Chapter 9
Pharmaceuticals and Personal Care Products

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9.1 Introduction

9.1.1 A Brief Chronology

When the industrial revolution started, there was a consensus that rivers, lakes, and mainly the oceans were able to absorb and transform entirely the pollution produced by the humans. In the next century, particularly after the Second World War, an impressive "turnover" in the human population-growing factor was observed. The main reasons for this huge expansion of the population were the exponential production of foods, which passed from manual to mechanized process and the development of important drugs, in special the antibiotics, penicillin being the most representative example. The mechanization in the agriculture reduced significantly the needs of labor force in the cultivated lands, oppositely to the requests of the modern industry. This reality brings about a strong emigration of peoples from the field to the cities. Besides a rapid and non-organized growing of the population, the modern industrial processes pass to demand quantities of water never before utilized and consequently leave behind ever-growing amounts of wastewater.

Until the middle of the twentieth century, there was no conscience about the potential problems related to any inorganic or organic compound wasted in soil, rivers, lakes, and oceans or even in the atmosphere. Probably the Minamata disaster was the starting point of concern about the effects of pollution. In the following years, the conscience of the Americans was waked up for DDT problems. In sequence, peoples realized that the capacity of our rivers, lakes, oceans, soil, and atmosphere to accept all kinds of pollutants is finite and started to look with more care for all aspects involving our environment.

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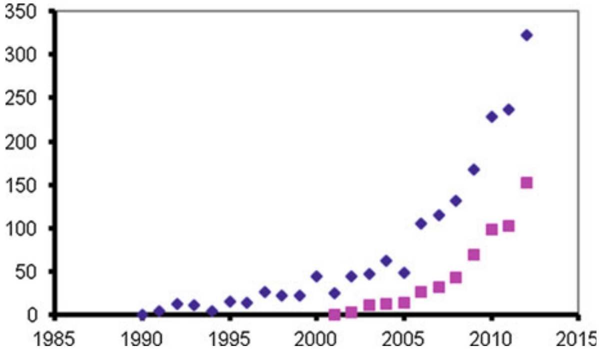
Fig. 9.1 Number of research publications per year using "emerging contaminants" with (■) and without quotation marks (◆) using the Web of Science database



In the following years, with the evolution of the analytical instrumentation, the limits of detection were lowered tremendously and in consequence the number of compounds monitored in water grew remarkably. Many "new" compounds are now referred as "emerging compounds"; once among these new analytes, pharmaceutical and products of personal care started to be monitored in waters with increasing frequency in the last years.

A search in the Web of Sciences presents some interesting aspect. Using the words emerging contaminants, a total of 1,836 papers were found (May 30, 2013), this designation being utilized for the first time in 1990. Between this year and the end of 2012, there are 1,712 papers. Making the same search putting "emerging contaminants" between quotation marks, a total of 564 papers were found till the end of 2012, being the first from 2001. Figure 9.1 depicts both series of data and demonstrates the exponential growing of research on the topic in question.

9.1.2 *What Are and Why Study Emerging Compounds?*

There is not a clear definition but, in principle, almost all the species synthesized for applications in the modern life can be classified as emerging compounds. All these compounds represent a potential risk for the environment, especially considering its extraordinary diversity. Nowadays, about three million synthetic compounds are known and this number is still growing at an accelerated rate and about 100,000 of these compounds are produced regularly for the most diverse applications, equivalent to 200 million tons per year. From this impressive amount, 20–30 % are estimated that attain the aquatic environment and we know almost nothing about the effects of these compounds individually or in association with other compounds on the environment. There are aspects as embryonary defects, DNA damage, cancer, or even fish sex exchange attributed to different emerging compounds. We need to understand exactly the sources of these compounds, their reactivity, distribution, lifetime, secondary products, and even environmental problems unrevealed until now, involving, short-, medium-, or long-term processes.

9.1.3 Scope of This Chapter

Emerging contaminants is a theme extremely ample and in this chapter we are restricted to pharmaceuticals and personal care products in water. Even restricting to these two issues, the subject of this chapter remains complex and difficult to cover in details. In this sense, this chapter is limited to discuss the development of voltammetric methods focused in the quantification of pharmaceuticals and personal care products.

9.2 Overview

Pharmaceuticals and personal care products are used for many centuries but their monitoring and the evaluation of their effects on the environment and on humans is still a relatively new subject. Until the starting of the 1990s, the main attention was focused on the heavy metals and the persistent organic pollutants. In the industrialized countries, this problem decreased significantly due to the strong control of the pollution sources. At this time, many scientists realized that there are a myriad of man-made chemicals, utilized in the industry, agriculture, and also pharmaceuticals and personal care products that are still unregulated and potentially can produce adverse effects on the environment and on the humans.

Only in the pharmaceutical area, there are more than 3,000 pharmaceutically active compounds (analgesics, anti-inflammatory drugs, antibiotics and antihistamines, β-blockers, lipid regulators, contraceptives, antidiabetics, antipsychotics, estrogens, antidepressants, anticonvulsionants, antiepileptics, stimulants, impotence drugs, etc.) that are used in human medicine. The main part of these pharmaceuticals is excreted in urine and feces and attains the aquatic environment water via wastewater and the effects of all these products alone or in combination are still not well known. In association with the pharmaceuticals, personal care products are normally studied and the acronym PPCP was coined and adopted by many authors.[1]

Books,[1,2] reports,[3–5] and reviews[6–11] dealing with different aspects of emerging contaminants discuss their potential sources, the complexity of their removal, and the importance of significantly increasing research efforts related to these issues. The majority of the researchers that are working in this area utilize pre-concentration processes associated with separation techniques, such as solid-phase extraction-liquid chromatography–electrospray-tandem mass spectrometry (SPE-LC-ESI-MS/MS),[12] ultraperformance liquid chromatography-mass spectrometry (UPLC-MS/MS),[13] liquid chromatography coupled to fluorescence detection[14] or combining gas chromatography/mass spectrometry (GC/MS), and liquid chromatography/quadrupole time-of-flight mass spectrometry (LC-QTOF-MS)[15] among other alternatives. Even so, some authors demonstrate that mass spectroscopy needs also many improvements, once the databases and libraries presently available have mostly been developed for the metabolomic field.[16]

Even taking into account that the techniques mentioned above produce very reliable data, Greenwood and col.[17] detach that the infrequent spot (bottle) sampling is unlikely to fulfill the developing needs. Representative sampling is a key requisite to generate precise information about water quality and the authors detach that a range of alternative tools are emerging and even considering the fact that these ones do not have the same low level of uncertainly, they can provide more representative data, often at lower cost. The electroanalytical technique is one of the most promising possibilities, until now not adequately explored.

9.3 Voltammetric Analysis

Electroanalytical techniques are well established and their applications are rapidly growing, spreading to the most different fields, among them the pharmaceutical area. The extraordinary advances obtained with the modern instruments and techniques turned electroanalysis more sensitive, rapid, and also more selective to solve many analytical problems. For the quantification of pharmaceutical and personal care products (PPCP), the literature presents many research articles describing the use of different voltammetric techniques, mainly focusing the quantification of products in their unprocessed form or in the final commercial form, or quantifying pharmaceuticals and/or their metabolites in human body fluids, but until now there are only few studies focusing on the analysis of these compounds in surface water, groundwater, wastewater, or drinking water. Many of these studies present very good sensitivity and have potential to be employed in the analysis of these compounds in aqueous matrix. In the following sections we discuss the (relatively small number of) studies involving the determination of PPCP in water, as also selected examples, demonstrating the applicability of the electroanalytical techniques for the analysis for this purpose.

In the literature, a series of good reviews about the use of electroanalytical methods for determination of pharmaceuticals,[18] the utilization of chemical-modified electrodes,[19] or even focusing on the utilization of voltammetric techniques in association with flow injection analysis[20] demonstrate the great potentialities of the use of electroanalysis for quantification of low levels of pharmaceutical compounds. In the following sections, these aspects are addressed and selected examples are presented. A classification based on the electrode materials was chosen for giving the lecturer an outlook of the developments in the area.

9.3.1 Mercury Electrodes

Mercury electrodes were determinant for the development in the early days of electroanalytical techniques. Starting by polarography developed by Heyrovsky in 1922, mercury electrodes were fundamental for the development of many electroanalytical methods. The elevated purity attainable for metallic mercury, the excellent overpotential for hydrogen reduction, and the fact that the electrode is renewable turn this electrode very attractive for the analysis of pharmaceutical compounds. The first paper was published in 1948.[21] In the following years the number of articles that appeared was relatively small, but with the evolution of the instrumentation and especially with the advent of the hanging mercury drop electrode (HMDE), the applications utilizing mercury electrodes associated to adsorptive processes spread out and the number of studies grew significantly.

Adsorptive processes on mercury electrodes are very favorable techniques for the quantification of low concentrations of a series of organics, among them pharmaceutical compounds. The perfectly smooth surface of mercury associated with the very reproducible electrode area turns HMDE the electrode of choice for adsorptive processes, with the peculiar advantage of be completely renewable just by the opening (and closing) of the mercury flow.

Using HMDE, the analysis of triamcinolone acetonide (TAA) was performed by square-wave voltammetry (SWV) and a detection limit of 3.0×10^{-10} mol L^{-1} was attained.[22] The method was successfully applied for the analysis of TAA in tablets and in serum, without pretreatment of the samples. The quantification of haloperidol was performed under controlled adsorptive accumulation onto HMDE and was applied in low concentrations of the bulk form to pharmaceutical formulations and human fluids. A limit of quantification (LOQ) of 3.83×10^{-10} mol L^{-1} was calculated by the authors.[23] In another study of the same research group, ethinylestradiol was investigated and a detection limit of 5.9×10^{-10} mol L^{-1} was reported.[24] The analysis of cefoperazone in pharmaceutical formulations and in human plasma was carried by pre-concentration followed by SWV onto an HMDE, attaining a detection limit of 4.5×10^{-10} mol L^{-1}.[25] The analysis of the antifungal antibiotic griseofulvin, used for treatment of phatogenic mycotic diseases, was performed by adsorptive stripping analysis using HMDE and a limit of quantification of 5.8×10^{-10} mol L^{-1} was reported.[26] In another study, the same author developed methodology for gatifloxacin analysis, attaining detection limits of 1.5×10^{-9} and 2.2×10^{-9} mol L^{-1} in the bulk form and in human serum, respectively.[27] The analysis of tobramycin, a broad-spectrum antibiotic against Gram-positive bacteria, was performed utilizing linear sweep voltammetry and a limit of quantification of 3.44×10^{-9} mol L^{-1} was attained.[28] In a study focused on the quality control of tinidazole, a drug utilized for treatment of trichomonas infection, methodology for quantification of this drug was developed and applied for tablets and also in biological fluids and the detection limit attained was 4.5×10^{-10} mol L^{-1}. In this study, it was observed that the addition of CTAB increases significantly the voltammetric signal of tinidazole.[29] The association of

ASV and square-wave voltammetry for the analysis of rosiglitazone was explored in human urine and plasma samples. The detection limit attained for this drug was 3.2×10^{-11} mol L^{-1} using only 120 s of pre-concentration.[30] Our search indicates that presently there are studies on HMDE for the quantification of insecticides and metals in wastewater, groundwater, superficial water, and drinking water, but any study involving real samples.

9.3.2 *Other Metallic Electrodes*

The use of other metals for electroanalytical purposes is nowadays very frequent and still growing. All solid electrodes, compared to mercury electrodes, present some disadvantages such as difficulty to control the reproducibility and the renovation of its surface can be a challenge. Conversely, mercury can be used only in a limited anodic potential region, and this hampers the oxidation of many organic molecules. Many solid electrodes can be utilized in this region and this is an aspect that can be explored with these electrodes. The use of metals as electrodes for the quantification of pharmaceutical compounds was considerably explored in the last years and their use is still growing. Among the noble metals (normally considered inert) platinum and gold are more widely used, followed by palladium. Applications involving copper, lead, silver, and ruthenium are also reported in the literature.

Gold electrodes were utilized for the quantification of tetracycline, chlorotetracycline, and oxytetracycline using a screen-printed electrode (SPE) in a flow cell. The limit of detection for the three cyclones was 9.6×10^{-7} mol L^{-1}, 5.8×10^{-7} mol L^{-1}, and 3.5×10^{-7} mol L^{-1}, quantified in pharmaceutical products and foods.[31] Gold electrodes can also be easily modified with self-assembled monolayers (SAMs) and in some occasions the structure formed on the surface of the electrode can favor the electrochemical process. The quantification of vitamin B-12 was done on a gold electrode modified by a monolayer of mercaptoacetic acid and the limit of quantification attained in this case was 1.0×10^{-9} mol L^{-1}.[32] The quantification of the antidepressant trazodone was done using a static and a rotating platinum disk electrode and the detection limits attained were 2.5×10^{-6} mol L^{-1} for the static electrode and 1.72×10^{-6} mol L^{-1} for the rotating electrode.[33] The deposition of platinum over gold electrodes and its association with flow injection analysis (FIA) allow to perform 90-analysis per hour and detection limit of 7.8×10^{-7} mol L^{-1}.[34]

Palladium was electrodeposited on gold electrodes constructed from recordable CDs and was utilized for dipyrone quantification under flow injection analysis. The limit of detection attained was 1×10^{-7} mol L^{-1}, the volume utilized in the FIA was only 100 μL, and the time required for each analysis was 40 s.[35] Arrays of microelectrodes modified by electrodeposition of palladium, platinum, and a mixture of platinum + palladium were utilized for the quantification of the components of a mixture containing ascorbic acid, dopamine, epinephrine, and dipyrone.[36] Lead films plated on glassy carbon or gold electrodes point to a promising way to determine low levels of pharmaceutical products. Very low detection levels for the quantification of testosterone, trimethoprim, sildenafil citrate, folic acid, rutin, glipizide, and rifampicine, situated between 2×10^{-8} and 9×10^{-11} mol L^{-1} were reported in different studies carried out by the same research group.[37]

The formation of Cu(III) on the surface of the electrode in alkaline medium was explored to catalyze the oxidation of acetyl salicylic acid. The quantification of this compound in pharmaceutical formulations was done using amperometric measurements in association with batch injection analysis (BIA). A detection limit of 4.8×10^{-7} mol L^{-1} and a frequency of 60-determination per hour were reported.[38] There is a series of studies where silver is involved in the quantification of pharmaceutical products, mainly as nanoparticle or in the form an insoluble compound, sometimes amalgamated. One interesting study involving solid silver electrodes describes the determination of trihalomethanes (THMs) in waters and utilizes a very clever process. On the silver electrode maintained as cathode, the THM is electrolyzed to release the halide (chloride or bromide). In a second step, the previously freed halide ions are collected on the second silver electrode, and anodically polarized, forming the corresponding silver halide film, which adheres to this electrode surface. In sequence, the collected film is reduced using differential pulse voltammetry (DPV). The detection limit reported was 12 nmol L^{-1} for bromoform and 50 nM L^{-1} for chloroform.[39] Thioridazine was quantified utilizing cyclic voltammetric measurements with ruthenium, platinum, and glassy carbon electrodes. The best results were obtained with ruthenium and the linear region was situated in the concentration range of 5×10^{-5} and 1×10^{-3} mol L^{-1}.[40]

Bismuth film electrode (BiFE) was developed to replace mercury film electrodes. More recently, BiFEs were also utilized for the quantification of vitamin B-12 in pharmaceutical products, with a detection limit of 3.3×10^{-8} mol L^{-1} after a pre-concentration of only 30 s.[41] Sildenafil citrate was quantified on BiFE films prepared ex situ using a glassy carbon electrode as substrate. A limit of detection of 1.8×10^{-8} mol L^{-1} was attained with 120 s of deposition.[42]

9.3.3 Carbon Electrodes

9.3.3.1 Conventional Carbon Electrodes

Carbon electrodes usually present good conductivity, broad potential windows, and low background current. Its wider potential window compared with the other classes of electrodes confers them an ample set of applications in electroanalysis. The origin and the treatment of its surface can be determinant of electron transfer reactivity, so as the predominance of edge plane toward basal plane in this surface will determine faster electron transfer kinetics. A variety of treatments to improve the electrode performance and to obtain reproducible surfaces have been proposed, but there is not a “definitive prescription.”

Glassy carbon electrodes (GCE) are the most used electrodes for many applications, including PPCP analysis, due to their proprieties such as excellent electrical conductivity and mechanical stability, wide potential range, impermeability to gases, chemical inertness (even to concentrated acids), and reproducible performance.[43] There are many studies where GCE was employed for quantification of very low concentration of pharmaceuticals and representative examples are the following: For the quantification of tegaserod, this compound was adsorbed on the glassy carbon electrode at open circuit, at pH 9.0. After this step, the medium is exchanged and the DPV is processed. A detection limit of 3.0×10^{-10} mol L^{-1} was obtained under 3-min pre-concentration.[44] The association of amperometry and BIA for isoniazid quantification leads to a very sensitive response, with a detection limit calculated as 4×10^{-9} mol L^{-1} and an unusual linear region of response situated from 5×10^{-8} to 1.0×10^{-3} mol L^{-1}.[45] Adsorptive accumulation was explored for the direct quantification of levofloxacin in human urine, which was only diluted (1,000 times) before the measurements in acetate buffer (pH 5.0). A detection limit of 5×10^{-9} mol L^{-1} was obtained utilizing 5 min of pre-concentration at +0.4 V.[46] Trimetazidine was quantified in tablet dosage form and in urine. Both samples were diluted in buffer solution and the analyte was pre-concentrated on the electrode for 300 s, at open circuit, under vigorous stirring. In sequence, the solution was replaced for another, with the same buffer and the square-wave voltammogram was recorded. A detection limit of 2×10^{-8} mol L^{-1} was attained.[47] The antihypertensive and antianginal agent amlodipine besylate in pharmaceutical, urine, and serum was quantified exploring cyclic and square-wave voltammetry. The best pH encountered was 11.0, the ideal pre-concentration potential was determined as 0.0 V, and the deposition time established as ideal was 180 s. Under these conditions a detection limit of 1.4×10^{-8} mol L^{-1} was reached.[48] The quantification of amisulpride was optimized for quantification in dosage forms, serum, urine, and gastric juice by oxidation using DPV and SWV. The response obtained at pH 7.0 was the most favorable and the detection limits attained were 2.2×10^{-8} mol L^{-1} using DPV and 3.6×10^{-8} mol L^{-1} when SWV was the technique utilized.[49] The same authors' research group also developed studies involving vardenafil present in dosage forms and in serum. The detection limits determined in electrolyte solutions were calculated as 2.27×10^{-8} mol L^{-1} using DPV and 6.56×10^{-8} mol L^{-1} using SWV. In the presence of serum the detection limits achieved were evaluated as 2.53×10^{-8} mol L^{-1} using DPV and 2.69×10^{-8} mol L^{-1}.[50] The analysis of levodopa and carbidopa in mixtures was developed, based on the reductive peak of first and the oxidative peak of the second when in mixture. In this study, the analysis of levodopa was not affected by the presence of carbidopa, whereas for the quantification of this last, it was necessary to utilize a nafion, turning the surface selective to carbidopa. The detection limit obtained for levodopa was 4.2×10^{-8} mol L^{-1} and for carbidopa (using the nafion film) was 3.8×10^{-7} mol L^{-1}.[51]

Pyrolytic graphite electrodes have also been utilized for quantification of very low levels of pharmaceutical compounds. The quantification of acetyl salicylic acid and caffeine was done employing an edge plane pyrolytic graphite electrode.

Detection limits for acetyl salicylic acid were 1×10^{-8} mol L^{-1} and for caffeine 8×10^{-9} mol L^{-1}.[52] A comparative study involving pyrolytic graphite with different surfaces (basal × edge planes) was carried out for hydrocortisone. The edge plane electrode showed a better performance, with greater sensitivity, and for hydrocortisone the detection limit attained was 8.8×10^{-8} mol L^{-1}. The same electrode was utilized to quantify hydrocortisone in blood plasma and any interference was observed.[53] Diclofenac was studied by SWV using edge plane pyrolytic graphite. A detection limit of 6×10^{-9} mol L^{-1} was evaluated for this analyte.[54] The surface of pyrolytic graphite favors the adsorption of many different catalytic species on its surface and the majority of the recent papers involve the utilization of some modifiers on its surface.

Screen printing electrodes (SPE) are gaining preference for many applications, in special for screening procedures outside of a conventional laboratory. The construction of SPE makes use of thick-film technology and it is a very convenient form of mass production of disposable electrochemical sensors (units with individual electrodes or more commonly comprised by an arrangement with the three electrodes). These electrodes are constructed by deposition of conductive carbon inks on the surface of an inert substrate (PVC and ceramic materials are preferred). To obtain reproducible units, the film dimensions should be identical. Advantages such as the very low cost of these electrodes, the possibility of printing a large number of units (with the same ink to obtain similar electrodes or with different inks producing differentiated units), and the possibility of mix modifier to tailor the characteristics of the electrode are attractive aspects of this kind of electrodes.

Applications of SPE have been growing in the last years and in some cases the quantification attained is 10^{-8} mol L^{-1}. The quantification of sildenafil was performed by SWV at pH 4.5, the detection limit was calculated as 5.5×10^{-8} mol L^{-1} and the method was successfully applied to pharmaceuticals and to spiked urine samples.[55] The direct oxidation of methionine was achieved on SPE in a multivitamin complex, without noticeable interferences, and the detection limit calculated was 9.5×10^{-6} mol L^{-1}.[56] The quantification of the anticancer drug flutamide was performed by DPV on bare SPE and a detection limit of 8×10^{-7} mol L^{-1} was reported.[57] The association of amperometry and FIA was explored for the rapid quantification of procaine in pharmaceutical formulations using SPE. A frequency of 36 analysis was attained and the limit of detection was calculated as 6.0×10^{-6} mol L^{-1}.[58]

9.3.3.2 Carbon Paste Electrodes

Carbon paste electrodes (CPE) were introduced by Adams in 1958 [59] and along the years the applications of this kind of electrodes have grown tremendously. Initially it was prepared by the mixture of mineral oil and graphite powder but with time the group of heterogeneous electrodes grew tremendously. The main reasons for this fantastic expansion are the simplicity of preparation of carbon pastes, the facility to renew the electrode surface, the versatility for the introduction of new constituents in the paste, and the very low costs of basic materials (mineral oil and carbon powder) to prepare CPE. Studies involving unmodified paste electrodes are nowadays not so common, and the reasons are easy to understand, once researchers have access to a several modifiers that can improve CPE signal. An excellent revision focused on the electroanalysis of organic compounds at CPE[60] covered the years 2004–2008. In this period, 80 % of the papers reported modified CPEs. Even unmodified electrodes can lead to very good results, as can be seen in the following examples: For the analysis of melatonin, the adsorption of this compound was explored in association with alternating current voltammetry and a detection limit of 9×10^{-11} mol L^{-1} was attained.[61] For the quantification of the diuretic drug indapamide CPEs were explored using different techniques. Exploring the adsorption of the compound on the electrode and DPV, a detection limit of 5×10^{-9} mol L^{-1} was reported.[62] For the determination of physcion the adsorptive process on the CPE was also explored, but during the potential scan the reduced product was immediately oxidized by the dissolved oxygen and consequently was available for a new reduction. This enhanced significantly the sensitivity of the method and a detection limit of 8×10^{-11} mol L^{-1} was obtained.[63]

Besides the classical CPE, there are almost infinite possibilities related to modifications of the paste, as also related to the "inert" mineral oil. Recent papers describe the utilization of modified electrodes with porphyrins, able to detect 1.6×10^{-13} mol L^{-1} dopamine in pharmaceuticals[64] or even 1.1×10^{-14} mol L^{-1} for ascorbic acid in beverages and pharmaceutical samples.[65]

9.3.3.3 Boron-Doped Diamond Electrodes

Synthetic diamonds are basically produced by chemical vapor deposition (CVD) or by the high-pressure/high-temperature (HPHT) processes and date from 1952 and 1955, respectively. In the 1980s, researchers developed the process to implant ions on these diamonds, turning the films much more conductive. In 1992 the first paper presenting the polycrystalline boron-doped diamond (BDD) electrodes was published[66] and in the following years the applications of these electrodes grew exponentially, and many of the applications were devoted to pharmaceutical quantification. The preference for this kind of electrodes is attributed to many properties such as the following: low and reproducible background current, almost unaffected by adsorptive processes, elevated electrochemical stability in both alkaline and acidic medium, and owns one of the widest usable potential windows. These properties are induced by morphologic factors, crystallographic orientation, and presence of impurities (non-diamond sp^2 carbon), which turns these electrodes significantly different from the other conventional carbon-based electrodes discussed before.

The utilization of BDD for analysis of nitrofurantoin was performed with electrodes recovered with different amounts of boron and a detection limit of 8.15×10^{-9} mol L^{-1} of the studied compound was related.[67] Naproxen was oxidized on BDD in nonaqueous medium and this electrochemical process was explored for the accurate quantification of this compound in pharmaceutical formulations. DPV was the most favorable technique, allowing the quantification of low concentrations of naproxen. The detection limit was calculated as 3×10^{-8} mol L^{-1}.[68] Tetracycline and its derivatives were quantified in drug formulation using GC, as-deposited BDD, and anodized BDD associated with FIA + amperometry. The anodized BDD leads to the best signals and to the lowed detection limit, calculated as 1×10^{-8} mol L^{-1} of tetracycline.[69]

Another important field of application for BDDs is in the electrolytic degradation processes, where the wider potential window provided by these electrodes is fundamental for an efficient process. There are more than 200 studies dealing with BDD and electrolysis, 13 of them focusing on the decomposition of pharmaceuticals, all of them published after 2001. For application in large scale (as in a wastewater treatment) there are still challenges such as the construction of large electrodes and the design of cells of high performance.

9.3.3.4 Fullerenes, Graphenes, and Nanotubes

Fullerenes, graphenes, and nanotubes are new forms of carbon that present many interesting properties and have emerged as the most investigated nanostructure materials of the last years. Fullerenes emerged in the end of the 1980s and started to be produced commercially in 1991. The existence of nanotubes was mentioned in the 1950s, but only in 1991 this material was separated from the soot of arc discharge and in sequence was obtained using a CVD process. The existence of graphene was also previewed before middle of the last century, but only in 2004 its production was started.

A myriad of sensors utilizing these carbon forms were intensely developed in these relatively short period and due to their special structural features and unique electronic properties, upstanding results were attained for many applications. Glassy carbon electrodes modified with fullerene-C-60 were utilized for methylprednisolone quantification in pharmaceuticals and human biological fluids. The presence of C-60 produced a marked enhancement of the DPV signal in comparison with the bare electrode. The detection limit was estimated as 5.6×10^{-9} mol L^{-1}.[70] Enhanced electrochemical response for carbamazepine was achieved with a GCE modified with a nanostructured film of C-60. Utilizing DPV, the limit of detection obtained was 1.62×10^{-8} mol L^{-1} and the method was satisfactorily applied to pharmaceutical formulations, spiked human serum, and urine samples.[71] The electrochemical response to acyclovir was also improved when a glassy carbon electrode was modified with fullerene-C-60. Under optimized conditions, a detection limit of 1.48×10^{-8} mol L^{-1} of this antiviral drug was attained.[72]

Carbon nanotube electrodes (single- and multi-wall) present characteristics that make them very attractive for many voltammetric applications. Their utilization for quantification of pharmaceutical compounds is significant, and advantages such as high sensitivity and stability, good repeatability, lower oxidation potential, and absence of fouling effect are reported. Electrodes modified with nanotubes can lead to very sensitive responses, such as the ones obtained for the quantification of trifluoperazine using a GCE modified with multi-walled carbon nanotubes. According to the authors,[73] an adsorptive process was explored for enhancement of the signal and after the optimization of the process, a detection limit of 7.49×10^{-10} mol L^{-1} was attained. The quantification of the antiviral drug vanganciclovir was performed using a multi-walled carbon nanotube-modified GCE. Adsorptive accumulation process enhanced significantly the signal obtained and a detection limit of 1.52×10^{-9} mol L^{-1} was attained for this compound.[74] Triamcinolone, a doping agent prohibited for athletes, was quantified using an edge plane pyrolytic graphite electrode modified with single-wall carbon nanotubes and using the same pyrolytic graphite electrode modified with fullerene-C-60. The authors concluded that electrode modified with the nanotubes was more sensitive than the one modified with fullerenes. A detection limit of 8.9×10^{-10} mol L^{-1} was attained when the single-walled carbon nanotube-modified electrode was utilized.[75] Analysis of pharmaceuticals and real urine samples was performed, with good agreement with chromatographic analysis.

Graphene presents a freestanding 2D structure with one-atom thickness and rapidly is becoming one of the hottest topics in the field of material science, physics, chemistry, and nanotechnology since it was first isolated in 2004. Applications of graphene to tailor sensors of differentiated performance are growing rapidly and will be a hot topic in the following years, as will be illustrated. For the quantification of paracetamol, a GCE was recovered with graphene that produced an intense decrease in the oxidation potential of this analyte and an excellent electrocatalysis for the determination of this pharmaceutical compound. A detection limit of 3.2×10^{-8} mol L^{-1} was calculated for this compound.[76] Lower detection limits were obtained utilizing composites containing graphene. For the quantification of rutin, a composite based on cyclodextrin/reduced graphene/nafion leads to detection limits of 2×10^{-9} mol L^{-1} of rutin.[77] A composite containing gold nanoparticles/L-cysteine/graphene/nafion deposited on GCE was utilized for the quantification of theophylline. Responses in a wide linear range (4×10^{-9} to 6×10^{-5} mol L^{-1}) were recorded and the detection limit for this electrode was calculated as 4×10^{-10} mol L^{-1} of theophylline.[78] For the quantification of quercetin, a composite of p-aminothiophenol-functionalized graphene oxide/gold nanoparticles produced amazing sensitivity. For this compound, a detection limit of 3×10^{-13} mol L^{-1} was obtained using SWV.[79]

A comparison between the development of sensors based on these new forms of graphite shows that nanotubes are at this moment the most utilized material and this probably can be attributed to the facility of acquisition and utilization of this material. Graphene, even being the “youngest” of these materials, in few years surpassed the fullerenes use as sensing material, probably due to the fact that this last requires chemical modification before its utilization.

9.3.3.5 Other Electrodes

Besides the solid metallic electrodes, the utilization of metal films, nanoparticles, and insoluble compounds immobilized on the solid electrodes is a field with plenty of opportunities and there are many aspects to be explored. Noble metals are able to catalyze many electrochemical reactions. Mercury and gold are the most favorable surfaces to explore adsorptive pre-concentration,[80,81] which allow detection in the 10^{-12} mol L^{-1} region. Mercury is still among the best sensors and in the starting of the last century, polarography was responsible for the popularity of electroanalytical techniques. Unfortunately many countries are considering the possibility of discontinuing the use of mercury electrodes. Alternative ways are the utilization of mercury films or mercury amalgams. The use of mercury film on carbon fiber microelectrodes was explored for the quantification of folic acid and mitoxantrone, obtaining detection limits of 9×10^{-10} and 5×10^{-10} mol L^{-1}, respectively.[82] Silver amalgam was utilized for the quantification of folic acid and the detection limit calculated was 5×10^{-10} mol L^{-1}.[83]

Low detection limits were also attained using gold electrodes modified by thiocompounds. A study involving simultaneous self-assembled films containing corrole-SH and other thiol derivatives generated a very sensitive sensor for dopamine, free from interferences of species commonly present in blood. A detection limit of 5.3×10^{-12} mol L^{-1} was obtained for a direct determination of dopamine in human plasma 80 times diluted.[84] The grafting of molecular imprinting polymers (MIPs) was executed via photopolymerization of acrylamide and trimethylolpropane trimethacrylate on a gold electrode surface. A sensor with wide concentration working region (10^{-9} to 10^{-3} mol L^{-1}) was obtained and its detection limit was calculated as 1×10^{-10} mol L^{-1}.[85]

The use of carbon paste electrodes (CPE) for the quantification of trace amounts of pharmaceuticals has been also explored due to the versatility of this electrode, an attractive aspect many times considered by the researchers. The intense adsorption of vardenafil on CPE was explored for its quantification in commercial formulations and in human serum with high sensitivity, attaining a detection limit of 3×10^{-10} mol L^{-1}.[86] CPE modified with dysprosium hydroxide nanowires[87] or lanthanum hydroxide nanowires[88,89] also presented sensitivities in the 10^{-10} mol L^{-1} region. CPE modified with carbon nanotubes and DNA was explored for the quantification of DL-alpha-tocopherol. A detection limit of 1.3×10^{-10} mol L^{-1} was attained in this study.[90] The utilization of clay in the CPE produced an effective improvement in the quantification of nifedipine (LOD: 3.9×10^{-10} mol L^{-1}) and nimodipine (LOD: 4.8×10^{-10} mol L^{-1}).[91] Octyl-bonded silica (C-8) was introduced in a CPE to enhance the quantification of doxazosin (LOD: 7.4×10^{-10} mol L^{-1}).[92] The use of 1,2-dibromocyclohexane as the paste binder created an ingenious way to obtain a self-catalytic carbon paste electrode for the detection of vitamin B-12. A detection limit of 8.5×10^{-10} mol L^{-1} was attained[93] for this vitamin.

There are many other studies that can be found in the literature, but the aim of this chapter is to give to the readers an overlook concerning to what was developed until now and about the potential represented by the electroanalytical techniques for the continuous monitoring of emerging pollutants in water and wastewater. Unfortunately, the number of applications to real samples is still very reduced (as will be seen in the next section) but a significant increase in these applications can be expected in the future.

9.4 Voltammetric Determination of PPCP

The number of papers dedicated to the electrochemical quantification of the constituents of commercial products is remarkably significant in comparison with the ones dealing with their determination in natural waters and wastewater. This huge difference is motivated by many factors, among them: The need of analytical control of these components is essential for the quality of the products manufactured; procedures for the analysis of these products were established for relatively long time in their matrixes, but still to be established in wastewater; the conscience about emerging contaminants is relatively new and the direct analysis of these compounds in wastewater can be more complex than in pharmaceutical products. An evaluation on the papers dedicated to analysis of PPCP in water indicates some preference for sensors containing the new forms of graphite (nanotubes, graphenes, and fullerenes—particularly considering their relatively short life).

Multiwalled carbon nanotubes (MWCNT) deposited on GC were explored for the quantification of carbamazepine in wastewater and in pharmaceuticals.[94] The results compared well with the ones obtained by chromatography and the detection limit attained using linear sweep voltammetry was 4×10^{-8} mol L^{-1} for carbamazepine. GC covered with MWCNT was utilized for quantification of the dihydroxybenzene isomers (hydroquinone, catechol, and resorcinol) in artificial wastewater.[95] The electrocatalytic proprieties afforded by the MWCNT produce an intense anticipation of the oxidation peaks, so as a good separation between them, allowing the direct quantification of the three compounds. In another study, composites containing epoxy and MWCNT and epoxy + MWCNT + silver-modified zeolites were utilized for the quantification of ibuprofen by different techniques. The authors verified better responses for the composite containing silver-modified zeolites, reporting a detection limit of 4×10^{-7} mol L^{-1} ibuprofen.[96] According to them, this electrode presents potential both for degradation and simultaneously its control. A study comparing the performance of BDD, GC, and MWCNT-epoxy composites for the degradation of ibuprofen demonstrated a superior performance of the composite electrode.[97] The authors verified an additional enhancement in the performance of this electrode in the presence of chloride ions. In another study, the potential of MWCNT for the removal of natural and synthetic endocrine disrupting estrogens was also evaluated in a kinetic and mechanistic study.[98] The authors concluded that nanotubes present good potential for removal of estrogens from aqueous phase at relatively lower concentrations.

Graphene was immobilized on gamma Fe_2O_3 nanoparticles and presented high performance in removal processes of endocrine-disrupting compounds from water.[99] This strategy minimizes the graphene-graphene interaction, and maintained a very high graphene active area. An additional advantage is the fact that the resulting material favors its magnetic separation after the adsorption of the endocrine disruptors. Graphene was associated to platinum nanoparticles to form a composite on a GC electrode after electropolymerization of mercaptonicotinic acid in the presence of 17 beta-estradiol. After the removal of the template, the electrode presented good linear response in the range of $4\text{–}60 \times 10^{-9}$ mol L^{-1}, the limit of detection being calculated as 2×10^{-9} mol L^{-1}. The sensor was applied for 17 beta-estradiol quantification in mackups with good recovery.[100] Recently, the favorable characteristics of graphene were also explored to adsorb pharmaceuticals and personal care products from wastewater and their quantification by gas chromatography-mass spectrometry.[101] The limit of quantification calculated for nine different pharmaceutical products was situated between 13 and 115 ng L^{-1}.

Fullerene-C-60 was immobilized on glassy carbon by evaporation of a CH_2Cl_2 solution. The adsorbed fullerene was cycled in 1 M NaOH for its reduction and the electrode was utilized for bisphenol quantification in wastewater.[102] The detection limit was determined as 3.7×10^{-9} mol L^{-1}. The association of fullerenes and MWCNT was explored for the quantification of the endocrine disruptor vinclozolin in wastewater. A glassy carbon electrode was polished and a solution containing both carbon forms (MWCNT:C-60 = 2:1) were cast on the electrode that was dried at air. This electrode was applied for vinclozolin in optimized conditions, attaining a detection limit of 9.1×10^{-8} mol L^{-1}.[103] This sensor was successfully applied to the detection of vinclozolin in wastewater, obtaining a recovery ranging from 97.6 to 103.6 %.

Glassy carbon electrodes were also utilized for pharmaceutical quantification in wastewater. The redox characteristics of domperidone were critically investigated by DPV and CV. The limit of quantification of this compound was evaluated as 6.1×10^{-7} mol L^{-1}.[104] The procedure proposed shown a good recuperation for the pure form (98.2 ± 3.1 %) and a very satisfactory value for wastewater (95.0 ± 2.9 %). The quantification of triclosan on glassy carbon was studied in the presence of sodium dodecyl sulfate, which contributes for the enhancement of the voltammetric signal. The detection limit calculated was 1.73×10^{-8} mol L^{-1}.[105] The procedure was successfully applied to analyze wastewater and personal care product samples.

Screen-printed electrodes were also used for quantification of PPCP in waters, wastewater, and sewage samples. A screen-printed carbon electrode was utilized for quantification of bisphenol A in river water and sewage samples, without pretreatment of the samples.[106] The presence of cetyltrimethylammonium bromide was very favorable, actuating as antifouling and preconcentrating agent. A limit of detection of 5.1×10^{-8} mol L^{-1} was obtained in this study. A screen-printed silver electrode was utilized to quantify the content of aluminum chlorohydrate content in antiperspirant deodorants. A single drop (50 μL) was sufficient for the analysis.[107] The detection limit was calculated as 3.03 mg L^{-1}.

Mercury electrode was utilized for the quantification of pyrithione in seawater. The cathodic stripping analysis was performed in the presence of Triton X-100, with the aim of separating the desired peak from the signal from the interfering thiol compounds. A detection limit of 1.5×10^{-9} mol L^{-1} was attained using 60-s pre-concentration.[108]

Silver electrodes and its amalgam were also explored for analytical purposes. Trihalomethanes were quantified at submicromolar concentrations in water, using a three-step stripping process. The trihalomethane was reduced on a silver cathode, forming halides, which were captured at a silver halide anode. The insoluble AgX formed was then reduced using differential pulse voltammetry. Using this procedure, bromoform and chloroform can be detected in the 1.2×10^{-8} and 5×10^{-8} mol L^{-1} in water.[39] Silver amalgam was employed for quantification of ketoconazole in pharmaceuticals and in shampoos. The best conditions were determined, a detection limit of 1.2×10^{-7} mol L^{-1} was calculated, and the method was applied to shampoos and cream samples with good recovery.[109] Composites involving nanoparticles were also explored for the determination of different compounds. Zinc hydroxide nanoparticles were utilized for the quantification of 21 different parabens in aqueous solution. The detection limit was situated in the low micromolar region.[110]

Biosensors, immunosensors, and aptosensors present elevated selectivity or even specificity for a distinct target. This aspect is an important advantage in very complex matrixes such as wastewater or sewage water. Enzymes can be utilized both for the generation of a detectable species[111] or to eliminate some target of interest[112] in the complex sample. The use of immunosensors can produce very sensitive and selective responses. Recombinant single-chain antibody fragments were utilized for constructing a very sensitive sensor for atrazine, using a screen-printed electrode incorporating a conducting polymer, which enables direct mediatorless reaction.[113] This sensor presented very high sensitivity and its detection limit was 4.6×10^{-10} mol L^{-1}. An aptosensor for tetracycline detection was developed using an ssDNA aptamer that selectively binds to tetracycline as recognition element. To immobilize the ssDNA aptamer, it was biotinylated and bonded to the streptavidin-modified surface of a gold screen-printed electrode.[114] The detection limit was calculated as 1×10^{-8} mol L^{-1}.

Microelectrodes (single or arrays) also can be explored for the monitoring of species of interest in natural waters. An array of amalgamated gold microelectrodes was utilized to evaluate biogeochemical response of native sediments following its capping with a clean layer of a “clean” material.[115] In this study it was observed that the oxygen penetration into sand capping material extend only a few centimeters, maintaining so the sediment anaerobic. This kind of sensor arrangement is very important for better understanding the biogeochemical processes that affect natural water reservoirs. The possibility of measure *in situ* processes that occur in the seafloor is of great importance for understanding aspects of the sediment biogeochemistry and about the exchanges that occur in the ocean.[116] Information about the flux of metallic and organic compounds can contribute for a better understanding of the multiple processes that occur there. Microelectrodes can be very versatile, favoring even the determination of analytes in very small samples. One interesting example that illustrates this aspect is the study dealing with the effects of the makeup based on lead salts, utilized by ancient Egyptians.[117] Measurements made with only few cells demonstrate that the low solubility of the metal was sufficient to activate the specific oxidative stress responses of keratinocytes, producing more nitrogen monoxide and stimulating immunological defenses.

For the future, many progresses can be envisioned. The use of arrays of different electrodes and the treatment of the data so obtained with chemometrics will increase the power of the obtained information. New nanostructured materials will amplify the possibilities for this purpose.

9.5 Final Remarks

Studies focused on emerging contaminants are still in its beginning and constitute a field plenty of challenges to be faced. There are a myriad of aspects to be studied and will require huge efforts to rationalize the multifaceted aspects involving these compounds. Emerging contaminants can be found almost everywhere (air, water, soil, waste, foods, drinks, tissues, plants, milk, etc.) and its real number is unknown (pharmaceuticals, creams, pesticides, hormones, veterinary products, illicit drugs, surfactants, plasticizers, solvents, plastics components, catalyzers, etc.).

Only recently the deleterious effects caused by emerging contaminants started to be considered seriously and it is urgent to take actions to control or at least minimize their effects. The development of strategies to screen continuously these compounds in water is an important task to bring valuable information, which is essential to take decisions. Analytical data will be also fundamental for the optimization of treatment processes, such as the ones which utilize strong oxidants (chlorination, ozonation, H_2O_2), processes which employ electro-oxidation, retention processes based in membranes (reverse osmosis, membranes for nano-filtration), and bioreactors or even active sludge—all can be beneficed with precise and continuous monitoring of the income and the outcome of emerging compounds. And the electroanalytical methods can strongly contribute in this direction.

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