as a carbon source and is placed inside a quartz tube that is taken to a temperature-controlled oven. The tube is then filled with an inert gas, and the laser is focused on the graphite. Then, successive laser pulses are used as an energy source to uniformly vaporize the carbon, while the inert gas stream entrains the generated species, depositing them in a copper collector, located at the opposite end of the tube (Figure 8). After, the system is cooled by water to obtain the material (Terrones, 2003; De Bonis et al., 2015; Sajid et al., 2016).

Figure 8: Example of experimental setup for the laser ablation technique with inert atmosphere.

Laser ablation can also be performed in solution. This liquid technique gained prominence and attracted the interest of the scientific community due to its ability to produce stable nanostructures whose physical structure and chemical properties can only be altered by changing the experimental conditions used, such as the liquid medium or the laser parameters. Furthermore, when compared to the laser ablation technique performed in an inert atmosphere, the thermodynamic conditions in the ablation technique in solution result in more extreme temperature and pressure values, higher than that obtained for the gases. These conditions are necessary so that these conditions make the active species, generated by the laser, react more with each other, or with the molecules of the liquid medium and present greater stability (De Bonis et al., 2015).

4 Use of carbon nanomaterials in the development of electrochemical sensors

As previously seen, carbon nanomaterials gained increasing prominence, and their use in the development of sensors and biosensors for various applications in electroanalysis was continuously described in the literature due to the remarkable chemical and physical characteristics that these materials have, such as high surface area and excellent electrical conductivity, which facilitate the electronic transfer promoting the electrocatalysis.

In recent years, several graphene-based sensors and biosensors, or graphene-related materials, such as doped graphene, graphene oxide, and reduced graphene oxide, were reported in the literature. Several applications were described, such as environmental analysis for detection of metal ions such as Pb^{2+} and Cd^{2+} and pesticide analysis.

Khan et al. (2015) utilized a sensor based on polyaniline-grafted graphene oxide- WO_3 nanocomposite for application as a chromium(III) chemisensor. The sensor showed a detection limit of $0.031 \text{ nmol l}^{-1}$. According to the authors, the method is promising for potential applications in the environmental and healthcare fields (Khan et al., 2015).

In another paper, Alam et al. (2017a, 2017b) described that the use of a sensor of glassy carbon electrode (GCE) was fabricated using reduced graphene oxide/zinc oxide composite for 2-nitrophenol detection. The sensor presented a low detection limit of 0.27 nmol l^{-1} (Alam et al., 2017a, Alam et al., 2017b). These authors also developed a selective chemical sensor based on reduced graphene oxide/hydroxyapatite nanocomposites for the analysis of bis-phenol A. Their proposed sensor presented a detection limit of 60.0 pmol l^{-1} and also proved suitable for analysis in environmental samples (Alam et al. 2017a, Alam et al. 2017b).

Hussein et al. (2019) developed a selective Ag^+ ionic sensor based on polyvinyl chloride/mixed graphene-CNT nanocomposites. A detection limit of $14.78 \text{ pmol l}^{-1}$ was obtained, with the possibility of future applications in environmental samples (Hussein et al., 2019).

Devices such as electrochemical sensors were also widely employed in food analysis and clinical applications, such as detection of glucose, ascorbic acid, uric acid, and in drugs.

In order to guarantee the quality of the results obtained and to validate the analytical method, the sensors and biosensors developed are usually evaluated for some parameters that determine their analytical performance, such as sensitivity, selectivity, limit of detection and quantification, repeatability, and reproducibility. Different modifications of the same base electrode can generate sensors with different specificities for a particular analyte.

Graphene is extremely sensitive to the changes in the chemical environment to which it is inserted. This allows that any molecular perturbation can be easily detected, which contributes to the development of improved and highly sensitive electrochemical sensors. In addition, graphene can form composites with other materials such as polymers, nanoparticles, and biomolecules, such as DNA and enzymes, by means of physical adsorption or chemical bonding. As a result, combining the thermal, electrical, optical, and mechanical properties of graphene with the properties and functions of several other components, new materials and innovative analytical systems can be created, providing new opportunities for the sustainable progress of chemical analyses (Xiao-Mei et al., 2011).

In 2014, Jiang and Du developed an electrochemical sensor based on a glass-carbon electrode modified with a nanocomposite of gold (Au), palladium (Pd), and reduced graphene oxide (RGO) for individual and simultaneous determination of dopamine (DA), ascorbic acid (AA), and uric acid (UA), which are important molecules for physiological processes in human metabolism. The analysis of these species in body fluids (serum and urine) is a very valuable diagnostic indicator. As a result, for individual detection, the proposed sensor presented a wide linear response range, 0.1–1000, 0.01–100, and 0.02–500 $\mu\text{mol l}^{-1}$, and detection limits of 0.02, 0.002, and 0.005 $\mu\text{mol l}^{-1}$ for AA, DA, and UA, respectively. In the simultaneous detection, the sensor presented separate and well-defined oxidation peaks. In addition, the sensor was applied in urine samples, showing good sensitivity and selectivity for the determination of AA, UA, and DA. The good response in terms of sensitivity and selectivity of Au-Pd-OGR-modified ECV can be explained by the presence of some oxygenated functional groups on the surface of reduced graphene oxide, thus, increasing its electrical conductivity and its biocompatibility, in addition to excellent electrocatalytic activity exerted by Au and Pd nanoparticles (Jiang & Du, 2014).

Recently, Pothipor et al. (2019) described the use of a biosensor based on graphene-poly (3-aminobenzoic acid)-modified electrodes and porous-hollowed silver-gold nanoparticle labeling for prostate cancer detection. The developed biosensor presented a highly satisfactory performance, with a detection limit of 0.13 pg ml^{-1} , better than the clinically relevant level in human serum. The sensor is promising for the diagnosis of prostate cancer and other medical applications (Pothipor et al., 2019).

Another example of the use of electrodes modified with graphene was the work performed by Kesavan and John (2016), in which a sensor was prepared by the electrochemical reduction of graphene oxide (GO) with 2,4-diamino-1,3,5-triazine (aminotriazine-AT) on the surface of a vitreous carbon electrode. This electrode was applied in the determination of paracetamol (PA) in the presence of UA, which is an important interference agent for the determination of PA in human urine. At usual therapeutic doses, PA is completely metabolized and is eliminated in the urine. However, the consumption of high doses of PA can cause serious liver damage, inflammation of the pancreas, and renal failure. The modified electrode (GCE-GO-AT) proposed by Kesavan and John (2016) presented excellent electrocatalytic activity for simultaneous determination of PA and UA, successfully separating both their voltammetric signals. It was possible to determine PA even at higher concentrations of UA (up to 50 times more concentrated). The linear response range found for the proposed sensor was 0.04–100 $\mu\text{mol l}^{-1}$, and the detection limit was 0.68 nmol l^{-1} . The practical application of this sensor was also demonstrated when simultaneously determining the concentrations of PA and UA in human urine samples (Kesavan & John, 2016).

Many studies showed that electron conductivity, electron-donor properties, and the binding ability of graphene could be significantly increased by controlling its morphology and tailoring its electronic structure (Tang, Zhou & Chen, 2013). Nitrogen-doped graphene (NG) is an example of material that has been applied in electrocatalysis and development of electrochemical biosensor due to its capability to enhance the sensitivity and biocompatibility of graphene in biosensing applications (Wu et al., 2011).

Yang et al. (2017) proposed, for the first time, an efficient and universal streptavidin-functionalized nitrogen-doped graphene (NG) and used this material to develop a highly sensitive electrochemical immunosensor for tumor marker detection. The streptavidin-functionalized NG was characterized by transmission electron microscopy (TEM), electrochemical impedance spectrum, and cyclic voltammetry (CV). The immunosensor showed high electrochemical activity, larger specific surface area, and was successfully applied in human serum samples with a wide linear range of 0.02–12.0 ng ml^{-1} , and detection limit of 0.01 ng ml^{-1} , using carcinoembryonic antigen (CEA) as model analyte, providing a promising platform for electrochemical immunosensing applications (Yang et al., 2017).

Nitrogen-doped graphene is also reported to be functionalized with metal nanoparticles such as platinum nanoparticles (PtNPs). The interest in PtNP-functionalized NG (PtNPs@NG) for electrochemical sensor development steadily increased due to its high electrocatalytic activity and free electron mobility. Yang et al. (2015a), Yang et al. (2015b) reported a novel electrochemical glucose biosensor modified with PtNPs@NG and glucose oxidase (GOx). The fabricated biosensor was characterized using transmission electron microscopy, high-resolution transmission electron microscopy, X-ray photoelectron spectroscopy, static water contact angle, ultraviolet–visible (UV-vis) spectroscopy, electrochemical impedance spectra, and cyclic voltammetry, re-

spectively. The GOx immobilization on PtNPs@NG was performed in a way that retained its bioactivity. The proposed glucose biosensor was applied in five human serum samples as well as the reference method (enzyme catalytic spectrophotometry) and showed a quasi-reversible and fast electron transfer process with a linear range from 0.005 to 1.1 mmol L⁻¹ and a detection limit calculated to be 0.002 mmol L⁻¹. The electrochemical glucose biosensor also exhibited excellent selectivity, sensitivity, good reproducibility, and acceptable stability, which demonstrates that it is a promising platform for the development of excellent electrochemical biosensors (Yang et al. 2015a, 2015b).

The determination of L-Dopa (or Levodopa) is of great importance because it is the immediate precursor of DA and is used in the treatment of Parkinson's disease. DA cannot be administered orally, as it does not pass through the bloodstream barrier. Thus, L-Dopa is administered and converted into dopamine by the action of the enzyme dopa-decarboxylase, thereby, stimulating the production of dopamine in the body. Leite et al. (2012) developed a sensor using a pyrolytic graphite electrode (PGE) modified with chloro(pyridine)bis(dimethylglyoximate)cobalt(III) (Co(DMG)₂CIPy) adsorbed on MWCNTs for the determination of L-Dopa in pharmaceutical formulations. At the end of the studies, this sensor presented a linear response in the concentration range of 3–100 μmol L⁻¹ and a detection limit of 0.86 μmol L⁻¹, demonstrating that the proposed sensor is a viable alternative for the determination of L-Dopa in pharmaceutical samples (Leite et al., 2012).

Recently, Sooraj and collaborators also developed a sensor for L-Dopa determination in human urine and pharmaceutical samples using copper nanoparticle grafted with molecular imprinted polymer on MWCNTs (CuNPs/MWCNT-MIPs). The non-covalent interaction between L-Dopa and the functional groups present in the selective binding sites of the polymer composite sorbent is mainly responsible for the recognition property. The electrochemical investigation shows that the imprinted (CuNPs/MWCNT-MIP) material has good recognition capacity toward L-Dopa with a detection limit of 7.23 nmol L⁻¹. The developed sensor also showed a good selectivity, being able to discriminate between L-Dopa and structurally related compounds such as DA, UA, 3,4-dihydroxyphenylacetic acid, and homovanillic acid (Sooraj et al., 2020).

Anođić et al. (2019), aiming at the determination of dopamine, developed carbonaceous nanomaterial-modified carbon paste electrodes (CPEs) with MWCNTs in their native and functionalized (ox-MWCNT) forms. Under optimized conditions, the method presented a linear concentration range of 16.15–192.70 ng mL⁻¹ DA and a low detection limit of 4.89 ng mL⁻¹. The sensor was successfully applied for DA determination in injection (Anođić et al., 2019).

Another work using CNTs in the modification of electrochemical sensors was performed by Majidi et al. (2016) who developed a sensor for the determination of tryptophan (Trp) in biological samples (urine, saliva, and blood serum). In order to carry out this study, the researchers used a golden screen-printed electrode (SPEAu) modified with MWCNTs (SPEAu-MWCNT) with Trp aptamers immobilized on the surface of this sensor. Sensitive and effective analytical methods for the determination of Trp in clinical studies and medical studies, particularly in neuroscience and oncology, are extremely important, as Trp is one of the essential amino acids for human life. The sensor showed excellent sensitivity, selectivity, and precision for the detection of Trp in real samples presenting a linear response range of 1.0×10^{-11} to 1.0×10^{-4} mol L⁻¹ and a detection limit of 4.9×10^{-12} mol L⁻¹. This sensor is extremely promising as it is a simple, efficient, portable, and miniaturized system (Majidi et al., 2016).

Upadhyay and Srivastava (2019) describe an extremely relevant work, an enantioselective electrochemical sensor that, for the first time, discriminates atorvastatin isomers (ATS). The sensor was developed based on a glassy carbon electrode (GCE) modified with a functionalized MWCNT with hydroxypropyl-β-cyclodextrin (HBC). According to the authors, the method developed demonstrated outstanding advantages of chiral nanocomposite-modified electrodes such as excellent enantioselectivity, high stereospecificity, and good reproducibility. Under optimized experimental conditions, the anodic oxidation peak current ratio (ISS/IRR) of SS-ATS to RR-ATS was found to be 3.62 (Upadhyay & Srivastava, 2019).

Rahimi-Nasrabadi and collaborators developed a glass-based carbon-modified sensor modified with a composite based on fullerene (C₆₀) and CNTs for the determination of diazepam in real samples, such as blood serum, urine, and pharmaceutical formulations. After the development of the glass-carbon electrode modified with a nanocomposite based on fullerene (C₆₀), CNTs, and ionic liquid (1-butyl-3-methylimidazolium tetrafluoroborate), it showed good electrocatalytic activity in relation to reduction of diazepam in one linear response range of 0.3–700 μmol L⁻¹ and a detection limit of 0.087 μmol L⁻¹. This sensor presented good stability and repeatability, and its application for the determination of diazepam in real samples was satisfactory (Rahimi-Nasrabadi, Khoshroo & Mazloun-Ardakani, 2017).

Prasad, Kumar, and Singh described in their work a pencil graphite electrode modified with a molecularly imprinted polymer (MIP) using functionalized fullerene (C₆₀) as a nanomediator for ultratrace analysis of primaquine (PQ). The functional monomer employed by the authors was the 2,4,6-trisacrylamido-1,3,5-triazine, and the antimalarial drug (PQ) was used as a template for the molecular imprinting with the “surface grafting-

from" approach. In this composite, the fullerene assists the electron transfer between the recognition sites and the electrode, inducing electrocatalytic action and thereby greatly extending the electrode kinetics. The importance of PQ determination in different matrices (blood plasma, urine, and pharmaceutical formulations) is related to the fact that PQ is the only anti-malarial drug that is active against latent liver forms of relapsing malaria and useful for the treatment of pneumocystis infections. Therefore, Prasad and collaborators validated the proposed sensor for complex matrices of human blood plasma, urine, and pharmaceuticals, without any matrix effect and cross-reactivity. The linear response ranges were found to be: 2.7–848.5, 4.2–827.4, 3.4–795.2, and 4.8–803.2 nM for aqueous, blood plasma, urine, and pharmaceutical samples, respectively, with detection limits lower than 0.80 nM (Prasad, Kumar & Singh, 2016).

Recently, Zang and Li evaluated the electrochemical activity of dopamine (DA) using a glassy carbon electrode modified with non-covalent self-assembly of porphyrin-diazocine-porphyrin (PDP) and fullerene (C_{60}). Several works in the literature reported that porphyrin derivatives have exceptionally high affinity with fullerene, forming efficient electron transfer supramolecular assemblies. In the work described by Zhang and Li, the PDP- C_{60} /GCE composite-modified electrode exhibited high electrocatalytic activity for DA detection. The anodic peak current increased linearly with increasing concentration of DA in the range of 0–200 μ M. The detection limit was found to be 0.015 μ M. Thus, the proposed sensor showed high sensitivity, satisfactory selectivity, excellent repeatability, and stability, showing that PDP- C_{60} /GCE is a potential electrode material for dopamine analysis in real samples (Zhang & Li, 2020).

Rather et al. (2016) reported the first-time synthesis of the fullerene-graphene oxide nanocomposite (C_{60} -GO), conjugate by 1,3-dipolar cycloaddition reaction between fullerene (C_{60}), and azide-functionalized graphene oxide (GO- N_3). The C_{60} -GO nanocomposite was characterized by UV-vis spectroscopy, electrochemical and field emission electron microscopy (FESEM), and Fourier transform infrared spectroscopy (FTIR). Then, using surface-bound diazonium salts to give a phenyl-modified conjugate interface, fullerene-graphene oxide nanocomposite was immobilized on the surface of glassy carbon electrode (GCE) forming C_{60} -GO-Ph-GCE. After that, an electrochemical reduction (ER) was performed in an aqueous solution of potassium hydroxide (1.0 M KOH) to produce highly conductive films of C_{60} GO-Ph at the electrode surface with electrocatalytic properties. In this step, the sensor was named ERC $_{60}$ -GO-Ph-GCE and was applied in the determination of homovanilic acid (HVA), a biomarker for Parkinson's disease, over a concentration range from 0.1 to 7.2 μ M. The detection limit of the proposed sensor was found to be equal to 0.03 μ M, which indicates good efficiency, high sensitivity, and makes this device suitable for the detection of HVA in biological fluids. The monitoring of HVA in patients suffering from Parkinson's disease is extremely important as DA undergoes catabolism by monoamine oxidase and catechol-O-methyl transferase to give HVA and 3,4-dihydroxyphenylacetic acid (DOPAC). Thus, electrochemical methods are promising tools that showed good results in providing quick and sensitive analysis of biomarkers in biological fluids (Rather et al., 2016).

The development of biosensors, enzymatic or non-enzymatic, for the detection of glucose in biological fluids gained prominence because of the interest in the application to the clinical diagnosis of diabetes, as they are relatively low-cost devices with fast and accurate responses, good stability, sensitivity, and selectivity. Sutradhar and Patnaik (2017) recently developed a gold nanoparticle-functionalized fullerene (C_{60})-modified vitreous carbon electrode using thiol-capped gold nanoparticle-based nanocomposite using 3-amino-5-mercapto-1,2,4-triazole as the ligand for glucose analysis. This sensor showed electrocatalytic activity, effective electron transfer capacity, linear response range of 0.02–0.8 mmol l⁻¹, detection limit of 22.0 μ mol l⁻¹, good stability, besides good selectivity in relation to possible interferents (Sutradhar & Patnaik, 2017).

Numerous studies involving electrochemical sensors and biosensors using graphene, CNTs, and fullerene were constantly described in recent literature for the determination of drugs and compounds of clinical interest. In this article, certain trends were highlighted instead of comprehensively covering all the published literature. Table 1 shows some examples highlighting the analyte of interest, the electrode, the modification used, and the limit of detection obtained.

Table 1: Electrochemical sensors based on carbon nanomaterials for drugs and clinical interest compound determination.

Analyte	Electrode	Modifier	Sample	LOD (mol l ⁻¹)	References
Piroxicam Nimesulide	GCE	RGO/PEDOT: PSS	Pharmaceuticals	1.0×10^{-7}	Wong, Santos & Fatibello-filho, 2017
Omeprazole	GCE	GO-NiZnFe ₂ O ₄	Pharmaceuticals Blood	2.4×10^{-9}	
Tramadol	CPE	NiFe ₂ O ₄ /graphene	Pharmaceuticals	1.5×10^{-8}	Afkhami, Bahiraei & Madrakian, 2017
Acetaminophen				3.6×10^{-9}	Afkhami et al., 2014a
Glucose	GCE	GO-MIP	Blood serum	3.0×10^{-9}	
Gemcitabine	GCE	GO-Bi	Pharmaceuticals	1.0×10^{-8}	Alexander et al., 2017
Codeine Acetaminophen	CPE	CoFe ₂ O ₄ /graphene	Pharmaceuticals Blood plasma Urine	5.0×10^{-8}	Tandel et al., 2017
				1.1×10^{-8}	Afkhami et al., 2014b
Carvedilol	GCE	MWCNT/MIP	Pharmaceuticals	1.6×10^{-5}	Coelho et al., 2016
Metronidazole	GCE	MWCNT/CTS-Ni	Pharmaceuticals Blood serum Urine	2.5×10^{-8}	Mao et al., 2017
Bromhexine				3.0×10^{-6}	Kutluay & Aslanoglu, 2014
Cisplatin	Platina Printed electrode	MWCNT/NiNPs	Pharmaceuticals	4.6×10^{-6}	Materon et al., 2015
Promethazine	CPE	MWCNT-COOH	Pharmaceuticals	5.9×10^{-6}	Marco et al., 2013
Gentamicin sulfate	CPE	MWCNT/SiAlNb/DNA	Pharmaceuticals Blood serum Urine	2.2×10^{-7}	Khalil & El-Aziz, 2016
		MWCNT			
Glucose/albumin	GCE	MWCNT-PEI-Cu	Pharmaceuticals Drinks	1.8×10^{-7}	Gutierrez, Rubianes & Rivas, 2016
Acetaminophen	GCE	MWCNT-β-cyclodextrin	Pharmaceuticals Urine	1.5×10^{-8}	Alam et al., 2018
Hydrochlorothiazide	CPE	MWCNT	Pharmaceuticals	1.4×10^{-8}	Salamanca-Neto et al., 2014
Enalapril maleate					
Aciclovir	GCE	Fullerene (C ₆₀)	Pharmaceuticals Blood plasma Urine	4.1×10^{-8}	Shetti, Malode & Nandibewoor, 2012
NE	GCE	C ₆₀ -MWCNT-IL	Blood serum Urine	1.5×10^{-8}	Mazloun-Ardakani & Khoshroo, 2014
IP				2.2×10^{-8}	
DA				1.5×10^{-8}	
Pyruvic Acid	GCE	C ₆₀ -MWCNT	Blood Urine	1.0×10^{-8}	Brahman et al., 2015
Glucose	GCE	MWCNTs-SnS ₂ -GOx	Blood serum	4.0×10^{-6}	Li, Qi & Wang, 2013a; Li et al., 2013b

GCE, glassy carbon electrode; CPE, CPE electrode; RGO, reduced graphene oxide; PEDOT, poly(3,4-ethylenedioxythiophene); PSS, poly(4-styrene sulfonate); PIR, Piroxicam; NIM, Nimesulide; OG, graphene oxide; MIP, molecularly printed polymer; MWCNT, multiwalled carbon nanotube; CTS-Ni, chitosan-nickel complex; NiNPs, nickel nanoparticles; PEI, polyethylenimine; HTZ, hydrochlorothiazide; ENP, enalapril maleate; IL, ionic liquid; NE, noradrenaline; IP, isoprenaline; DA, dopamine; GOx, glucose oxidase.

5 Final considerations

From this review, it was possible to verify that the chemistry of nanomaterials is very dynamic. Applications such as determination of pharmaceutical compounds, disease diagnosis, and other medical applications justify the growing scientific interest in these materials. Particularly, in relation to electrochemical sensors, it was possible to verify that carbonaceous materials are often used in the form of composites with polymeric materials or metallic nanoparticles in the development of sensors, presenting excellent analytical performance. In this way, the electrochemical sensors became increasingly promising because of their relatively low cost compared to other conventional analytical methods, besides less reagent expense, quick and easy execution, making it possible and feasible to apply these devices in various analyses of environmental interest, food, and, in particular, analyses of drugs and compounds of clinical interest.

References

- Afkhami, A.; Khoshsavar, H.; Bagheri, H.; Madrakian, T. Preparation of NiFe₂O₄/graphene nanocomposite and its application as a modifier for the fabrication of an electrochemical sensor for the simultaneous determination of tramadol and acetaminophen. *Anal. Chim. Acta* **2014a**, 831, 50–59.
- Afkhami, A.; Khoshsavar, H.; Bagheri, H.; Madrakiana, T. Facile simultaneous electrochemical determination of codeine and acetaminophen in pharmaceutical samples and biological fluids by graphene–CoFe₂O₄ nanocomposite modified CPE electrode. *Sens. Actuat. B*, **2014b**, 203, 909–918.
- Afkhami, A.; Bahrarai, A.; Madrakian, T. Application of nickel zinc ferrite/graphene nanocomposite as a modifier for fabrication of a sensitive electrochemical sensor for determination of omeprazole in real samples. *J. Colloid Interface Sci.* **2017**, 495, 1–8.
- Alam, M. K.; Rahman, M. M.; Abbas, M.; Torati, S. R.; Asiri, A. M.; Kim, D.; Kim, C. G. Ultra-sensitive 2-nitrophenol detection based on reduced graphene oxide/ZnO nanocomposites. *J. Electroanal. Chem.* **2017a**, 788, 66–73.
- Alam, M. K.; Rahman, M. M.; Elzwawy, A.; Torati, S. R.; Islam, M. S.; Todo, M.; Asiri, A. M.; Kim, D.; Kim, C. Highly sensitive and selective detection of Bis-phenol A based on hydroxyapatite decorated reduced graphene oxide nanocomposites. *Electrochim. Acta* **2017b**, 241, 353–361.
- Alam, A. U.; Qin, Y.; Hawlader, M. M. R.; Hu, N.-X.; Deen, M. J. Electrochemical sensing of acetaminophen using multi-walled carbon nanotube and β -cyclodextrin. *Sens. Actuat. B: Chem.* **2018**, 254, 896–909.
- Alexander, S.; Baraneedharan, P.; Balasubrahmanyam, S.; Ramaprabhu, S. Highly sensitive and selective non enzymatic electrochemical glucose sensors based on graphene oxide-molecular imprinted polymer. *Mater. Sci. Eng. C* **2017**, 78, 124–129.
- Anojčić, J.; Guzvány, V.; Kónya, Z.; Mikov, M. Rapid, trace-level direct cathodic voltammetric determination of dopamine by oxidized multi-walled carbon nanotube-modified carbon paste electrode in selected samples of pharmaceutical importance. *Ionics* **2019**, 25, 6093–6106.
- ANVISA. Agência Nacional de Vigilância Sanitária. Farmacopeia Brasileira, volume 1. 5^a Ed. Brasília, **2010**.
- Ariga, K.; Minami, K.; Shrestha, L. K. Nanoarchitectonics for carbon-material-based sensors. *Analyst* **2016**, 141, 2629–2638.
- Asadian, E.; Ghalkhani, M.; Shahrokhian, S. Electrochemical sensing based on carbon nanoparticles: a review. *Sens. Actuat. B: Chem.* **2019**, 293, 183–209.
- Baig, N.; Sajid, M.; Saleh, T. A. Recent trends in nanomaterial-modified electrodes for electroanalytical applications. *TrAC* **2019**, 111, 47–61.
- Boehm, H. P.; Clauss, A.; Fischer, G. O.; Hofmann, U. Thin carbon leaves. *Z. Naturforsch.* **1962**, 17b, 150–153.
- Bosi, S.; Ros, T. D.; Spalluto, G.; Prato, M. Fullerene derivatives: an attractive tool for biological applications. *Eur. J. Med. Chem.* **2003**, 38, 913–923.
- Brahman, P. K.; Pandey, N.; Topkaya, S. N.; Singhai, R. Fullerene–C₆₀–MWCNT composite film based ultrasensitive electrochemical sensing platform for the trace analysis of pyruvic acid in biological fluids. *Talanta* **2015**, 134, 554–559.
- Coelho, M. K. L.; Giarola, J. F.; Silva, A. T. M.; Tarley, C. R. T.; Borges, K. B.; Pereira, A. C. Development and application of electrochemical sensor based on molecularly imprinted polymer and carbon nanotubes for the determination of carvedilol. *Chemosensors* **2016**, 4, 15.
- De Bonis, A.; Curcio, M.; Santagata, A.; Rau, J. V.; Galasso, A.; Teghil, R. Fullerene-reduced graphene oxide composites obtained by ultrashort laser ablation of fullerite in water. *Appl. Surf. Sci.* **2015**, 336, 67–72.
- Ferey, L.; Raimbault, A.; Rivals, I.; Gaudin, K. UHPLC method for multiproduct pharmaceutical analysis by Quality-by-Design. *J. Pharm. Biomed. Anal.* **2018**, 148, 361–368.
- Geim, A. K.; Novoselov, K. S. The rise of graphene. *Nat. Mater.* **2007**, 6, 183–191.
- Ghany, N. A. A.; Elsherif, S. A.; Handal, H. T. Revolution of graphene for different applications: state-of-the-art. *Surf. Interfaces*, **2017**, 9, 93–106.
- Gilje, S.; Han, S.; Wang, M.; Wang, K. L.; Kaner, R. B. A chemical route to graphene for device applications. *Nano Lett.* **2007**, 7, 3394–3398.
- Gogotsi, Y.; Presser, V. *Carbon Nanomaterials*, 2a. ed.; CRC Press: Florida, 2014.
- Gutierrez, F. A.; Rubianes, M. D.; Rivas, G. A. Electrochemical sensor for amino acids and glucose based on glassy carbon electrodes modified with multi-walled carbon nanotubes and copper microparticles dispersed in polyethylenimine. *J. Electroanal. Chem.* **2016**, 765, 16–21.
- Hun, X.; Wang, S.; Wang, S.; Zhao, J.; Luo, X. A photoelectrochemical sensor for ultrasensitive dopamine detection based on single-layer NanoMoS₂ modified gold electrode. *Sens. Actuat. B Chem.* **2017**, 249, 83–89.
- Hussein, M. A.; Alam, M. M.; Asiri, A. M.; Al-amshany, Z. M.; Hajeeassa, K. S.; Rahman, M. M. Ultrasonic-assisted fabrication of polyvinyl chloride/mixed graphene-carbon nanotube nanocomposites as a selective Ag⁺ ionic sensor. *J. Compos. Mater.* **2019**, 53, 2271–2284.
- Iijima, S. Helical microtubules of graphite carbon. *Nature* **1991**, 354, 56–58.

- Jiang, J.; Du, X. Sensitive electrochemical sensors for simultaneous determination of ascorbic acid, dopamine, and uric acid based on Au-Pd-reduced graphene oxide nanocomposites. *Nanoscale* **2014**, 6, 11303–11309.
- Justino, C. I. L.; Gomes, A. R.; Freitas, A. C.; Duarte, A. C.; Rocha-santos, T. A. P. Graphene based sensors and biosensors. *Trends Anal. Chem.* **2017**, 91, 53–66.
- Kesavan, S.; John, A. S. Stable determination of paracetamol in the presence of uric acid in human urine sample using melamine grafted graphene modified electrode. *J. Electroanal. Chem.* **2016**, 760, 6–14.
- Khalil, M. M.; El-Aziz, G. M. A. Multiwall carbon nanotubes chemically modified CPE electrodes for determination of gentamicin sulfate in pharmaceutical preparations and biological fluids. *Mater. Sci. Eng. C* **2016**, 59, 838–846.
- Khan, Anish.; Khan, A. A. P.; Rahman, M. M.; Asiri, A. M.; Alamry K. A. Preparation of polyaniline grafted graphene oxide–WO₃ nanocomposite and its application as a chromium(III) chemisensor. *RSC Adv.* **2015**, 5, 105169.
- Kimmel, D. W.; LeBlanc, G.; Meschievitz, M. E.; Cliffl, D. E. Electrochemical sensors and biosensors. *Anal. Chem.* **2012**, 84, 658–707.
- Krätschmer, W.; Lamb, L. D.; Fostiropoulos, K.; Huffman, D. R. Solid C₆₀: a new form of carbon. *Nature* **1990**, 347, 354–358.
- Kroto, H. W.; Curl, R. F.; Smalley, R. E. C.; Heath, J. R.; O’Brien, S. C. C₆₀: Buckminsterfullerene. *Nature* **1985**, 318, 162–163.
- Kutluay, A.; Aslanoglu, M. Nickel nanoparticles functionalized multi-walled carbon nanotubes at platinum electrodes for the detection of bromhexine. *Sens. Actuat. B* **2014**, 192, 720–724.
- Leite, F. R. F.; Maroneze, C. M.; Oliveira, A. B.; Santos, W. T. P.; Damos, F. S.; Luz, R. C. S. Development of a sensor for L-Dopa based on Co(DMG)zClPy/multi-walled carbon nanotubes composite immobilized on basal plane pyrolytic graphite electrode. *Bioelectrochemistry* **2012**, 86, 22–29.
- Lenik, J.; Nieszporek, J. Construction of a glassy carbon ibuprofen electrode modified with multi-walled carbon nanotubes and cyclodextrins. *Sens. Actuat. B: Chem.* **2018**, 255, 2282–2289.
- Li, H.; Qi, Z.; Wang, J. Layer-by-layer processed polymer solar cells with self-assembled electron buffer layer. *Appl. Phys. Lett.* **2013a**, 102, 213.
- Li, J.; Yang, Z.; Tang, Y.; Zhang, Y.; Hu, X. Carbon nanotubes-nanoflake-like SnS₂ nanocomposite for direct electrochemistry of glucose oxidase and glucose sensing. *Biosens. Bioelectron.* **2013b**, 41, 698–703.
- Li, Z.; Wang, L.; Li, Y.; Feng, Y.; Feng, W. Carbon-based functional nanomaterials: Preparation, properties and applications. *Compos. Sci. Technol.* **2019**, 179, 10–40.
- Maduraiveeran, G.; Jin, W. Nanomaterials based electrochemical sensor and biosensor platforms for environmental applications. *Trends Environ. Anal. Chem.* **2017**, 13, 10–23.
- Majidi, M. R.; Omid, Y.; Karami, P.; Johari-Ahar, M. Reusable potentiometric screen-printed sensor and label-free aptasensor with pseudo-reference electrode for determination of tryptophan in the presence of tyrosine. *Talanta* **2016**, 150, 425–433.
- Mao, A.; Li, H.; Yu, L.; Hu, X. Electrochemical sensor based on multi-walled carbon nanotubes and chitosan-nickel complex for sensitive determination of metronidazole. *J. Electroanal. Chem.* **2017**, 799, 257–262.
- Marco, J. P.; Borges, K. B.; Tarley, C. R. T.; Ribeiro, E. S.; Pereira, A. C. Development of a simple, rapid and validated square wave voltametric method for determination of promethazine in raw material and pharmaceutical formulation using DNA modified multiwall carbon nanotube paste electrode. *Sens. Actuat. B*, **2013**, 177, 251–259.
- Materon, E. M.; Wong, A.; Klein, S.; Liu, J.; Sotomayor, M. D. P. T. Multi-walled carbon nanotubes modified screen-printed electrodes for cis-platin detection. *Electrochim. Acta* **2015**, 158, 271–276.
- Mazloum-Ardakani, M.; Khoshroo, A. High performance electrochemical sensor based on fullerene-functionalized carbon nanotubes/ionic liquid: determination of some catecholamines. *Electrochem. Commun.* **2014**, 42, 9–12.
- Monthieux, M.; Kuznetsov, V. L. Who should be given the credit for the discovery of carbon nanotubes? *Carbon*, **2006**, 44, 1621–1623.
- Novoselov, K. S.; Geim, A. K.; Morozov, S. V.; Jiang, D.; Zhang, Y.; Dubonos, S. V.; Grigorieva, I. V.; Firsov, A. A. Electric field effect in atomically thin carbon films. *Science* **2004**, 306, 666–669.
- Oliveira, A. X.; Silva, S. M.; Leite, F. R. F.; Kubota, L. T.; Damos, F. S.; Luz, R. C. S. Highly sensitive and selective basal plane pyrolytic graphite electrode modified with 1,4-naphthoquinone/MWCNT for simultaneous determination of dopamine, ascorbate and urate. *Electroanalysis* **2013**, 25, 723–731.
- Oliveira, A. E. F.; Braga, G. B.; Tarley, C. R. T.; Pereira, A. C. Thermally reduced graphene oxide: synthesis, studies and characterization. *J. Mater. Sci.* **2018**, 53, 12005–12015.
- Østergaard, J. UV imaging in pharmaceutical analysis. *J. Pharm. Biomed. Anal.* **2018**, 147, 140–148.
- Pandey, H.; Khare, P.; Singh, S.; Singh, S. P. Carbon nanomaterials integrated molecularly imprinted polymers for biological sample analysis: a critical review. *Mater. Chem. Phys.* **2020**, 239, 121966.
- Pothipor, C.; Wiriayakun, N.; Putnin, T.; Ngamaroonchote, A.; Jakmunee, J.; Ounnunkad, K.; Laocharoensuk, R.; Aroonyadet N. Highly sensitive biosensor based on graphene–poly (3-aminobenzoic acid) modified electrodes and porous-hollowed-silver-gold nanoparticle labelling for prostate cancer detection. *Sens. Actuat. B Chem.* **2019**, 296, 126657.
- Prasad, B. B.; Kumar, A.; Singh, R. Molecularly imprinted polymer-based electrochemical sensor using functionalized fullerene as a nano mediator for ultratrace analysis of primaquine. *Carbon* **2016**, 109, 196–207.
- Radushkevich L. V.; Lukyanovich V. M. O struktureugleroda, obrazujucesja, pri termiceskom razlozenii okisiugleroda na zeleznom kontakte. *Zurn. Fisic. Chim.* Translated into *J. Phys. Chem. Russia* **1952**, 26, 88–95.
- Rahimi-Nasrabadi, M.; Khoshroo, A.; Mazloum-Ardakani, M. Electrochemical determination of diazepam in real samples based on fullerene-functionalized carbon nanotubes/ionic liquid nanocomposite. *Sens. Actuat. B*, **2017**, 240, 121–131.
- Rather, J. A.; Khudaish, E. A.; Munam, A.; Qurashi, A.; Kannan, P. Electrochemically reduced fullerene–graphene oxide interface for swift detection of Parkinsons disease biomarkers. *Sens. Actuat. B*, **2016**, 237, 672–684.
- Sajid, M. I.; Jamshaid, U.; Jamshaid, T.; Zafar, N.; Fessi, H.; Elaissari, A. Carbon nanotubes from synthesis to in vivo biomedical applications. *Int. J. Pharm.* **2016**, 501, 278–299.
- Salamanca-Neto, C. A. R.; Tarly, C. R. T.; Homura, P. H.; Sartori, E. R. Electrochemical evaluation and simultaneous determination of binary mixture of antihypertensives hydrochlorothiazide and enalapril in combined dosage forms using carbon nanotubes paste electrode. *Ionics* **2014**, 21, 1615–1622.

- Schroeder, V.; Savagatrup, S.; He, M.; Lin, S.; Swager, T. M. Carbon nanotube chemical sensors. *Chem. Rev.* **2019**, *119*, 599–663.
- Sena, M. M.; Freitas, C. B.; Silva, L. C.; Pérez, C. N.; Paula, Y. O. Determinação espectrofotométrica simultânea de paracetamol e ibuprofeno em formulações farmacêuticas usando calibração multivariada. *Quim. Nova* **2007**, *30*, 75–79.
- Shah, K. A.; Tali, B. A. Synthesis of carbon nanotubes by catalytic chemical vapour deposition: a review on carbon sources, catalysts and substrates. *Mater. Sci. Semicond. Process.* **2016**, *41*, 67–82.
- Shetti, N. P.; Malode, S. J.; Nandibewoor, S. T. Electrochemical behavior of an antiviral drug acyclovir at fullerene-C60-modified glassy carbon electrode. *Bioelectrochemistry* **2012**, *88*, 76–83.
- Silveira, J. F. R. V.; Pagnussati, R. A.; Kleinpaul, J.; Paupitz, R.; Muniz, A. R. Nanoporous carbon superstructures based on covalent bonding of porous fullerenes. *Carbon* **2018**, *130*, 424–432.
- Soldano, C.; Mahmood, A.; Dujardin, E. Production, properties and potential of graphene. *Carbon* **2010**, *48*, 2127–2150.
- Son, M.; Ham, M. H. Low-temperature synthesis of graphene by chemical vapor deposition and its applications. *FlatChem* **2017**, *5*, 40–49.
- Song, H.; Zhang, X.; Liu, Y.; Su, Z. Developing graphene-based nanohybrids for electrochemical sensing. *Chem. Rec.* **2019**, *19*, 534–549.
- Sooraj, M. P.; Nair, A. S.; Pillai, S. C.; Hinder, S. J.; Mathew, B. CuNPs decorated molecular imprinted polymer on MWCNT for the electrochemical detection of L-Dopa. *Arab. J. Chem.* **2020**, *13*, 2483–2495.
- Sutradhar, S.; Patnaik, A. A new fullerene-C60–nanogold composite for non-enzymatic glucose sensing. *Sens. Actuat. B*, **2017**, *241*, 681–689.
- Syama, S.; Mohanan, P. V. Comprehensive application of graphene: emphasis on biomedical concerns. *Nano-Micro Lett.* **2019**, *11*, 6.
- Tandel, R.; Teradala, N.; Satpatib, A.; Jaladappagaria, S. Fabrication of the electrochemically reduced graphene oxide-bismuth nanoparticles composite and its analytical application for an anticancer drug gemcitabine. *Chin. Chem. Lett.* **2017**, *28*, 1429–1437.
- Tang, Q.; Zhou, Z.; Chen, F. Graphene-related nanomaterials: tuning properties by functionalization. *Nanoscale* **2013**, *5*, 4541–4583.
- Terrones, M. Science and technology of the twenty-first century: synthesis, properties, and applications of carbon nanotubes. *Annu. Rev. Mater. Res.* **2003**, *33*, 499–501.
- Trojanowicz, M. Analytical applications of carbon nanotubes: a review. *Trends Anal. Chem.* **2006**, *25*, 480–489.
- Upadhyay S. S.; Srivastava, A. K. Hydroxypropyl β -cyclodextrin cross-linked multiwalled carbon nanotube-based chiral nanocomposite electrochemical sensors for the discrimination of multichiral drug atorvastatin isomers. *New J. Chem.* **2019**, *43*, 11178–11188.
- Walcarius, A. Electrocatalysis, sensors and biosensors in analytical chemistry based on ordered mesoporous and macroporous carbon-modified electrodes. *Trends Anal. Chem.* **2012**, *38*, 79–97.
- Wiles, P. G.; Abrahamson, J. Carbon fibre layers on arc electrodes—I: Their properties and cool-down behavior. *Carbon*, **1978**, *16*, 341–349.
- Wong, A.; Santos, A. M.; Fatibello-filho, O. Determination of piroxicam and nimesulide using an electrochemical sensor based on reduced graphene oxide and PEDOT:PSS. *J. Electroanal. Chem.* **2017**, *799*, 547–555.
- Wu, P.; Cai, Z. W.; Gao, Y.; Zhang, H.; Cai, C. X. Enhancing the electrochemical reduction of hydrogen peroxide based on nitrogen-doped graphene for measurement of its releasing process from living cells. *Chem. Commun.* **2011**, *47*, 11329.
- Xiao-Mei, C.; Wu, G.-H.; Jiang, Y.-Q.; Wang, Y.-R.; Chen, X. Graphene and graphene-based nanomaterials: the promising materials for bright future of electroanalytical chemistry. *Analyst* **2011**, *136*, 4631–4640.
- Yang, W.; Ratinac, K. R.; Ringer, S. P.; Thordarson, P.; Gooding, J. J.; Braet, F. Carbon nanomaterials in biosensors: should you use nanotubes or graphene? *Angew. Chem. Int. Ed.* **2010**, *49*, 2114–2134.
- Yang, Z.; Cao, Y.; Li, J.; Jian, Z.; Zhang, Y.; Hu, X. Platinum nanoparticles functionalized nitrogen doped graphene platform for sensitive electrochemical glucose biosensing. *Anal. Chim. Acta* **2015a**, *871*, 35–42.
- Yang, C.; Denno, M. E.; Pyakurel, P.; Venton, B. J. Recent trends in carbon nanomaterial-based electrochemical sensors for biomolecules: a review. *Anal. Chim. Acta* **2015b**, *887*, 17–37.
- Yang, Z.; Lan, Q.; Li, J.; Wu, J.; Tang, Y.; Hu, X. Efficient streptavidin-functionalized nitrogen-doped graphene for the development of highly sensitive electrochemical immunosensor. *Biosens. Bioelectron.* **2017**, *89*, 312–318.
- Yildiz, G.; Aydogmus, Z.; Cinar, M. E.; Senkal, F.; Ozturk, T. Electrochemical oxidation mechanism of eugenol on graphene modified CPE electrode and its analytical application to pharmaceutical analysis. *Talanta* **2017**, *173*, 1–8.
- Zhang, L.; Li, X.; Huang, Y.; Ma, Y.; Wan, X.; Chan, Y. Controlled synthesis of few-layered graphene sheets on a large scale using chemical exfoliation. *Carbon* **2010**, *48*, 2380.
- Zhang, M.; Li, J. Preparation of porphyrin derivatives and C60 supramolecular assemblies as a sensor for detection of dopamine. *Dyes Pigm.* **2020**, *173*, 107966.
- Zhao, X.; Cou, L. Comparative analysis of graphene grown on copper and nickel sheet by microwave plasma chemical vapor deposition. *Vacuum*, **2018**, *153*, 48–52.