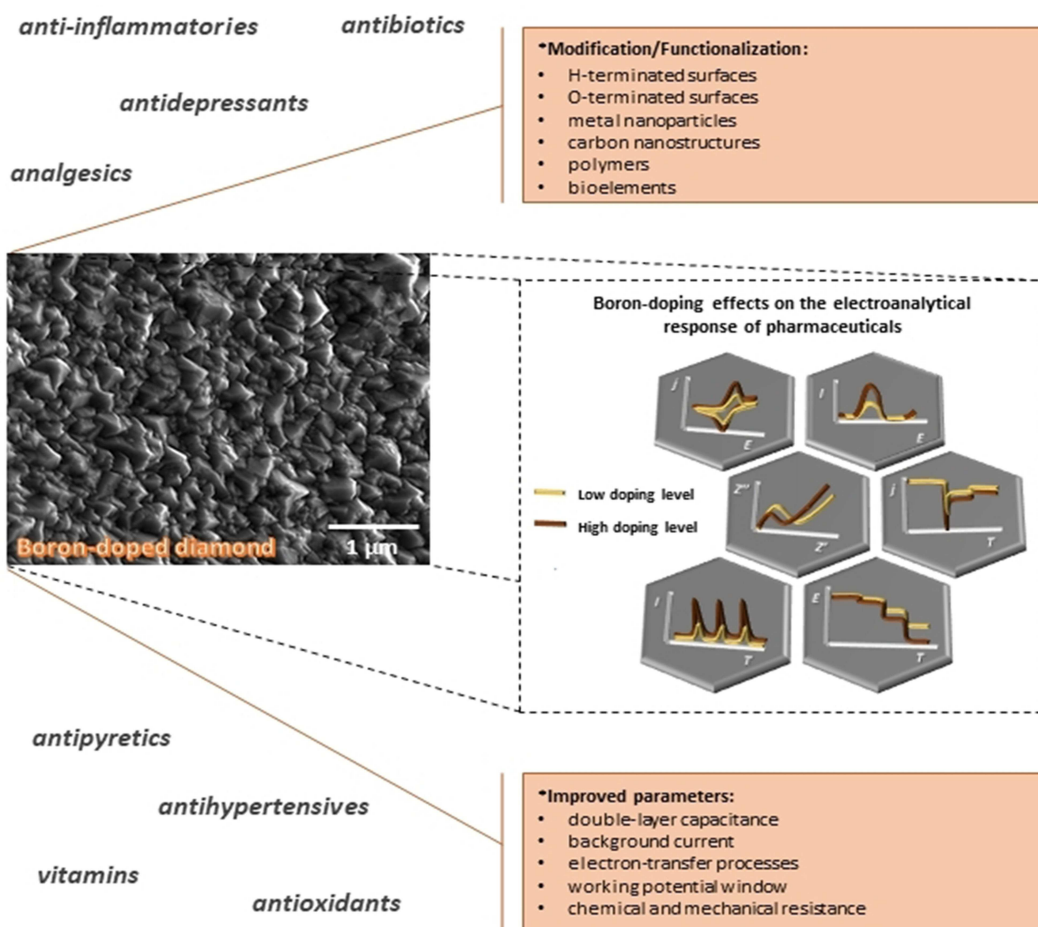


Electroanalysis of Pharmaceuticals on Boron-Doped Diamond Electrodes: A Review

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Boron-doped diamond (BDD) electrodes possess outstanding physical, chemical, and electronic properties and have been successfully, yet in a limited way, explored in the electroanalysis of substances with therapeutic action (analgesics, antipyretics, antibiotics, anti-inflammatories, antihypertensives, antidepressants, vitamins, and others) in diverse milieus (pharmaceutical formulations, urine, serum, whole blood, surface waters, seawaters, groundwater, wastewaters, etc.). Therefore, in this

1. Introduction

Pharmaceuticals are drugs employed in human and veterinary medicines, which are categorized based on their therapeutic action, such as antibiotics, analgesics, anti-inflammatories, antihypertensives, antidepressants, etc. Over the last decades, their worldwide consumption has been extensively augmented due to the recognized benefits in guaranteeing populations' health and in other relevant sectors of our modern society, namely livestock, aquaculture, agriculture, among others. However, beyond the clear positive impacts of their use, scientific evidences have been pointing to the ubiquitous presence of pharmaceutical compounds in the environment.^[1] Therefore, concern has increasingly been raised and great efforts have been made by the scientific community and governmental authorities to restrain the problem and to characterize the sources, fate, exposure levels and potential effects of these contaminants of emerging concern.^[2]

Quantification of pharmaceuticals in biological (urine, serum, whole blood, etc.) and environmental (surface waters, seawaters, sludge, sediments, groundwater, wastewaters, etc.) samples is usually performed by one or a combination of various chromatographic techniques.^[1a] However, the routine and extensive application of these methods is not free of

Review, a broad overview of the available scientific information on recent progress and achievements of the application of bare or modified BDD electrodes to the bioanalytical and environmental detection of pharmaceutical compounds is presented. The main parameters, for example boron concentration, applied operational conditions during pretreatment, chemical and physical structure, and other influential factors on the electroanalytical BDD electrodes performance, are discussed.

disadvantages considering the common usage of organic solvents (being most of them not green solvents) and the typical complex extraction and purification steps needed before analysis.

Additionally, many conventional analytical systems are not miniaturizable or suitable for in vivo real-time studies and, consequently, they do not address how drug kinetics correlates with the target functions over time.^[3]

Electrochemical devices have progressively paved their way as cost-effective routine screening tools, serving as expeditious and complementary methods to the traditional ones. In this context, boron-doped diamond (BDD) electrodes possess remarkable physical, chemical and electronic properties, when compared with the other type of carbon electrodes, and have been successfully explored in electroanalysis of biologically active organic substances in different matrices.^[4] Thus, this study reviews the available scientific information (from 2013 to 2018) about development and applications of bare or modified BDD electrodes to electroanalysis of the most important classes of pharmaceutical compounds (antibiotics, analgesics, anti-inflammatories, antihypertensives, antidepressants and vitamins). The main influential parameters on the electroanalytical BDD electrode performance, namely the boron concentration, the applied potentials during pretreatment, chemical and physical structure, among others, are critically discussed.

2. Overview of the Electrochemical Performance of the BDD Electrode

Intrinsic diamond is a good electrical insulator due to the wide band gap between the valence and conduction bands; 5.47 eV at 300 K.^[5] However, studies have shown that hydrogen termination introduces "surface conductivity" into intrinsic diamond in the presence of water.^[6] On the other hand, highly boron-doped polycrystalline diamond films, fabricated by chemical vapor deposition (CVD) methods, have electrical conductivity equivalent to semi-metallic levels.^[7]

The introduction of boron atoms into the diamond lattice of tetrahedrally bonded carbon atoms imposes a *p*-type doping. The boron atoms insert electron accepting holes owing to its electron deficiency relative to the carbon atom. Usual doping levels are between 10^{18} – 10^{21} atoms cm^{-3} , while the higher doping value gives the approximately 1:100, boron to carbon ratio.^[7] In addition, the conductivity of diamond film increases

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with the doping content due to the increase in boron acceptor states, approximately 0.37 eV above the diamond valence band.

At the highest levels of doping, in the region of 1:100 boron/carbon ratios, films with resistivities lower than 0.1 Ωcm are achievable.^[7b] This conductivity, coupled with the unique attributes of diamond, results in an electrode with several highly desirable properties. The effect of boron concentration on the electrochemical features of BDD electrodes has been widely studied.^[8] Incorporating boron into the diamond lattice at concentrations in excess of $2\text{--}3 \times 10^{20}$ B atoms cm^{-3} results in metallic-like conductivity, while lower doped BDD electrodes have semiconductive character, which strongly affects electrochemical properties of BDD electrodes.^[8b,c,9]

An electrochemical working potential window of around 3.0 V (from -1.0 V to 2.0 V vs SCE) is easily reached for high-

quality BDD films. This is due to the higher overpotential for hydrogen evolution and for oxygen evolution reactions in comparison to other more traditional electrode materials such as gold, platinum and glassy carbon.^[10] This wide potential window allows the investigation of numerous species that are only electroactive at highly anodic or cathodic potentials (mainly for outer sphere redox couples).

Another outstanding feature of BDD electrodes is their low double-layer capacitance along with a low background current, thus resulting in enhanced signal-to-background ratios.^[11] Double-layer capacitance and background voltammetric currents are commonly one order of magnitude lower than the one for glassy carbon electrodes of the same geometric area.^[12] This feature of BDD makes it ideal for use in electroanalysis, because it reduces the detection and/or quantification limits



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that could be reached. The reported low capacitance is due to (i) the low density of states (DOS)^[13] near Fermi level, (ii) the chemical stability of the sp^3 diamond structure and the lack of higher order oxide groups on the electrode surface and (iii) negligible surface processes, *i.e.* surface oxidation and reduction.^[14]

Heavily doped diamond electrodes (doping levels above 4×10^{21} atoms cm^{-3}) exhibit increasing sp^2 carbon impurities at the diamond surface, which increases the background current and decreases the potential window.^[15] However the dimensional stability of these BDD electrodes is similar to typical diamond electrodes, which are much more durable than glassy carbon electrodes and therefore can be used for direct electrolysis applications.^[16] The presence of non-diamond carbon and carboxylic functional groups across the BDD surface can greatly increase the double-layer capacitance of the electrode. Such impurities may be removed by acid washing (*e.g.* potential cycling of the BDD electrode in moderately concentrated (5 mol L^{-1} H_2SO_4 or HNO_3) and re-hydrogenation in hydrogen plasma.^[17]

High quality BDD electrodes not only show a lack of carbon-oxygen functionalities at the surface, but also a resistance to adsorbing species, presumably due to the absence of surface carbonyl functionalities, thus making them highly resistant to electrode fouling.^[12] This property widens BDD electrodes potential applications in the detection of biological species, such as dopamine, which are known to foul significantly at electrode surfaces made from other materials.^[18] Resilience against organic contaminants, coupled with a mechanical and chemical robustness to extreme experimental conditions^[7a,18c,19] makes BDD thin films highly versatile and unique electro-analytical tools.

It is well-known that BDD produced via CVD processes has a hydrogen-termination surface. This surface provides relatively high electron transfer (ET) rates to many redox couples involving a single ET. Hydrogen-terminated diamond electrodes surfaces are free of specifically adsorbed species and carbon-oxygen functionalities. Nevertheless, the electrochemical properties of diamond can be altered by electrochemically oxidizing the BDD surface and introducing carbon-oxygen functionalities.^[20] The BDD surfaces can be oxidized while being boiled in strong acid,^[21] treated by oxygen plasma,^[19c,22] induced by anodic oxidation,^[19c,23] or inadvertently, during electrochemical usage, if used extensively for oxidation processes at potentials higher than 1.0 V ^[24] or still by long-term exposure to air.^[25]

Ferro and coauthors^[26] chemically characterized the surface of an "as-prepared", an electrochemically oxidized and a thermally oxidized BDD electrode. X-ray photoelectron spectroscopy (XPS) revealed that the "as-prepared" doped diamond resulted in a relatively low oxygen-bonded carbon content (mainly alcohols and ethers), while the oxidized electrodes displayed greater carbon-oxygen surface speciation (alcohols, ethers, carbonyls, carboxyl groups and esters). Regarding the stability of the oxygenated groups at the diamond surface, several groups established that these species display an intrinsic stability and that the recovery of the pristine surface is

achievable only by using a hydrogen plasma treatment.^[19c,26–27] However, hydrogen functionalities can be also formed at BDD surfaces by using cathodic polarization in acid media.^[28]

It is known that the analytical performance of BDD electrodes greatly depends on their surface termination. In this sense, Suffredini and coauthors^[28c] carried out cyclic voltammetry (CV) experiments on BDD electrodes in aqueous solutions of $K_4[Fe(CN)_6]$ or ferrocene, to evaluate the effect of electrochemical pre-treatments on these well-known redox systems. These authors showed that, for both systems, markedly quasi reversible CV responses are observed on anodic treated BDD electrodes while the expected reversible behaviors were observed after a cathodic pre-treatment. Therefore, the electrochemical response of BDD electrodes is extremely affected by the kind of pre-treatment applied on their surfaces. The beneficial effect of cathodic pre-treatments at BDD electrodes has been further observed in numerous electroanalytical studies.

In this context, Ivandini and coauthors^[29] studied the electrochemical oxidation of oxalic acid by CV on an as prepared (H-terminated) highly-doped BDD film electrode and after anodic polarization (O-terminated) for 20 min at 3 V (E vs SCE), in a phosphate buffer solution at pH around 2. Additionally, a hydrogen plasma treated (for 20 min) vitreous carbon electrode was used for comparison. The attained results showed the superior performance of H-terminated BDD surfaces for the oxalic acid detection as compared to the O-terminated one. A well-defined oxidation peak was observed only on both H-terminated electrodes, although the current response was low on the vitreous carbon electrode due to its amorphous and complex surface. According to these authors, these results confirm the importance of the superficial termination control of the BDD electrode for the detection of some charged molecules.

Salazar-Banda and coauthors^[25c] reported that the electrochemical response of cathodically treated BDD electrode surfaces changes with time of exposition to air, resulting in a dynamic electrochemical behavior. After a cathodic pretreatment (-3.0 V vs HESS hydrogen electrode prepared in the same solution, for 30 min), the H-terminated BDD electrodes display a progressive decrease on the electron transfer rate for the $Fe(CN)_6^{4-/3-}$ redox couple (seen as a loss of the couple reversibility as a function of time exposed to atmospheric conditions). This dynamic behavior was associated to oxidation of the H-terminated surface by oxygen from the air, contained in the thin layer of water naturally formed on the surface of solids exposed to air.^[30] As a result, the BDD electrode needs to be cathodically pretreated just before the electrochemical experiments are carried out to ensure reproducible results, mainly if the electrode was not used for a long period of time.^[25c]

Later, Salazar-Banda and coauthors,^[31] based on CV and electrochemical impedance spectroscopy data, established the optimum charge density to ensure high electrochemical activity of the BDD surfaces without producing any undesired fouling of the surface. This is because significant physical degradation of BDD surfaces after repeated cathodic polarizations was evidenced. Hence, the optimized cathodic pretreatment that could

be safely used when electrochemical experiments are carried out on BDD electrodes was found to be -9 C cm^{-2} passed at -1 A cm^{-2} .

Therefore, the investigations cited above demonstrated that the electrochemical response of the BDD electrode is affected by the atoms bonded to the carbon on the BDD surface. For electroanalysis applications, the H-terminated BDD surfaces appeared to be more efficient than the O-terminated BDD surfaces.

3. Electroanalysis of Pharmaceuticals

Although the sale of most of the drugs is controlled, the large and routinely use of pharmaceuticals have been promoting increased and cumulative negative impacts in the environment. Bare or modified BDD electrodes have been used as a versatile tool for the quantification of several pharmaceutical compounds (antihypertensive, analgesic and antipyretic drugs, antibiotics, anti-inflammatory drugs, vitamins, antidepressants and others) in different types of samples (pharmaceuticals formulations, urine, tap water, serum, etc.) as it can be observed in Tables 1–2, which summarize the published studies from 2013 to 2018. The reported electroanalytical performances of the BDD electrodes with different boron contents have been mostly assessed by CV, square-wave voltammetry (SWV), differential pulse voltammetry (DPV), batch injection analysis systems with multiple-pulse amperometric (BIA-MPA), batch injection analysis with pulsed amperometric detection (BIA-PAD) and flow injection analysis systems with multiple-pulse amperometric (FIA-MPA) (Tables 1 and 2).

3.1. Antihypertensives

Hydrochlorothiazide (HCTZ) is a thiazide diuretic compound, which increases the renal excretion of water and electrolytes, widely used for the treatment of hypertension and cardiovascular diseases. As a result of its popularity, this pharmaceutical has been extensively studied by different research groups. Santos and coauthors quantified HCTZ and losartan (LOS) by SWV and DPV methodologies.^[4h] LOS is an angiotensin II antagonist; it reduces hypertension by suppressing the effects of angiotensin II of rennin angiotensin-aldosterone system. The authors used Britton-Robinson (BR) buffer solution (pH 9.5) at the BDD electrode (doping level of 8000 ppm). Before the analyses, the surface was anodically pretreated in a $0.5\text{ mol L}^{-1}\text{ H}_2\text{SO}_4$ solution by applying 0.5 A cm^{-2} for 40 s. The calibration curve was linear in the concentration range from 4.0×10^{-6} to $7.4\times 10^{-5}\text{ mol L}^{-1}$ for HCTZ and LOS with SWV and 3.0×10^{-6} to $7.4\times 10^{-5}\text{ mol L}^{-1}$ for HCTZ and LOS with DPV. The detection limit was $1.8\times 10^{-6}\text{ mol L}^{-1}$ for HCTZ and 9.8×10^{-7} for LOS by SWV and $1.2\times 10^{-6}\text{ mol L}^{-1}$ for HCTZ and 9.5×10^{-7} for LOS by DPV. The suggested method was successfully applied in the determination of HCTZ and LOS in pharmaceutical formulations with average recoveries equal to 98% for HCTZ and 102% for LOS. Eisele and coauthors quantified HCTZ and valsartan (VAL) by

SWV methodology.^[4n] VAL is an angiotensin II receptor antagonist. The authors used BR buffer solution (pH 5.0) at the BDD electrode (8000 ppm of boron). Before the analyses, the surface was electrochemically pretreated in a $0.5\text{ mol L}^{-1}\text{ H}_2\text{SO}_4$ solution: first an anodic pretreatment (0.5 A cm^{-2} , 30 s), which was followed by a cathodic one (-0.5 A cm^{-2} , 150 s). The calibration curve was linear in the concentration range from 1.97×10^{-6} to $8.81\times 10^{-5}\text{ mol L}^{-1}$ for HCTZ and 9.88×10^{-6} to $2.20\times 10^{-4}\text{ mol L}^{-1}$ for VAL. The calculated detection limits were $0.639\times 10^{-7}\text{ mol L}^{-1}$ for HCTZ and 9.35×10^{-7} for VAL. The suggested method was applied in dosage formulations. Analysis of authentic samples containing HCTZ and VAL showed no interference from the common additives and excipients. In addition, there are methodologies developed by other research groups for the simultaneous detection of HCTZ with enalapril,^[4ah] metoprolol,^[4bk] ramipril^[4ca] and with more of one pharmaceutical as described by Morais and coauthors that used AML, amiloride hydrochloride and atenolol.^[4cb]

Ferreira Vitoreti and coauthors quantified captopril (CAP) by SWV methodology.^[4o] CAP is the first orally active and specific inhibitor of Angiotensin Converting Enzyme (ACE). It blocks the conversion of angiotensin I to angiotensin II by inhibiting the angiotensin converting enzyme and inactivates. The authors used BR buffer solution (pH 9.0) at the BDD electrode (doping level of 800 ppm). CAP oxidation reveals well-defined irreversible oxidation peaks. The calibration curve was linear in the concentration range from 9.20×10^{-5} to $4.60\times 10^{-4}\text{ mol L}^{-1}$, resulting in a detection limit of $1.65\times 10^{-7}\text{ mol L}^{-1}$. The suggested method was applied in pharmaceutical formulations and the recovery values were in the range 97–98%. Similarly, Gimenes and coauthors quantified HCTZ and CAP by batch-injection analysis with multiple-pulse amperometric methodology.^[4ag] The authors used acetic acid/acetate buffer solution (pH 4.7) at the BDD electrode (doping level of 8000 ppm). Before the use for the first time, the BDD electrode was anodically pretreated by applying 0.01 A for 1000 s in a 0.04 mol L^{-1} BR buffer solution (pH 2.0) and then cathodically pretreated by applying -0.01 A for 1000 s in a $0.1\text{ mol L}^{-1}\text{ H}_2\text{SO}_4$ solution. The calibration curve was made using the concentration range from 2.7×10^{-5} to $8.1\times 10^{-5}\text{ mol L}^{-1}$ for CAP and 1.0×10^{-5} to $3.0\times 10^{-5}\text{ mol L}^{-1}$ for HCTZ. The detection limits determined were $1.4\times 10^{-7}\text{ mol L}^{-1}$ for CAP and 2.7×10^{-7} for HCTZ. The suggested method was applied in pharmaceutical formulations with recovery values in the range 97–110%.

Švorc and coauthors quantified amlodipine (AML) by DPV methodology.^[4z] AML is currently the most frequently used drug for hypertensive patients. It inhibits calcium ions to be transported into vascular smooth muscle and cardiac muscle to protect the target organs. The authors used BR buffer solution (pH 5.0) at the BDD electrode (doping level of 1000 ppm). AML oxidation is irreversible with single and well-shaped peak at a potential of 0.75 V (vs. Ag/AgCl/ 3 mol L^{-1} KCl electrode). The responses were linear in the concentration range from 2×10^{-7} to $6\times 10^{-6}\text{ mol L}^{-1}$, resulting in a detection limit of $7\times 10^{-8}\text{ mol L}^{-1}$. The suggested method was applied in pharmaceutical formulations and urine. The recovery values were in the range of 94% and 106%. Similarly, Mansano and coauthors

Table 1. Review of recent works (2013–2018) concerning electroanalysis of pharmaceuticals on bare or modified boron-doped diamond electrodes.							
Analyte	Class	Boron content [ppm]	Detection technique	Linear range [μM]	Limit of detection [μM]	Real sample	Ref.
Antihypertensives							
hydrochlorothiazide and losartan	antihypertensive	8000	square-wave voltammetry and differential pulse voltammetry	4.0–74 (square wave voltammetry) and 3.0–74 (differential pulse voltammetry)	1.8 (hydrochlorothiazide) and 0.98 (losartan) by square-wave voltammetry and 1.2 (hydrochlorothiazide) and 0.95 (losartan) by differential pulse voltammetry	pharmaceutical formulation	[4 h]
captopril	antihypertensive	800	square-wave voltammetry	92.04–460	0.165	pharmaceutical formulation	[4o]
amlodipine	anti-tumor and anti-diabetic agents as well as HIV protease inhibitor	10000	differential pulse voltammetry	0.2–6	0.07	pharmaceutical formulation and urine	[4z]
hydrochlorothiazide	diuretic and angiotensin ii receptor antagonist; antihypertensive (propranolol) and diuretic (hydrochlorothiazide)	8000	square-wave voltammetry	1.97–88.1 (hydrochlorothiazide) and 9.88–220 (valsartan)	0.639 (hydrochlorothiazide) and 0.935 (valsartan)	pharmaceutical formulation	[4n]
propranolol and hydrochlorothiazide	antihypertensive (propranolol) and diuretic (hydrochlorothiazide)	8000	batch injection analysis with multiple pulse amperometric detection	10–50 (propranolol) and 5.3–26.3 (hydrochlorothiazide)	0.17 (propranolol) and 1.9 (hydrochlorothiazide)	pharmaceutical formulation	[4db]
captopril and hydrochlorothiazide	antihypertensive and diuretic	8000	batch injection analysis with multiple pulse amperometric detection	27–81 (captopril) and 10–30 (hydrochlorothiazide)	0.14 (captopril) and 0.27 (hydrochlorothiazide)	pharmaceutical formulation	[4ag]
amlodipine, hydrochlorothiazide and valsartan	antihypertensive	8000	square-wave voltammetry	0.49–7.2 (amlodipine), 2.9–45 (hydrochlorothiazide) and 9.7–130 (valsartan)	0.23 (amlodipine), 0.75 (hydrochlorothiazide) and 0.62 (valsartan)	pharmaceutical formulation	[4aj]
amlodipine and hydrochlorothiazide	antihypertensive and diuretic	8000	square-wave voltammetry	0.2–9.1 (amlodipine) and 4.0–100 (hydrochlorothiazide)	0.060 (amlodipine) and 2.00 (hydrochlorothiazide)	synthetic urine	[4am]
amlodipine and valsartan	antihypertensive	8000	square-wave voltammetry	0.497–28.6 (amlodipine) and 19.8–280 (valsartan)	0.0764 (amlodipine) and 0.193 (valsartan)	pharmaceutical formulation and urine	[4ai]
hydrochlorothiazide and enalapril	antihypertensive	8000	flow injection analysis systems with multiple-pulse amperometric	0.40–8.00 (hydrochlorothiazide) 0.03–1.00 (enalapril)	0.20 (hydrochlorothiazide) and 0.01(enalapril)	pharmaceutical formulation	[4ah]
nebivolol	antihypertensive	–	square-wave voltammetry	0.25–15	0.032	pharmaceutical formulation	[4ak]
amlodipine and atenolol	antihypertensive	–	batch injection analysis with pulsed amperometric detection	5–25	0.074 (amlodipine) and 0.073 (atenolol)	pharmaceutical formulation	[4bl]
amlodipine and atenolol	antihypertensive	8000	square-wave voltammetry	2.9–33 (amlodipine) and 9.8–190 (atenolol)	0.17 (amlodipine) and 0.22(atenolol)	pharmaceutical formulation	[4bf]
metoprolol and hydrochlorothiazide	antihypertensive	8000	differential pulse voltammetry	1.2–23(metoprolol) and 0.50–19 (hydrochlorothiazide)	0.077 (metoprolol) and 0.38 (hydrochlorothiazide)	pharmaceutical formulation	[4bk]
prazosin	antihypertensive	8000	flow injection analysis systems with multiple-pulse amperometric	2–200	0.5	pharmaceutical formulation	[4ba]
amiloride and furosemide	antihypertensive	8000	batch injection analysis systems with multiple-pulse amperometric	11.27–601.27 (amiloride) and 36.28–483.64 (furosemide)	0.48 (amiloride) and 2.84 (furosemide)	pharmaceutical formulation	[4bh]
febuxostat	treatment of hyperuricemia and chronic gout	–	square-wave voltammetry	0.75–20	0.095	pharmaceutical formulation	[4cc]
ramipril	angiotensin-converting enzyme inhibitor	8000	square-wave voltammetry	1.96–36.7	0.027	pharmaceutical formulation	[4ca]

Table 1. continued

Analyte	Class	Boron content [ppm]	Detection technique	Linear range [μM]	Limit of detection [μM]	Real sample	Ref.
Antihypertensives							
amlodipine and atorvastatin calcium	treat high blood pressure and coronary artery disease	–	square-wave voltammetry	2.0–28 (amlodipine) and 1.0–50 (atorvastatin calcium)	0.028 (amlodipine) and 0.38 (atorvastatin calcium)	pharmaceutical formulation	[4cf]
amlodipine, ami, hydrochlorothiazide and atenolol	antihypertensive	8000	square-wave voltammetry	0.90–31 (amlodipine), 8.7–125 (ami), 29–260 (hydrochlorothiazide) and 11–91 (atenolol)	0.30 (amlodipine), 0.09 (ami), 0.08 (hydrochlorothiazide) and 0.06 (atenolol)	pharmaceutical formulation and tap water	[4cb]
nifedipine and atenolol	treatment of arterial hypertension	–	differential pulse voltammetry	3.98–107 (nifedipine) and 1.99–47.2 (atenolol)	0.612 (nifedipine) and 0.999 (atenolol)	pharmaceutical formulation	[4cu]
pindolol	antihypertensive	8000	differential pulse voltammetry	0.04–10.0	0.026	pharmaceutical formulation, urine and human serum	[4cr]
indapamide	antihypertensive	8000	square-wave voltammetry	0.099–4.3	0.056	pharmaceutical formulation	[4ct]
hydrochloride verapamil	antihypertensive	8000	flow injection analysis systems with multiple-pulse amperometric	0.8–40.0	0.16	pharmaceutical formulation and urine	[4co]
Analgesics and Antipyretics							
codeine	analgesic and antitussive agent	1000	differential pulse voltammetry	0.1–60	0.08	pharmaceutical formulation, urine	[4i]
paracetamol, caffeine, and orphenadrine	analgesic and antipyretic drug (paracetamol), stimulant to the central nervous and cardiovascular system (caffeine) and anti-muscarinic drug (orphenadrine)	–	square-wave voltammetry	0.54–61 (paracetamol) and 0.78–35 (caffeine and orphenadrine)	0.23 (paracetamol), 0.096 (caffeine) and 0.084 (orphenadrine)	pharmaceutical formulation	[4c]
paracetamol and nimesulide	analgesic and antipyretic (paracetamol) and anti-inflammatory (nimesulide)	8000	batch injection analysis systems with multiple-pulse amperometric	330–1654 (paracetamol) and 32–162 (nimesulide)	1.94 (paracetamol) and 0.963 (nimesulide)	pharmaceutical formulation	[4f]
diclofenac and codeine	analgesic (diclofenac) and analgesic (codeine)	8000	batch injection analysis with amperometric detection	10.0–50.0 (diclofenac) and 7.1–35.7 (codeine)	1.1 (diclofenac) and 1.0 for (codeine)	pharmaceutical samples	[4cy]
scopolamine	analgesic, sedative and anticonvulsant	8000	differential pulse voltammetry and square wave voltammetry	1.0–110	0.90 and 0.84	pharmaceutical formulation	[4x]
paracetamol and ascorbic acid	analgesic antipyretic (paracetamol) and vitamin (ascorbic acid)	1000	differential pulse voltammetry	1–200 (paracetamol) and 1–50 (ascorbic acid)	0.17 (paracetamol) and 0.52 (ascorbic acid)	pharmaceutical formulation	[4ac]
paracetamol and ibuprofen	analgesic and antipyretic drug)	8000	differential pulse voltammetry	20–400	7.1 for paracetamol and 3.8 for ibuprofen	pharmaceutical samples	[4dc]
codeine and paracetamol	opioid analgesic and antitussive (codeine) and analgesic and antipyretic (paracetamol)	8000	square-wave voltammetry	0.40–9.6 (codeine) and 0.20–95.8 (paracetamol)	0.00119 (codeine) and 0.018 (paracetamol)	human urine or serum samples	[4ao]
paracetamol and tramadol	analgesic and antipyretic analgesic	8000	flow injection analysis systems with multiple-pulse amperometric	1.0–100 (paracetamol) 0.08–10 (tramadol)	0.03 (paracetamol) and 0.04 (tramadol)	urine and human serum	[4ap]
caffeine, ibuprofen and paracetamol	alkaloid from the xanthine group (caffeine) and analgesic and antipyretic drug (ibuprofen and paracetamol)	8000	flow injection analysis systems with multiple-pulse amperometric	3.0–60.0 (caffeine); 10.0–205.0 (ibuprofen) and 14.0–281.0 (paracetamol)	0.16 (caffeine); 0.13 (ibuprofen) and 0.15 (paracetamol)	pharmaceutical formulation	[4ad]

Table 1. continued

Analyte	Class	Boron content [ppm]	Detection technique	Linear range [μM]	Limit of detection [μM]	Real sample	Ref.
Antihypertensives							
paracetamol, caffeine and aspirin	antipyretic and analgesic (paracetamol), psychoactive substance (caffeine), non-steroidal anti-inflammatory (aspirin)	–	square-wave voltammetry	33.08–827 (paracetamol); 25.75–643.75 (caffeine) and 27.75–693.75 (aspirin)	3.95 (paracetamol); 1.43 (caffeine) and 7.27 (aspirin)	pharmaceutical formulation	[4br]
sulfamethoxazole, trimethoprim and phenazopyridine	synthetic antibiotic (sulfamethoxazole), antibacterial (trimethoprim) and analgesic (phenazopyridine)	8000	batch injection analysis systems with multiple-pulse amperometric	15.8–1260 (sulfamethoxazole); 6.89–138 (trimethoprim) and 4.69–188 (phenazopyridine)	0.79 (sulfamethoxazole); 0.52 (trimethoprim) and 0.23 (phenazopyridine)	pharmaceutical formulation	[4bi]
pterostilbene	anticancer, anti-inflammatory, anti-proliferative, antioxidant, and analgesic agent	–	square-wave adsorptive anodic stripping voltammetry	0.02–3.90	0.004	dietary supplement	[4bq]
dopamine and paracetamol	neurotransmitter (dopamine) and analgesic and antipyretic (paracetamol)	–	differential pulse voltammetry	0.20–100 (dopamine) and 0.5–1000 (paracetamol)	0.054 (dopamine) and 0.14 (paracetamol)	pharmaceutical formulation, human urine, whole blood and serum samples	[4bo]
paracetamol and caffeine	analgesic and antipyretic (paracetamol) and psychoactive substance (caffeine)	1000	differential pulse voltammetry	0.2–500 (paracetamol) and 0.01–20 (caffeine)	0.036 (paracetamol) and 0.0028 (caffeine)	pharmaceutical formulation and energy drink	[4bj]
epinephrine and paracetamol	neurotransmitter (epinephrine) and analgesic and antipyretic (paracetamol)	20000	flow injection analysis systems with amperometric detection	0.60–30.0 (epinephrine) and 0.80–70.0 (paracetamol)	0.50 (epinephrine) and 0.70 (paracetamol)	synthetic serum samples	[4bz]
paracetamol, caffeine and propyphenazone	analgesic and antipyretic (paracetamol and propyphenazone) and psychoactive substance (caffeine)	–	square-wave voltammetry	6.62–331 (paracetamol); 5.15–206 (caffeine) and 4.34–217 (propyphenazone)	0.033 (paracetamol); 0.039 (propyphenazone) and 0.030 (caffeine)	pharmaceutical formulation	[4cj]
paracetamol, caffeine and carisoprodol	analgesic and antipyretic (paracetamol) psychoactive substance (caffeine) and muscle relaxant (carisoprodol)	8000	square-wave voltammetry	2.99–283 (paracetamol), 2.99–84.8 (caffeine) and 19.9–207 (carisoprodol)	0.768 (paracetamol), 0.771 (caffeine) and 3.11 (carisoprodol)	pharmaceutical formulation	[4bv]
paracetamol, caffeine and propyphenazone	analgesic and antipyretic (propyphenazone and paracetamol) and psychoactive substance (caffeine)	–	batch injection analysis systems with multiple-pulse amperometric	66.2–562 (paracetamol), 10.3–82.4 (caffeine) and 21.7–217 (propyphenazone)	0.01 (paracetamol); 0.51 (caffeine) and 1.30 (propyphenazone)	pharmaceutical formulation	[4ck]
paracetamol, aspirin and caffeine	analgesic and antipyretic (paracetamol), nonsteroidal anti-inflammatory (aspirin) and psychoactive substance (caffeine)	8000	batch injection analysis systems with multiple-pulse amperometric	5–520 (paracetamol), 7–660 (aspirin) and 6–140 (caffeine)	1.59 (paracetamol), 1.28 (aspirin) and 0.41 (caffeine)	pharmaceutical formulation	[4cp]
Antibiotics							
ciprofloxacin	antibiotic	8000	batch injection analysis systems with multiple-pulse amperometric	1–100	0.3	pharmaceutical formulation and high and low-fat milk sample	[4v]
erythromycin	antibiotic	1000	square-wave voltammetry	6800–68100	1100	water sample	[4an]
ciprofloxacin	antibiotic	8000	square-wave voltammetry and differential pulse voltammetry	2.50–50.0 (square wave voltammetry) and 0.50–60.0 (differential pulse voltammetry)	2.46 (square wave voltammetry) and 0.44 (differential pulse voltammetry)	synthetic urine	[4af]

Table 1. continued							
Analyte	Class	Boron content [ppm]	Detection technique	Linear range [μM]	Limit of detection [μM]	Real sample	Ref.
Antihypertensives							
sulfamethoxazole and trimethoprim	antibiotic	–	batch injection analysis systems with multiple-pulse amperometric	40–198 (sulfamethoxazole) and 7–35 (trimethoprim)	0.9 (sulfamethoxazole) and 0.6 (trimethoprim)	–	[4al]
ciprofloxacin	antibiotic	–	differential pulse voltammetry	0.005–0.05 and 0.05–10	0.005	wastewater effluent	[4az]
metronidazole	antibiotic and antiparasitic	3500	square-wave voltammetry	0.2–4.2	0.065	injection and human urine samples	[4aw]
n-acetylcysteine and gentamicin sulfate	antioxidant (n-acetylcysteine) and broad-band antibiotic (gentamicin sulfate)	–	differential pulse voltammetry	12.25–300 (n-acetylcysteine) and 0.35 - 86.85 (gentamicin sulfate)	9.35 (n-acetylcysteine) and 2.98 (gentamicin sulfate)	–	[4av]
ciprofloxacin	antibiotic	1000	differential pulse voltammetry	0.74–20	0.60	pharmaceutical formulation and model human urine samples	[4dg]
oxacillin	antibiotic	–	–	50–1000	3.80	pharmaceutical formulation, urine and river water	[4bx]
levofloxacin	antibiotic	–	square-wave voltammetry	10–80.9	2.88	urine and human serum	[4cg]
ciprofloxacin	antibiotic	20000	square-wave voltammetry	0.15–2.11	0.05	human serum	[4ce]
cefalexin	antibiotic	–	differential pulse voltammetry	0.5–700	0.01	river water, human urine and pharmaceutical formulation	[4bw]
Anti-inflammatories							
ibuprofen	anti-inflammatory	around 8000	differential pulse voltammetry	20–400	5	pharmaceutical formulation	[4e]
nimesulide	anti-inflammatory	8000	flow injection analysis with multiple-pulse amperometric	0.20–80	0.081	pharmaceutical samples	[4cz]
diclofenac	anti-inflammatory	8000	square-wave voltammetry	0.49–5.41	0.115	pharmaceutical formulation and synthetic urine	[4r]
phenanthrenequinone dioxime	antimicrobial, anti-HIV, anti-inflammatory and potential anticancer	–	differential pulse voltammetry	0.3–7.0	0.22	blood samples	[4bn]
mesalazine	anti-inflammatory	1000	square-wave voltammetry	2.9–390	0.7	pharmaceutical formulation and human urine	[4 cm]
colchicine	anti-inflammatory	8000	flow injection analysis systems with multiple-pulse amperometric	0.1–500	0.0214	pharmaceutical formulation and urine	[4cq]

Table 1. continued							
Analyte	Class	Boron content [ppm]	Detection technique	Linear range [μM]	Limit of detection [μM]	Real sample	Ref.
Antihypertensives							
piroxicam	anti-inflammatory	8000	square-wave voltammetry	0.5–11	0.16	pharmaceutical formulation, synthetic urine and tap water pharmaceutical formulation and human urine	[4cs]
ibuprofen	anti-inflammatory	8000	differential pulse voltammetry	0.949–66.9	0.41		[4cv]
Vitamins							
α-tocopherol or vitamin E and ubiquinone vitamin B2	lipophilic antioxidant	–	flow injection analysis	0.5–100 (α-tocopherol or vitamin E and ubiquinone)	0.04 (α-tocopherol or vitamin E) and 0.02 (ubiquinone)	–	[4d]
	vitamin	–	square-wave voltammetry	0.02–35	0.0037	pharmaceutical formulation and urine samples.	[4bm]
folic acid	vitamin	–	square-wave voltammetry	0.1–167	0.030	pharmaceutical formulation	[4ay]
pyridoxine	vitamin	1000	differential pulse voltammetry	7–47	3.76	pharmaceutical formulation and urine samples	[4bb]
melatonina and pyridoxine dopamine and pyridoxine	treatment of jet-lag effects (melatonina) and vitamin (pyridoxine)	–	square-wave voltammetry	4.3–430 (melatonina) and 49–850 (pyridoxine)	0.6 (melatonina) and 6.6 (pyridoxine)	dietary supplements	[4bt]
	neurotransmitter (dopamine) and vitamin (pyridoxine)	–	differential pulse voltammetry	0.1–100 and 100–600 (dopamine) and 0.4–100 and 100–800 (pyridoxine)	0.06 (dopamine) and 0.22 (pyridoxine)	human serum	[4by]
ascorbic acid	vitamin	8000	differential pulse voltammetry	5–200	1.1	commercial pharmaceutical preparations	[4 dm]
Antidepressants							
fluoxetine	antidepressant	1000	cyclic voltammetry, square-wave voltammetry, differential pulse voltammetry, and amperometry	0.05–0.5 (cyclic voltammetry, square-wave voltammetry, differential pulse voltammetry) and 0.05–0.4(amperometry)	0.982 (cyclic voltammetry), 0.037 (differential pulse voltammetry), 0.530 (square-wave voltammetry) and 4.680 (amperometry)	tap water	[4b]
amitriptyline	antidepressant	8000	differential pulse voltammetry	1.05–92.60	0.52	pharmaceutical formulation	[4 m]
imipramine	antidepressant	4000	differential pulse voltammetry	1.5–19.4	0.5	pharmaceutical formulation	[4bu]
imipramine	antidepressant	8000	square-wave voltammetry	0.17–2.53	0.0435	pharmaceutical formulation	[4cd]

Table 2. Review of recent works related to electroanalysis of pharmaceuticals for different class on boron-doped diamond electrode.							
Analyte	Class	Boron content [ppm]	Detection technique	Linear range [μM]	Limit of detection [μM]	Real sample	Ref.
levodropropizine	cough suppressant	–	differential pulse voltammetry and square-wave voltammetry	0.2–100 (differential pulse voltammetry and square-wave voltammetry)	0.00102 0.0130	pharmaceutical formulation	[4a]
caffeine and chlorogenic acid	stimulant to the central nervous (caffeine) and antioxidant and antiradical activity (chlorogenic acid)	–	square-wave voltammetry	4.12–28.8 (caffeine) and 5.64–147 (chlorogenic acid)	0.551 (chlorogenic acid) and 1.26 (caffeine)	commercial beverage (instant coffee, cola and energy drink)	[4k]
tryptophan and tyrosine	precursors of neurotransmitters	–	differential pulse voltammetry	5–500	5	–	[4j]
rutin	antioxidant	–	square-wave voltammetry	0.016–0.16	0.0028	dietary supplement	[4 g]
bezafibrate	fibrates	8000	square wave voltammetry	0.1–9.1	0.098	pharmaceutical formulation	[4cw]
hydroquinone	skin-lightening agent.	8000	batch injection analysis with amperometric	10–2000	0.016	pharmaceutical formulation	[4cx]
ambroxol	antioxidant	–	detection square-wave voltammetry	0.05–0.7	0.01	pharmaceutical formulation and spiked human urine sample	[4q]
ketoconazole and ciclopiroxolamine	antifungal agents	–	square-wave voltammetry	0.29–3.13 (ketoconazole) and 25.3–419 (ciclopiroxolamine)	0.0829 (ketoconazole) and 6.66 (ciclopiroxolamine)	pharmaceutical formulation and cosmetic.	[4 t]
n-acetylcysteine	mucolytic agent	ca. 10^{21} cm^{-3}	flow injection analysis amperometry	50–500	0.01	pharmaceutical formulation	[4w]
diphenhydramine and 8-chlorotheophylline	antiemetics	ca. 8000	batch injection analysis with multiple pulse amperometric detection	10–80 (8-chlorotheophylline) and 10–60 (diphenhydramine)	0.11 (8-chlorotheophylline) and 0.15 (diphenhydramine)	pharmaceutical formulation	[4 s]
estrone	hormone	8000	differential pulse voltammetry and square-wave voltammetry	0.20–2.0 (differential pulse voltammetry) and 0.10–2.0 (square-wave voltammetry)	0.20 (differential pulse voltammetry) and 0.10 (square-wave voltammetry)	water matrix	[4 l]
coumarin	polyphenolic compounds	8000	square-wave voltammetry	5–100	1.5	aqueous infusion	[4u]
methamphetamine	amphetamine	–	differential pulse voltammetry	0.07–80	0.05	human urine	[4ab]
yohimbine	indole alkaloid	1000	differential pulse voltammetry	250–90900	130	extract of the primary bark of natural aphrodisiac	[4aa]
17 β -estradiol	steroidal hormones	–	electrochemical impedance spectroscopy	1.0×10^{-8} – 1.0×10^{-3}	5.0×10^{-9}	water sample	[4p]
yohimbine	indole alkaloid	1000	flow injection analysis with amperometric detection	0.3–100	0.15	dietary supplement	[4y]
hydroxychloroquine	antimalarial	8000	square-wave voltammetry	0.1–1.9	0.06	pharmaceutical formulation and synthetic urine samples	[4da]

Table 2. continued

Analyte	Class	Boron content [ppm]	Detection technique	Linear range [μM]	Limit of detection [μM]	Real sample	Ref.
promethazine and codeine	antihistaminic (promethazine) and analgesic (codeine)	8000	batch injection analysis with multiple pulse amperometric detection	17.6–87.9 (promethazine) and 26.7–134 (codeine)	0.225 (promethazine) and 0.451 (codeine)	pharmaceutical samples	[4dd]
nicotine	stimulant	1000	differential pulse voltammetry	0.5–200	0.3	tobacco products and anti-smoking pharmaceuticals w	[4de]
loratadine	antihistaminic	–	square-wave voltammetry	0.98–19.0	0.78	pharmaceutical formulation	[4ae]
methotrexate	antimetabolic agent	1000	differential pulse voltammetry	0.05–25	0.01	pharmaceutical formulation and spiked human urine.	[4aq]
sulfamethoxazole	antimicrobial agents	–	square-wave voltammetry	0.1–100	0.024	surface water samples	[4 au]
zanamivir	antiviral	–	cyclic voltammetry	5–100	1.53 (oxidation) and 1.49 (reduction)	mucin	[4at]
rosuvastatin calcium	antilipidemic activity	8000	square-wave voltammetry	9.39–88.7	1.04	pharmaceutical formulation	[4ar]
trifluoperazine	antipsychotic	1000	differential pulse voltammetry	1.0–37	0.6	human urine sample	[4as]
theophylline	anti-asthmatic	20000	differential pulse voltammetry and square-wave voltammetry	2–380	0.91 (differential pulse voltammetry) and 1.45 (square wave voltammetry)	pharmaceuticals samples and human urine samples	[4df]
dopamine and uric acid	neurotransmitter(dopamine)	–	differential pulse voltammetry	0.30–0.50 (dopamine and uric acid)	0.27 (dopamine) and 2.1(uric acid)	–	[4bd]
5-nitroquinoline	antileishmanial	500–8000	differential pulse voltammetry	0.5–100	0.29	–	[4bp]
ivermectin and levamisole	anthelmintic drugs	8000	amperometry	0.60–50 (ivermectin) and 0.010–5.0 (levamisole)	0.30 (ivermectin) and 0.001 (levamisole)	pharmaceutical formulation and urine sample	[4bc]
furosemide	diuretic	8000	square-wave voltammetry	0.3–13	0.3	pharmaceutical tablets and urine	[4be]
naphazoline and zinc	naphazoline	8000	batch injection analysis - square-wave voltammetry	3.0–21.0	0.04		[4bg]
imatinib	anticancer drug	1000	differential pulse voltammetry	0.03–0.25	0.0063	human urine sample	[4ax]
diphenhydramine, 8-chlorotheophylline and pyridoxine	antihistamine (diphenhydramine), stimulant (chlorotheophyllin) and vitamin (pyridoxine)	8000	batch injection analysis with multiple pulse amperometric detection	10–30 for diphenhydramine and 20–60 for chlorotheophylline and pyridoxine	0.18 for diphenhydramine, 0.19 for chlorotheophylline and 0.54 for pyridoxine	pharmaceuticals samples	[4dh]
bromazepam and alprazolam	benzodiazepines	1000	differential pulse voltammetry	1–100 (bromazepam) and 0.8–100 (alprazolam)	0.31(bromazepam) and 0.64 (alprazolam)	pharmaceutical formulation	[4ch]
tadalafil	used for treating benign prostatic hyperplasia	8000	square-wave voltammetry	0.15–1.28	0.0195	pharmaceutical formulation	[4ci]
vanillin and caffeine	antioxidative and antimicrobial (vanillin) and stimulant for central nervous system (caffeine)	–	square-wave adsorptive anodic stripping voltammetry	6.6–660 (vanillin) and 1.3–520 (caffeine)	1.47 (vanillin) and 0.304 (caffeine)	commercial products (vanilla sugar, foamy instant coffee, and cola)	[4bs]

Table 2. continued

Analyte	Class	Boron content [ppm]	Detection technique	Linear range [μM]	Limit of detection [μM]	Real sample	Ref.
colchicine	treat gout.	–	differential pulse voltammetry	1–100	0.26	pharmaceutical formulation and human serum sample	[4cl]
flutamide	treatment of advanced prostate cancer.	1000	square-wave voltammetry	0.99–35.5	0.21	pharmaceutical formulation, water and urine	[4cn]
warfarin	blood anticoagulant	8000	batch injection analysis with multiple pulse amperometric detection	2–200	0.10	pharmaceutical formulations	[4di]
8-chlorotheophylline, caffeine, and diphenhydramine cocaine	stimulant (chlorotheophyllin and caffeine) and antihistamine (diphenhydramine) anesthetic	8000	batch injection analysis with multiple pulse amperometric detection	10–100 (8-chlorotheophylline), 10–140 (caffeine) and 10–100 (diphenhydramine)	0.31 (8-chlorotheophylline), 0.49 (caffeine), and 0.76 (diphenhydramine)	pharmaceutical formulations	[4dk]
		8000	batch-injection analysis system with square-wave voltammetric differential pulse voltammetry	20–99	0.89	seized cocaine samples	[4dl]
bromazepam and alprazolam	anticonvulsant, hypnotic, sedative and muscle-relaxant effects	1000	differential pulse voltammetry	1–100 (bromazepam) and 0.8–100 (alprazolam)	0.31 (bromazepam) and 0.64 (alprazolam)	commercial pharmaceutical preparations	[4dn]
5-o-caffeoylquinic acid, vanillin and caffeine	5-o-caffeoylquinic acid exhibit laxative effect, vanillin is a flavoring additive and caffeine a stimulant	–	square-wave adsorptive stripping voltammetry	2.8–1700 (5-O-caffeoylquinic acid), 3.3–3300 (vanillin), and 0.52–2100 (caffeine)	0.40 (5-O-caffeoylquinic acid), 0.38 (vanillin)	commercial samples	[4do]
cetirizine	antihistamines	1000	differential pulse voltammetry	0.067–0.54	0.016	pharmaceutical samples and urine	[4dp]
oxcarbazepine	anticonvulsant	8000	flow injection analysis system coupled to multiple-pulse amperometric detection	2.0–80.0	0.42	pharmaceutical samples and urine	[4dq]
pheniramine or chlorpheniramine associated with naphazoline dopamine and cysteamine	antihistamines	8000	batch-injection analysis system with multiple pulse amperometric	16–160 (chlorpheniramine and pheniramine) and 2–15 (naphazoline)	0.64 (pheniramine), 0.47 (chlorpheniramine) and 0.11 (naphazoline)	pharmaceutical samples	[4dr]
	neurotransmitter (dopamine) and thiol drug used for the treatment of cystinosis (cysteamine)	8000	flow injection analysis system coupled to multiple-pulse amperometric detection	0.50–1300 (dopamine) and 0.5–1500 (cysteamine)	0.011 (dopamine) and 0.013 (cysteamine)	serum and water river samples	[4du]
benzocaine	anesthetic	2500	differential pulse voltammetry	0.1–400	0.080	commercial pharmaceuticals and model human urine samples	[4ds]

using different SWV methodologies to simultaneous detection of: AML and VAL^[4ai] or AML, VAL and HCTZ^[4aj] and Pereira Silva and coauthors quantified HCTZ and AML also using SWV methodology.^[4am] In addition, there are methodologies developed by other research groups for the simultaneous detection of AML with atenolol^[4bf,bl] and with atorvastatin.^[4cf]

As both propranolol and hydrochlorothiazide are used simultaneously for the treatment of hypertension, Guimenes and coauthors developed a method for their simultaneous determination.^[4db] Prior the first use, the BDD (8000 ppm) electrode was anodically pretreated by applying 0.01 A for 1000 s in a 0.04 mol L⁻¹ BR buffer solution (pH 2.0) and then cathodically pretreated by applying -0.01 A for 1000 s in 0.1 mol L⁻¹ H₂SO₄ medium. For the simultaneous detection, the linear range obtained were 10.0–50.0 × 10⁻⁶ mol L⁻¹ for propranolol and 5.3–26.3 × 10⁻⁶ mol L⁻¹ for hydrochlorothiazide with detection limits of 1.7 × 10⁻⁷ and 1.9 × 10⁻⁶ for propranolol and hydrochlorothiazide, respectively. The proposed method presented recovery of 104 ± 6 % for propranolol and 98 ± 1 % for hydrochlorothiazide in pharmaceutical formulations.

Nigović and coauthors quantified nebivolol by SWV methodology.^[4ak] Nebivolol is a novel beta-blocker with a greater degree of selectivity for beta(1)-adrenergic receptors than other agents in this class. The authors used BR buffer solution (pH 8.0) at the BDD electrode (doping level of 1000 ppm). The net SWV response at 1.31 V related to the oxidation of nebivolol was obtained. The linear calibration curve (in the range 2.5 × 10⁻⁷–1.5 × 10⁻⁵ mol L⁻¹) used gave a detection limit of 3.2 × 10⁻⁸ mol L⁻¹. The suggested method was applied in pharmaceutical formulation and the recovery values were in the range 99–100 %.

Guedes and coauthors quantified prazosin by flow injection analysis with multiple-pulse amperometric detection.^[4ba] Prazosin acts as a potent and selective antagonist of α₁ receptors, promoting decrease in peripheral vascular resistance and venous return to the heart, which consequently leads to its therapeutic effect in the treatment of hypertension. The authors used phosphate buffer (pH 4.0) at the BDD electrode (doping level of 8000 ppm). A detection limit of 0.5 × 10⁻⁶ mol L⁻¹ was determined using the calibration curve in the concentration range from 2 × 10⁻⁶ to 2 × 10⁻⁴ mol L⁻¹. The suggested method was applied in pharmaceutical formulations and human urine with recovery values were in the range 98–100 %. Pereira and coauthors quantified amiloride and furosemide by batch injection analysis system with multiple pulse amperometric detection methodology.^[4bh] Amiloride hydrochloride (AMD) and furosemide (FMD) are diuretics used in therapeutic indications, such as arterial hypertension, cardiac insufficiency and hepatic cirrhosis. The authors used 0.1 mol L⁻¹ borate buffer (pH 10.0) at the BDD electrode (doping level of 8000 ppm). The calibration curve was linear in the concentration range from 3.0 to 160.0 mg L⁻¹ for AMD and 12.0 to 160.0 mg L⁻¹ for FMD. The detection limit was 0.13 mg L⁻¹ for AMD and 0.94 mg L⁻¹ for FMD. The suggested method was applied in pharmaceutical samples.

Scremin and coauthors quantified nifedipine and atenolol by SWV methodology.^[4cu] The authors used TRIS buffer solution

(pH 8.0) at the BDD electrode. The calibration curve was linear in the concentration range from 3.98 × 10⁻⁶ to 1.07 × 10⁻⁴ mol L⁻¹ for nifedipine and 1.99 × 10⁻⁶ to 4.72 × 10⁻⁵ mol L⁻¹ for atenolol. The detection limit was equal to 6.12 × 10⁻⁷ mol L⁻¹ for nifedipine and 0.999 × 10⁻⁶ for atenolol. The suggested method was applied in dosage forms.

Pereira and coauthors quantified pindolol (PND) by DPV methodology.^[4cr] PND is an antihypertensive agent indicated for patients in the treatment of angina, hypertension and cardiac arrhythmias; including pregnant women, because it is not teratogenic. The authors used 0.2 mol L⁻¹ phosphate buffer solution (pH 6.0) at the BDD electrode (doping level of 800 ppm). A linear response was reported over the concentration range from 4 × 10⁻⁸ to 1.0 × 10⁻⁵ mol L⁻¹, with a corresponding detection limit of 2.6 × 10⁻⁸ mol L⁻¹. The suggested method was applied pharmaceutical formulation, urine and human serum and the recovery values were in the range 92–97 %.

Rossi Salamanca-Neto and coauthors quantified indapamide hydrochloride (IND) by SWV methodology.^[4ct] IND is an antihypertensive drug classified as which has the function of reducing blood pressure a diuretic, in patients with mild to moderate disease. The authors used 0.01 mol L⁻¹ H₂SO₄ at the BDD electrode (doping level of 800 ppm). The calibration curve was linear in the concentration range from 9.9 × 10⁻⁸ to 4.3 × 10⁻⁶ mol L⁻¹, while the detection limit was 5.6 × 10⁻⁸ mol L⁻¹. The method was applied to commercial tablets, and the obtained results were statistically similar to those obtained by a spectrophotometric method.

Barbosa Lima and coauthors quantified verapamil hydrochloride (VP) by flow injection analysis system with multiple pulse amperometric detection.^[4c] VP is used to treat high blood pressure and ischemia (with and without angina) in humans. The authors used 0.1 mol L⁻¹ sulfuric acid at the BDD electrode (doping level of 8000 ppm). VP oxidation showed three merged oxidation peaks at around 1.4 V and upon reverse scan, one reduction peak at 0.0 V (vs. Ag/AgCl). By using the calibration curve (linear from 8 × 10⁻⁷ to 4.0 × 10⁻⁵ mol L⁻¹) the calculated detection limit was 1.6 × 10⁻⁷ mol L⁻¹. The suggested method was applied in urine and pharmaceutical formulations and the recovery values were in the range 99–103 %.

3.2. Analgesics

Codeine is an analgesic and antitussive agent which belongs to the family of opiates naturally found in the poppy plant, was quantified by Švorc and coauthors using DPV methodology.^[4i] The authors used BR buffer solution at pH 7.0 on BDD electrode (doping level of 1000 ppm). Codeine provided a single well-defined oxidation peak at 1.0 V vs. Ag/AgCl. The detection limit of 8 × 10⁻⁸ mol L⁻¹ was calculated and the calibration curve was linear in the range 1 × 10⁻⁷ to 6.0 × 10⁻⁵ mol L⁻¹. The method was applied in the determination of codeine in real samples including pharmaceutical tablets and human urine with results similar to those declared by manufacturer and obtained by reference high-performance liquid chromatography (HPLC)

method, respectively. Santos and coauthors quantified codeine and paracetamol (PAR) simultaneously by SWV methodology.^[4a] The authors used 0.2 mol L^{-1} acetate buffer solution at pH 4.0 on BDD electrode (doping level of 8000 ppm). The surface electrode was electrochemically pretreated in a $0.5 \text{ mol L}^{-1} \text{ H}_2\text{SO}_4$ solution as follows: anodically, by applying 40 mA cm^{-2} for 30 s, or cathodically, by applying -40 mA cm^{-2} for 180 s (the cathodic pretreatment was always preceded by an anodic pretreatment). The calibration curve was linear in the concentration range from 4×10^{-7} to $9.6 \times 10^{-6} \text{ mol L}^{-1}$ for codeine and 2×10^{-7} to $9.6 \times 10^{-5} \text{ mol L}^{-1}$ for PAR. Hence, the detection limit values were $1.1 \times 10^{-9} \text{ mol L}^{-1}$ for codeine and 1.8×10^{-8} for PAR. The proposed methodology was applied in the simultaneous determination of PAR and codeine in pharmaceutical tablets, with results similar (at 98% confidence level) to those obtained using a reference HPLC method. Additionally, adequate results were obtained when concentrations of PAR and codeine were determined in human urine or serum samples by addition-recovery.

Scopolamine is a tropane alkaloid drug with analgesic, sedative and anticonvulsant properties was quantified by Santos and coauthors using SWV methodology.^[4x] Prior to the experiments, the BDD electrode (doping level of 8000 ppm) was electrochemically pretreated in a $0.50 \text{ mol L}^{-1} \text{ H}_2\text{SO}_4$ solution, either anodically by applying 0.5 A cm^{-2} , during 30 s, or cathodically by applying -0.5 A cm^{-2} , during 120 s. CV studies indicated that the oxidation of scopolamine was irreversible at a peak potential of 1.59 V vs. Ag/AgCl ($3.0 \text{ mol L}^{-1} \text{ KCl}$) in a 0.50 mol L^{-1} sulfuric acid solution. The calibration curve was linear in the range 1.0×10^{-6} – $1.1 \times 10^{-4} \text{ mol L}^{-1}$ and the detection limit was $8.4 \times 10^{-7} \text{ mol L}^{-1}$. The method was successfully applied to the determination of scopolamine in pharmaceutical formulations with minimum sample preparation.

Sulfamethoxazole (SMX) is a synthetic antibiotic derived from sulfanilic acid that act as bacteriostatic and has been used for the treatment of bacterial infections, including urinary tract infections, pneumonia, chronic bronchitis, meningococcal meningitis and toxoplasmosis, trimethoprim (TMP) is an antibacterial drug commonly used in the prophylactic treatment of urinary, intestinal and respiratory infections and phenazopyridine hydrochloride (FZP) is a heterocyclic aromatic azo compound with analgesic characteristics. It is commonly used to reduce discomforts related to urinary tract infections (prostatitis, urethritis, cystitis, etc.) or irritations caused by infections, traumas, surgeries, endoscopic procedures, or the passage of sounds or catheters all of these compounds were quantified by Pereira and coauthors using a batch injection analysis with multiple pulse amperometric detection.^[4bi] For the electro-analytical determinations, the authors used a mixture of phosphate buffer (0.05 mol L^{-1} , pH 7.0) and methanol (70:30; v/v). The BDD electrode (doping level of 8000 ppm) was anodically pretreated by applying 0.01 A for 1000 s in 0.04 mol L^{-1} BR buffer solution and then cathodically pretreated by applying -0.01 A for 1000 s in a $0.1 \text{ mol L}^{-1} \text{ H}_2\text{SO}_4$ solution. The calibration curves were constructed from 4 mg L^{-1} to 320 mg L^{-1} , from 2 mg L^{-1} to 40 mg L^{-1} and from 1 mg L^{-1} to 40 mg L^{-1} for SMX, TMP and FZP, respectively. The detection

limits calculated for SMX, TMP and FZP were 0.20, 0.15 and 0.05 mg L^{-1} , respectively. The suggested methodology was successfully applied in pharmaceutical samples with recovery range of 94–102%, 95–104% and 96–104% for SMX, TMP and FZP, respectively. Pterostilbene is a natural dimethylether analogue of resveratrol, it has also been reported that pterostilbene has resveratrol-like health benefits as an anti-cancer, anti-inflammatory, anti-proliferative, antioxidant, and analgesic agent was quantified by Yiğit and coauthors using a adsorptive anodic stripping voltammetry methodology.^[4bq] The authors used $0.1 \text{ mol L}^{-1} \text{ HNO}_3$ solution containing $2 \times 10^{-4} \text{ mol L}^{-1}$ of cetyltrimethylammonium bromide on BDD electrode (doping level of 1000 ppm). Before the use, BDD electrodes were submitted to anodic and cathodic pretreatment procedures consisted of the polarization at 1.4 V and -1.4 V , respectively in $0.5 \text{ mol L}^{-1} \text{ H}_2\text{SO}_4$ for 180 s. The detection limit was $4.3 \times 10^{-9} \text{ mol L}^{-1}$ and the calibration curve was linear from 2×10^{-8} to $3.9 \times 10^{-6} \text{ mol L}^{-1}$. The proposed method was successfully applied to measure the concentration of pterostilbene in the commercial dietary supplements, with results similar to those obtained using a HPLC method at 95% confidence level.

Among the analgesic, PAR was studied by different research groups for simultaneous detection with other pharmaceuticals. PAR is an analgesic and antipyretic drug for relief of pain and fever reduction. Eisele and coauthors developed a SWV methodology for PAR detection with orphenadrine (ORPH), which is an antimuscarinic drug. It acts in the central nervous system and caffeine (CAF) acts as stimulant to the central nervous and cardiovascular systems. It increases the effectiveness of analgesic therapy.^[4c] Before the use, surface electrodes were anodically pretreated by setting 0.5 A cm^{-2} A during 30 s in $0.50 \text{ mol L}^{-1} \text{ H}_2\text{SO}_4$ followed by cathodic pretreatment at -0.5 A cm^{-2} during 150 s in the same solution. The calibration curve was linear to PAR, CAF, and ORPH in the concentration ranges 5.4×10^{-7} to $6.1 \times 10^{-5} \text{ mol L}^{-1}$, 7.8×10^{-7} to $3.5 \times 10^{-5} \text{ mol L}^{-1}$, and 7.8×10^{-7} to $3.5 \times 10^{-5} \text{ mol L}^{-1}$, respectively, with detection limits of $2.3 \times 10^{-7} \text{ mol L}^{-1}$, $9.6 \times 10^{-8} \text{ mol L}^{-1}$, and $8.4 \times 10^{-8} \text{ mol L}^{-1}$, respectively. The suggested methodology was applied to determine these analytes in pharmaceutical formulations yielding good average recoveries, ranging from 93% to 104% for PAR, from 95.0% to 107% for CAF, and from 95% to 103% for ORPH. These data indicate that the proposed method does not suffer from any significant effects of matrix interference. Pereira and coauthors developed a batch injection analysis with amperometric detection methodology for PAR and nimesulide (NIM) detection.^[4f] NIM is a widely used drug due to its good analgesic, anti-inflammatory and antipyretic properties. Prior the use, the BDD electrode (doping level of 8000 ppm) was anodically pretreated by applying 0.01 A for 1000 s in 0.04 mol L^{-1} BR buffer solution and then cathodically pretreated by applying -0.01 A for 1000 s in a $0.1 \text{ mol L}^{-1} \text{ H}_2\text{SO}_4$ solution. The authors used a mixture of $0.1 \text{ mol L}^{-1} \text{ H}_2\text{SO}_4$ in water and ethanol (70:30 v/v) for the analytical determinations. The calibration curve was linear in the concentration range from 3.30×10^{-4} to $1.66 \times 10^{-3} \text{ mol L}^{-1}$ for PAR and 3.2×10^{-5} to $1.6 \times 10^{-4} \text{ mol L}^{-1}$ for NIM. Therefore, detection limits of $1.9 \times$

$10^{-6} \text{ mol L}^{-1}$ for PAR and 9.63×10^{-5} for NIM were determined. The suggested method was successfully applied in the determination of PQD in blood samples with satisfactory recovery (97–103 %) and similar results (at a 95 % confidence level) to those obtained by liquid chromatography.

The administration of diclofenac (antero-steroid, antipyretic, analgesic and anti-inflammatory drug) combined with codeine, which is an opioid-derived analgesic, has recently been used to reduce opioid requirements. Gimenes and coauthors^[4cy] developed a method based on batch injection analysis with amperometric detection for their simultaneous determination in pharmaceutical samples. Before the first use, the BDD (8000 ppm) electrode was anodically pretreated by applying 0.01 A for 1000 s in a 0.04 mol L^{-1} BR buffer solution (pH = 2.0) and then cathodically pretreated by applying -0.01 A for 1000 s in a $0.1 \text{ mol L}^{-1} \text{ H}_2\text{SO}_4$. The linear range obtained for simultaneous detection were 1.0×10^{-5} to $5.0 \times 10^{-5} \text{ mol L}^{-1}$ for diclofenac and 7.1×10^{-6} to $3.6 \times 10^{-5} \text{ mol L}^{-1}$ for codeine with detection limits of 1.1×10^{-6} and 1.0×10^{-6} for diclofenac and codeine, respectively. The developed method had recovery values of 94–102 % for diclofenac and 99–115 % for codeine in pharmaceutical formulations.

Tysczuk-Rotko and coauthors quantified by a DPV methodology PAR and ascorbic acid (AA), which plays a key role in the formation and maintenance of collagen and is a powerful antioxidant that reacts with reactive oxygen species or free radicals.^[4ac] The authors used 0.1 mol L^{-1} acetate buffer (pH 6.0) at the BDD electrode (doping level of 1000 ppm) modified with Nafion® and lead films in order to the sensitivity of the stripping responses is increased and the separation of paracetamol and ascorbic acid signals is improved due to the modification of the BDD surface by the lead layer. The calibration curve was linear in the concentration range from 5×10^{-7} to $2.0 \times 10^{-4} \text{ mol L}^{-1}$ for PAR and 1×10^{-6} to $5.0 \times 10^{-4} \text{ mol L}^{-1}$ for AA. Detection limits of $1.7 \times 10^{-7} \text{ mol L}^{-1}$ for PAR and 5.2×10^{-7} for AA were estimated. The suggested method was successfully applied in the determination of PAR and AA in commercially available pharmaceutical formulations and the method was validated by high performance liquid chromatography coupled with diode array detector.

Lima and coauthors developed a simple and low cost method for the simultaneous determination of paracetamol and ibuprofen in pharmaceutical formulations by DPV using BDD electrodes.^[4dc] A $0.1 \text{ mol L}^{-1} \text{ H}_2\text{SO}_4$ solution with 10 % (v/v) ethanol was used as supporting electrolyte and prior the experiments the BDD electrode was anodically pretreated in a $0.5 \text{ mol L}^{-1} \text{ H}_2\text{SO}_4$ by applying 0.01 A for 60 s. The cathodic pretreatment was carried out by applying -0.01 A for 120 s in the same solution. For simultaneous detection, the linear ranges obtained were 2×10^{-5} to $4.0 \times 10^{-4} \text{ mol L}^{-1}$ for paracetamol and ibuprofen with detection limits equal to 7.1×10^{-6} and $3.8 \times 10^{-6} \text{ mol L}^{-1}$ for paracetamol and ibuprofen, respectively.

Santos and coauthors quantified PAR and tramadol (TRA) by flow injection analysis with multiple pulse amperometric detection.^[4ap] Tramadol is applied for treatment of moderate surgical pain, surgical pain in children, cancer pain control, obstetric pain and chronic pain. The authors used $0.05 \text{ mol L}^{-1} \text{ H}_2\text{SO}_4$ at the BDD electrode (doping level of 8000 ppm). Before

the analyses, the BDD electrode was anodically or cathodically pretreated in a $0.5 \text{ mol L}^{-1} \text{ H}_2\text{SO}_4$ by applying 0.04 A cm^{-2} or -0.04 A cm^{-2} during 30 s or 180 s, respectively. The calibration curve was linear in the concentration range from 1.0×10^{-6} to $1.0 \times 10^{-4} \text{ mol L}^{-1}$ for PAR and 8.0×10^{-8} to $1.0 \times 10^{-5} \text{ mol L}^{-1}$ for TRA. Detection limits as low as $3.0 \times 10^{-8} \text{ mol L}^{-1}$ for PAR and 4.0×10^{-8} for TRA were attained using the cathodically pretreated electrode. Moreover, the suggested method was successfully applied in the determination of PAR and TRA in urine and human serum with satisfactory recovery (91–105 %).

Chaves and coauthors developed a flow-injection analysis with multiple-pulse amperometric methodology for PAR, CAF and IB detection.^[4ad] The authors used a $0.1 \text{ mol L}^{-1} \text{ HNO}_3$ with 5 % (v/v) ethanol on BDD electrode (doping level of 8000 ppm). Prior to the measurements, the surface electrode was anodically pretreated in $0.5 \text{ mol L}^{-1} \text{ H}_2\text{SO}_4$ by applying 0.01 A for 60 s. The cathodic pretreatment was carried out by applying -0.01 A for 120 s using the same solution. The calibration curves were made in the following concentration ranges: 3×10^{-6} – $6.0 \times 10^{-5} \text{ mol L}^{-1}$ for CAF, 1.0×10^{-5} – $2.1 \times 10^{-4} \text{ mol L}^{-1}$ for IB, and 14×10^{-6} – $281 \times 10^{-6} \text{ mol L}^{-1}$ for PAR. The detection limits calculated were $1.6 \times 10^{-7} \text{ mol L}^{-1}$ for CAF, $1.3 \times 10^{-7} \text{ mol L}^{-1}$ for IB and 1.5×10^{-7} for PAR. The suggested method was successfully applied in the determination of CAF, IB and PAR in pharmaceutical samples with recovery range of 99–101 %, 103–109 % and 98–106 % for PAR, CAF and IB, respectively.

Yigit and coauthors quantified PAR, CAF and Aspirin (ASA) by SWV methodology.^[4br] The authors used phosphate buffer at pH 2.5 on the BDD electrode. Before the analyses, the surface electrode was anodically or cathodically pretreated in a $0.5 \text{ mol L}^{-1} \text{ H}_2\text{SO}_4$ by applying 1.8 V or -1.8 V for 180 s, respectively. 3.95×10^{-6} , 1.42×10^{-6} , and $7.28 \times 10^{-6} \text{ mol L}^{-1}$ were the detection limits calculated for PAR, CAF, and ASA, respectively. The calibration curves used were linear for all analytes in the range 5–125 $\mu\text{g mL}^{-1}$ (corresponding to 3.31×10^{-5} to $8.27 \times 10^{-4} \text{ mol L}^{-1}$ for PAR, 2.57×10^{-5} to $6.44 \times 10^{-4} \text{ mol L}^{-1}$ for CAF and 2.78×10^{-5} to $6.94 \times 10^{-4} \text{ mol L}^{-1}$ for ASA). The suggested method was successfully applied in the determination of PAR, CAF and ASA in pharmaceutical formulations with recovery ranging from 98 % to 108 % for PAR, 92 % to 104 % for CAF, and 92 % to 98 % for ASA. Tysczuk-Rotko and coauthors developed a DPV methodology for PAR and dopamine (DA).^[4b] DA is an important catecholamine neurotransmitter which plays a significant role in the proper functioning of the brain. The authors used 0.1 mol L^{-1} ammonium buffer solution (pH 8.3), 0.02 mol L^{-1} potassium sodium tartrate and $1.0 \times 10^{-5} \text{ Pb(II)}$ on a BDD electrode modified with Nafion® and lead films. The use of this electrode resolved the overlapped voltammetric waves of DA and PA into well-defined peaks with peak to peak separation of about 320 mV. The calibration curves were made in the ranges: 2.0×10^{-7} – $1.0 \times 10^{-4} \text{ mol L}^{-1}$ for DA and 5×10^{-7} – $1.0 \times 10^{-3} \text{ mol L}^{-1}$ for PAR. Consequently, the detection limits were $5.4 \times 10^{-8} \text{ mol L}^{-1}$ for DA and $1.4 \times 10^{-7} \text{ mol L}^{-1}$ for PAR. The suggested method was applied in the determination of DA and PAR in commercial pharmaceuticals as well as in human urine, whole blood and serum samples directly without any separation steps.

Sadok and coauthors developed a DPV methodology for PAR and CAF.^[4bj] The authors used a 0.1 molL⁻¹ H₂SO₄ solution containing metal ions on a BDD electrode modified with bismuth particles Nafion® covered to improve the oxidation peak currents of PAR and CAF. The detection limits of 3.6 × 10⁻⁸ molL⁻¹ for PAR and 2.8 × 10⁻⁹ molL⁻¹ for CAF were determined using calibration curve in the following ranges: 2.0 × 10⁻⁷–5.0 × 10⁻⁴ molL⁻¹ for PAR and 1 × 10⁻⁸–2.0 × 10⁻⁵ molL⁻¹ for CAF. The proposed methodology was successfully applied in the determination of PAR and CAF in commercial pharmaceuticals as well as in energy drinks.

Lourenção and coauthors developed a flow-injection analysis coupled to amperometric detection systems methodology for PAR and epinephrine (EP).^[4bz] The authors used 0.2 molL⁻¹ phosphate buffer (pH 7.0) solution on porous boron-doped diamond electrode (doping level of 20000 ppm). The calibration curve used were in the range from 6.0 × 10⁻⁷ to 3.0 × 10⁻⁵ molL⁻¹ for EP and 8.0 × 10⁻⁷ to 7.0 × 10⁻⁵ molL⁻¹ for PAR. The detection limits were determined as 5.0 × 10⁻⁷ molL⁻¹ for EP and 7.0 × 10⁻⁷ molL⁻¹ for PAR. The developed methodology was applied in the determination of EP and PAR in serum samples with satisfactory recovery (101–110%).

Moreover, different research groups developed detection and quantification methodologies for the simultaneous determination of PAR, CAF and some other pharmaceutical as propyphenazone,^[4cj,ck] carisoprodol^[4bv] and acetylsalicylic acid.^[4cp]

3.3. Antibiotics

Among the antibiotics, ciprofloxacin (CPX) was studied by different research groups. Montes and coauthors proposed a methodology based in batch injection analysis with amperometric detection.^[4v] The authors used BR buffer solution (pH 10.0) on BDD electrode (doping level of 8000 ppm). Before the use, the surface electrode was cathodically pretreated by applying -0.01 A for 1000 s in a 0.1 molL⁻¹ H₂SO₄ solution. The detection limit of 3 × 10⁻⁷ molL⁻¹ was calculated by using a calibration curve with linearity in the range from 1 × 10⁻⁶ to 1.0 × 10⁻⁴ molL⁻¹. The suggested method was successfully applied in the determination of CPX in pharmaceutical formulations and milk samples with satisfactory recovery (approximately 96% for both samples). In the methodology developed by Garbellini and coauthors was used SWV and DPV.^[4af] The authors used BR buffer solution (pH 7.0) on BDD electrode (doping level of 8000 ppm). Before the use, BDD electrodes were anodically pretreated by setting 0.5 Acm⁻² for 10 s, while the cathodic pretreatment was carried out at 0.5 and -0.5 Acm⁻² for 5 and 180 s, respectively, both in a 0.5 molL⁻¹ H₂SO₄ solution. In CV measurements, CPX electrooxidation was an irreversible process controlled by diffusion of the analyte to the electrode surface. The calibration curve was linear in the concentration range from 2.5 × 10⁻⁶ to 5.0 × 10⁻⁵ molL⁻¹ for SWV and 5 × 10⁻⁷ to 6.0 × 10⁻⁵ molL⁻¹ for DPV. The detection limit determined was 2.46 × 10⁻⁶ molL⁻¹ for SWV and 4.4 × 10⁻⁷ molL⁻¹ for DPV. Moreover, the CPX was successfully

determined in synthetic urine samples by DPV with satisfactory recovery (99–101%). The authors employed SWV to evaluate the interaction between CPX and double-stranded dsDNA (calf thymus in aqueous solution).

In the methodology developed by Gayen and coauthors, DPV and a modified BDD electrode were used for CFX determination.^[4az] The authors used 1 molL⁻¹ KH₂PO₄ (pH 4.5) electrolyte. The modified BDD electrode was prepared by depositing a layer of multiwalled carbon nanotubes (MWCNTs) dispersed in a porous Nafion® film. The porous-Nafion®-MWCNT/BDD electrode enhanced detection of CFX due to selective adsorption, which was accomplished by a combination of electrostatic attraction at -SO₃⁻ sites in the porous Nafion® film and the formation of charge assisted hydrogen bonding between CFX and -COOH MWCNT surface functional groups. In contrast, the bare BDD electrode was inactive for CFX oxidation. Before the use, BDD electrodes underwent an anodic pretreatment process (20 mAcm⁻² for 20 min) to clean the BDD electrode. Notwithstanding the possibility of different electrochemical responses by surface treatment of BDD, the authors did not verify such influence on the developed sensor, accomplishment only the anodic treatment. The calibration curves were made in the concentration range from 5 × 10⁻⁹ to 5 × 10⁻⁸ molL⁻¹ and 5 × 10⁻⁸ to 1.0 × 10⁻⁵ molL⁻¹. The detection limit was 5 × 10⁻⁹ molL⁻¹. The sensor was selective for CFX detection in the presence of other antibiotics and other nontarget water constituents. The suggested method was successfully applied in the determination of CPX in wastewater effluent with satisfactory recovery.

Radičová and coauthors was used SWV.^[4ce] The authors used an ammonium acetate buffer (pH 5) on BDD electrode (doping level of 20000 ppm). BDD electrodes were initially cleaned by CV (potential range from -2 to 2 V, scan rate 0.1 Vs⁻¹, repetition 15 times) in the supporting electrolyte. In CV measurements, CPX electrooxidation provided a well-defined irreversible oxidation peak at 1.15 V. The calibration curve was linear in the concentration range from 1.5 × 10⁻⁷ to 2.11 × 10⁻⁶ molL⁻¹. The detection limit was 5 × 10⁻⁸ molL⁻¹. The suggested method was successfully applied in the determination of CPX in human urine samples with recovery values varying from 97 to 102%.

Erythromycin is a broad-spectrum antibiotic often used as an alternative for patients showing sensitivity or allergy to penicillin and for penicillin-resistant infections, was quantified by Radičová and coauthors using SWV.^[4an] The authors used ammonium acetate buffer at pH 5 on BDD electrode (doping level of 1000 ppm). Prior to use, the BDD electrode was rinsed with deionized water and electrochemically cleansed using CV (potential range from -2 to 2 V, potential step 0.0025 V and scan rate 100 mVs⁻¹, repetition 15 times) in the supporting electrolyte. Erythromycin provided an irreversible oxidation peak at a potential of 0.87 V versus Ag/AgCl/KCl (3 molL⁻¹) electrode. The calibration curve was linear in the range 6.8 × 10⁻⁶–6.8 × 10⁻⁵ molL⁻¹ and the detection limit was 1.1 × 10⁻⁶ molL⁻¹. Erythromycin was successfully determined in several water samples with good recovery (from 89 to 107%).

Pereira and coauthors develop a methodology for simultaneous detection of sulfamethoxazole (SMX) and trimethoprim (TMP) using batch injection analysis with multiple pulse amperometric detection (BIA-MPA).^[4ai] The authors used 0.1 mol L⁻¹ phosphate buffer/methanol (v/v: 70/30) solution at pH 7.0 on BDD electrode. The BDD electrodes were anodically pretreated by setting 0.01 A for 1000 s in 0.04 mol L⁻¹ BR buffer (pH 2.0) followed by cathodic pretreatment -0.01 A V for 1000 s in 1 mol L⁻¹ H₂SO₄. The calibration curves had linearity in the concentration range from 4.0×10⁻⁵ to 1.98×10⁻⁴ mol L⁻¹ for SMX and 7×10⁻⁶ to 3.5×10⁻⁵ mol L⁻¹ for TMP. The detection limits were 9×10⁻⁷ mol L⁻¹ for SMX and 6×10⁻⁷ mol L⁻¹ for TMP. The proposed methodology yielded similar results to those obtained by liquid chromatography at a 95% confidence level.

Metronidazole is an antibiotic and antiparasitic medication that inhibits the synthesis of nucleic acids, was quantified by Ammar and coauthors using SWV methodology.^[4aw] The authors used 0.29 mol L⁻¹ Na₂SO₄ solutions at on BDD electrode (doping level of 3500 ppm). Prior to each experiment, the electrode surface was subjected to potential cycling conditions, in 0.5 mol L⁻¹ H₂SO₄ between -3.0 and 3.0 V at 5 Vs⁻¹ for 120 s, then rinsed with distilled water. The calibration curve was linear in the concentration range from 2×10⁻⁷ to 4.2×10⁻⁶ mol L⁻¹. The detection limit was 6.5×10⁻⁸ mol L⁻¹. The suggested method was successfully applied in the determination of metronidazole in injection and human urine samples (with satisfactory recovery (98–102 %)).

N-acetylcysteine (NAC) and gentamicin sulfate (GS) are biologically and pharmaceutically relevant thiol-containing compounds. NAC is well known for its antioxidant properties, whereas GS is an aminoglycoside that is used as abroad band antibiotic was quantified by Abt and coauthors using DPV methodology.^[4av] The authors used 0.1 mol L⁻¹ NaH₂PO₄ solution (pH 10.0) on BDD electrode. For surface activation, the working electrode was cycled from 0 to 2.5 V vs. Ag/AgCl until a stable CV was observed in 0.1 mol L⁻¹ NaH₂PO₄ electrolyte (i.e., approx. 20 cycles). The calibration curves were made from 1.2×10⁻⁵ to 3.0×10⁻⁴ mol L⁻¹ for NAC and 2×10⁻⁷ to 5.0×10⁻⁵ mol L⁻¹ for GS. The detection limits were 1.53×10⁻⁶ mol L⁻¹ for NAC and 1.74×10⁻⁶ mol L⁻¹ for GS.

Cinková and coauthors developed fast and simple method for ciprofloxacin detection in pharmaceutical samples using DVP and BDD electrodes.^[4dg] The BDD electrode was always rinsed with deionized water and the surface was pretreated by simple cycling in 0.5 mol L⁻¹ H₂SO₄ using potentials ranged from -2.0 to +2.0 V until a stable signal was detected. Using the previous treatment and a BR buffer solution, pH 4, as electrolyte, the authors obtained a linear range of 7.4×10⁻⁷ to 2.0×10⁻⁵ mol L⁻¹ with a detection limit of 9.1×10⁻⁷ mol L⁻¹. The proposed method presented recovery of 91–121% for model human urine samples and 88% for pharmaceutical dosages.

Oxacillin belongs to the class of penicillins that act as bactericidal agents by inhibiting the bacterial wall synthesis; they are mainly recommended for the treatment of bacterial infections caused by staphylococci and streptococci. Oxacillin i was quantified by Feier and coauthors using a DPV

methodology.^[4bx] The authors used 0.2 mol L⁻¹ acetate buffer (pH 4.5) as electrolyte and a BDD electrode (doping level of 1000 ppm). The calibration curve was linear in the range from 5.0×10⁻⁵ to 1.0×10⁻³ mol L⁻¹. The detection limit of 1.1×10⁻⁵ mol L⁻¹ was determined. The suggested method was successfully applied in the determination of oxacillin in capsules, spiked urine, blood samples and spiked river water with satisfactory recovery (93–102 %).

Levofloxacin (LEV) is a specific type of fluoroquinolone antibacterial agent. It exhibits a broad-spectrum of activity against most gram-negative pathogens, and some gram-positive bacteria by the inhibition of their DNA gyrase. LEV was quantified by Rkik and coauthors using a SWV methodology.^[4cg] The authors used a 1.4×10⁻³ mol L⁻¹ Na₂SO₄ solution (pH 5.5) and a bare BDD electrode (doping level of 3500 ppm). Prior to each experiment, the BDD electrode was subjected to potential cycling in 0.5 mol L⁻¹ H₂SO₄ between -3.0 and 3.0 V at 5 Vs⁻¹ for 120 s, then rinsed with double distilled water. The levofloxacin oxidation showed three irreversible defined peaks. An oxidation mechanism of the molecule was proposed, which included the transfer of two electrons and two protons leading to LEV N-oxide. The calibration curve was linear in the concentration range from 1.0×10⁻⁵ to 8.0×10⁻⁵ mol L⁻¹. The detection limit was 2.88×10⁻⁶ mol L⁻¹. The suggested method was successfully applied in the determination of levofloxacin in urine and human serum samples with appropriate recoveries (95–108 %).

Cefalexin are β-lactam antibiotics used to treat Gram-positive and Gram-negative bacterial diseases was quantified by Feier and coauthors by DPV methodology.^[4bw] The authors used a 0.2 mol L⁻¹ acetate buffer solution (pH 4.5) on BDD electrode. The calibration curve was linear in the concentration range from 5×10⁻⁷ to 7.0×10⁻⁴ mol L⁻¹. The detection limit was 1×10⁻⁷ mol L⁻¹. The suggested method was successfully applied in capsules, urine and Human serum samples with satisfactory recovery (92–95 %).

3.4. Anti-inflammatories

Different anti-inflammatories had electrolytic methodologies developed using BDD electrode. Ibuprofen, a nonsteroidal anti-inflammatory drug which has been used as an anti-inflammatory and antipyretic agent for the treatment of rheumatoid arthritis, degenerative joint diseases and other inflammatory rheumatic diseases was quantified by Lima and coauthors using DPV methodology.^[4e] The authors used 0.1 mol L⁻¹ H₂SO₄ with 10% (v/v) ethanol and verified a well-defined irreversible oxidation peak was observed at 1.65 V, with oxidation starting at ca. 1.55 V. Prior to use, the BDD electrode (doping level of 8000 ppm) was anodically pretreated by applying 0.01 A for 1000 s in 0.04 mol L⁻¹ BR buffer solutions. The calibration curve was linear in the concentration range from 2.0×10⁻⁵ to 4.0×10⁻⁴ mol L⁻¹. The detection limit was 5×10⁻⁶ mol L⁻¹. The suggested method was successfully applied in pharmaceutical formulations and compared with the British Pharmacopeia procedure. Other research group developed a similar method-

ology for ibuprofen detection, Švorc and coauthors using a DPV.^[4cv] The authors used $1 \text{ mol L}^{-1} \text{ HClO}_4$ and verified a well-defined irreversible oxidation peak was observed at 1.75 V. Prior to use, the BDD electrode (doping level of 8000 ppm) was pretreated by applying -2.5 V and 2.5 V in $1 \text{ mol L}^{-1} \text{ H}_2\text{SO}_4$ for 40 s. The calibration curve was linear in the concentration range from 9.55×10^{-7} to $6.7 \times 10^{-7} \text{ mol L}^{-1}$. The detection limit was equal to $0.41 \times 10^{-6} \text{ mol L}^{-1}$ for methodology developed with DPV and concentration range from 9.54×10^{-7} to $6.7 \times 10^{-5} \text{ mol L}^{-1}$ with the detection limit equal to $9.3 \times 10^{-7} \text{ mol L}^{-1}$ for methodology developed with SWV. The effect of interfering compounds such as ascorbic acid, dopamine, caffeine, uric acid and glucose on the current response of ibuprofen was verified and the suggested method was successfully applied in pharmaceutical formulations and spiked human urine samples with the significant range of recovery percentages (for pharmaceuticals: 100–107% and 100–105.0% by DPV and SWV, for urine: 95–107% and 97–103% by DPV and SWV).

Nimesulide is an anti-inflammatory high analgesic activity and non-steroidal antipyretic widely marketed. Lima and coauthors^[4cz] proposed a method for its determination using flow injection analysis with multiple-pulse amperometric detection at a BDD electrode (8000 ppm). The BDD electrode was initially cleaned with ethanol and conditioned in H_2SO_4 0.5 mol L^{-1} through cathodic and anodic treatment, applying -0.5 mA for 60 s and 11.7 mA for 30 s, respectively. The calibration curve was linear in the concentration range from 2×10^{-7} to $8 \times 10^{-5} \text{ mol L}^{-1}$ with detection limit of $8.1 \times 10^{-8} \text{ mol L}^{-1}$. The proposed method presented was applied in pharmaceutical formulations, yielding similar results to those obtained by the reference method.

Diclofenac (DCL) belongs to the class of the nonsteroidal anti-inflammatory drugs, and showed anti-inflammatory, analgesic, and antipyretic activity, being used in the treatment of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. Lucas and coauthors using SWV coupled to BDD electrode (doping level of 8000 ppm) developed an analytical methodology for identification and quantification DCL in tablets and synthetic urine.^[4cj] The authors used BR buffer solution (pH 2.0). Before the use, BDD electrodes were anodically (3.0 V) and cathodically (-2.0 V) pretreated in $0.50 \text{ mol L}^{-1} \text{ H}_2\text{SO}_4$ solution during 120 s. The calibration curve was linear in the concentration range from 4.9×10^{-6} to $5.41 \times 10^{-6} \text{ mol L}^{-1}$. The detection limit was $1.15 \times 10^{-7} \text{ mol L}^{-1}$. The suggested method was successfully applied in tablets and synthetic urine. The authors validated the obtained results with the chromatographic standard method in addition the authors conducted experiments by UV-Vis spectroscopy, computational calculations and some chromatographic techniques to obtain the mechanism of oxidation of the DCL.

Phenanthrenequinone (PQD) and its synthesized metal complexes, show antimicrobial, anti-HIV, anti-inflammatory and potential anticancer effects. It was quantified by Stanković and coauthors using a DPV methodology.^[4bn] The authors used BR buffer solution at pH 3.0 on BDD electrode (doping level of 1000 ppm). Before the use, surface electrodes were anodically pretreated by setting 2 V during 180 s in $1 \text{ mol L}^{-1} \text{ H}_2\text{SO}_4$

followed by cathodic pretreatment at -2 V during 180 s both in $1 \text{ mol L}^{-1} \text{ H}_2\text{SO}_4$. The calibration curve was linear in the concentration range from 3×10^{-7} to $7.0 \times 10^{-6} \text{ mol L}^{-1}$. The detection limit was $2.2 \times 10^{-7} \text{ mol L}^{-1}$. The suggested method was successfully applied in the determination of PQD in blood samples with satisfactory recovery (96–102%).

Mesalazine (5-ASA), is well-established compound used in the management of inflammatory bowel disease, was quantified by Štěpánková and coauthors using SWV methodology.^[4cm] The authors used BR buffer solution (pH 7.0) on BDD electrode (doping level of 1000 ppm). Before the use, the electrodes were submitted to anodic pretreatment by applying 3 V for 60 s followed by the cathodic pretreatment at -3 V during 300 s both in $0.5 \text{ mol L}^{-1} \text{ H}_2\text{SO}_4$. The calibration curve was linear in the concentration range from 2.9×10^{-6} to $3.9 \times 10^{-4} \text{ mol L}^{-1}$. The detection limit was $7 \times 10^{-7} \text{ mol L}^{-1}$. The suggested method was successfully applied in the determination of 5-ASA in pharmaceutical preparation and spiked human urine with satisfactory recovery (99–103%).

Colchicine (CO) is an anti-inflammatory used in treatment of acute gouty arthritis was quantified by Moreira and coauthors^[4cq] using multiple pulse amperometry (MPA) with flow injection analysis (FIA). The authors used $0.5 \text{ mol L}^{-1} \text{ H}_2\text{SO}_4$ on BDD electrode (doping level of 8000 ppm). Before the use, the surface electrodes were submitted to anodic pretreatment by applying 1.0 mA for 120 s followed by the cathodic pretreatment at -30.0 mA during 360 s both in $0.5 \text{ mol L}^{-1} \text{ H}_2\text{SO}_4$. The calibration curve was linear in the concentration range from 1×10^{-7} to $5 \times 10^{-4} \text{ mol L}^{-1}$. The detection limit was equal to $2 \times 10^{-8} \text{ mol L}^{-1}$. The suggested method was successfully applied in the determination of CO in pharmaceutical formulations and human urine with yields of 100.0% and 95.0%, respectively.

Piroxicam (PRX), is a nonsteroidal anti-inflammatory drug of the oxamic class with analgesic, anti-inflammatory and antipyretic properties, was quantified by Rosseto and coauthors using SWV methodology.^[4cs] The authors used BR buffer solution (pH 3.0) on BDD electrodes (doping level of 8000 ppm). Before the use, BDD electrodes were submitted to anodic pretreatment by applying 100.0 mA cm^{-2} for 30 s followed by the cathodic pretreatment at $-100.0 \text{ mA cm}^{-2}$ during 180 s both in $0.5 \text{ mol L}^{-1} \text{ H}_2\text{SO}_4$. The calibration curve was linear in the concentration range from 5×10^{-7} to $1.1 \times 10^{-5} \text{ mol L}^{-1}$. The detection limit was $1.6 \times 10^{-7} \text{ mol L}^{-1}$. The suggested method was successfully applied in synthetic urine and tap water samples with results like those obtained using a reference spectrophotometric methodology.

3.5. Vitamins

Some vitamins also had detection methodology developed based on the boron doped diamond electrode. Lipophilic antioxidants such as α -tocopherol (vitamin E, VE) and ubiquinone (coenzyme Q10, CoQ10) are indispensable micronutrients used to protect humans against diseases related to oxidative stress, including cardiovascular disease, cancer, cataracts, and age-related problem. Considering the importance of

these micronutrients to human, Kondo and coauthors,^[4d] developed a methodology by CV and flow-injection electrochemical measurements. Although the proposed methodology was not applied in a real sample, during the development, modifications were made to the BDD electrode with UV/ozone treatment where it was observed that the hydrogenated surface improved the electrochemical response of both analytes, thus obtaining a linearity of 5×10^{-7} to $1 \times 10^{-4} \text{ mol L}^{-1}$.

Similarly, several vitamins belonging to Complex B were used for the development of methodology. Among them is Riboflavin, commonly called vitamin B2, essential in the diet for the metabolism of amino acids and for maintenance in body.^[4bm] CV experiments demonstrated that riboflavin undergoes a diffusion-controlled quasi-reversible electron transfer reaction. Under optimized experimental conditions in BR buffer solution (pH 2.0), linear calibration curves were obtained in the wide range from 2×10^{-8} to $3.5 \times 10^{-5} \text{ mol L}^{-1}$, with detection limit of $3.7 \times 10^{-9} \text{ mol L}^{-1}$. The methodology was effectively applied for the determination of riboflavin in pharmaceutical preparations and urine sample analysis were present recovery values between 98 and 104%. It was verified that even in the presence of the most common interferents the proposed sensor can be applied.

Folic acid is another example of a vitamin belonging to the B complex, it is an essential vitamin and soluble in water, has great importance for human health especially in the period of rapid cell division and growth. CV and SWV were employed as analytical techniques in the development of methodology using a BDD electrode, anodically pretreated at 2.5 V in $1 \text{ mol L}^{-1} \text{ H}_2\text{SO}_4$ for 30 s to clean its surface followed by cathodic pretreatment by applying -2.5 V for 60 s to obtain a predominantly hydrogen-terminated surface on the working electrode.^[4ay] The analytical curve was linear in the SWV concentration range from 1×10^{-7} to $1.7 \times 10^{-4} \text{ mol L}^{-1}$ with the value of the detection limit of $3.0 \times 10^{-8} \text{ mol L}^{-1}$. The practical applicability of the method was successfully demonstrated for the analysis of pharmaceutical tablets with satisfactory recoveries (from 100 to 104%).

Different methodologies were developed for detection of pyridoxine, also known as vitamin B6 (VB6). This vitamin is essential for the metabolism of amino acids and for the maintenance of body cells. Kuzmanović and coauthors developed a simple methodology for VB6 individual detection.^[4bb] For this, the selected BDD electrode (doping level of 1000 ppm) was anodically pretreated by setting 2 V for 180 s in $1 \text{ mol L}^{-1} \text{ H}_2\text{SO}_4$ followed by a cathodic pretreatment at -2 V for 180 s to provide a well-defined VB6 oxidation peak at around 1.05 V vs. Ag/AgCl ($3 \text{ mol L}^{-1} \text{ KCl}$) in BR buffer solution (pH 6.0). The analytical curve using DPV was linear in the concentration range from 7×10^{-6} to $4.7 \times 10^{-5} \text{ mol L}^{-1}$ with a detection limit of $3.76 \times 10^{-6} \text{ mol L}^{-1}$. The developed methodology was successfully applied in the determination of VB6 in pharmaceuticals and urine samples with recoveries from 101 to 107%. In a methodology similar to that described by Kuzmanović and coauthors,^[4bb] Alpar and coauthors^[4bt] performed the simultaneous detection of VB6 and melatonin (MT), which is a derivative of tryptophan, primarily synthesized (from serotonin)

and released by pineal gland of humans and mammals. For this, a cathodic pretreatment was carried out by applying -1.7 V for 180 s in a $0.5 \text{ mol L}^{-1} \text{ H}_2\text{SO}_4$ solution to obtain a predominantly H-terminated BDD electrode surface allowing the separation (about 0.47 V) of the oxidation peaks of both compounds in BR buffer (pH 2.0) using CV measurements. The analytical curves based on SWV allowed the simultaneous determination of MT and VB6 in the ranges from 4.3×10^{-6} to $4.3 \times 10^{-4} \text{ mol L}^{-1}$ and from 4.9×10^{-5} to $8.5 \times 10^{-4} \text{ mol L}^{-1}$, with detection limits of $6.0 \times 10^{-7} \text{ mol L}^{-1}$ and $6.6 \times 10^{-6} \text{ mol L}^{-1}$, respectively. The proposed method was successfully tested in dietary supplements with recoveries from 92 to 109%.

Similarly, Li and coauthors developed a methodology for the concurrent detection of VB6 and dopamine (DA).^[4by] DA is an important neurotransmitter, which is used to treat Parkinson's disease and other neurological diseases. A porous boron-doped diamond (PBDD)/Ta, where many pores were formed on the surface of the BDD electrode by the dissolution and absorption of carbon atoms in a plasma atmosphere composed of equal proportions of H_2 and argon, was used to establish the reaction mechanisms of DA and vitamin B6 detection. The oxidation peak potentials were 0.124 V for DA and 0.66 V for VB6, respectively, with the oxidation peak currents gradually increasing with the amount of DA and B6. The reliable linear concentration ranges were $1 \times 10^{-7} \text{ mol L}^{-1}$ to $1.0 \times 10^{-4} \text{ mol L}^{-1}$ and 2×10^{-6} to $1.0 \times 10^{-4} \text{ mol L}^{-1}$, while the values of the detection limit were $6 \times 10^{-8} \text{ mol L}^{-1}$ and $2.1 \times 10^{-7} \text{ mol L}^{-1}$, for DA and VB6 respectively. The proposed method was successfully validated in human serum with recovery varying from 90 to 108%..^[4by] Ascorbic acid (AA) is the vitamin consumed worldwide on a large scale as an antioxidant agent in food, beverages and medicine. Sálusová and coauthors developed a method to its determination by using DPV and a BDD electrode.^[4dm] Prior the electrochemical measurements, the BDD electrode surface was pretreated by simple cycling in 1.5 mol L^{-1} sulfuric acid using potentials in the range from -2.0 to $+2.0 \text{ V}$ until a stable signal was observed (usually 5 cycles in CV). The linear range for the peak current of AA was linearly proportional to its concentration from 5×10^{-6} to $2 \times 10^{-4} \text{ mol L}^{-1}$, with a limit of detection of $1.1 \times 10^{-6} \text{ mol L}^{-1}$. The detection of AA in commercial pharmaceutical preparations, based on the standard additions method obtained recovery of 122%.

3.6. Antidepressants

Different antidepressant pharmaceuticals have an electroanalytical methodology developed. Fluoxetine (FXT), most usually known as Prozac®, was determined in tap water samples using SWV at BDD electrode.^[4b] In the proposed electroanalytical method, FXT can be directly determined in a $0.1 \text{ mol L}^{-1} \text{ Na}_2\text{SO}_4$. The electrochemical behavior and detection of FXT at BDD electrode were studied using CV, DPV, SWV and chronoamperometry (CA). The best performance in relation with the lowest detection limit was reached using DPV. The analytical curve was linear in the FXT concentration range of $5 \times$

10^{-8} – 5×10^{-7} mol L⁻¹, with a detection limit of 3.7×10^{-8} mol L⁻¹. The proposed method was applied with success in the determination of FXT in tap water samples. The accuracy of the applied method was proved by comparison the detection results with the conventional UV-Vis spectrophotometric method.

Another antidepressant pharmaceutical which was also used for the development of electroanalytical methodology was amitriptyline, which is part of the tricyclic group of antidepressant.^[4m] The determination of amitriptyline using a BDD electrode (8000 ppm), with cathodic pretreatment was successfully performed in 0.1 mol L⁻¹ H₂SO₄ solution as the support electrolyte. Under optimized DPV conditions, the analytical curve was linear in the concentration range of 1.05×10^{-6} – 9.26×10^{-5} mol L⁻¹, with a detection limit of 5.2×10^{-7} mol L⁻¹. The proposed method was successfully applied in pharmaceutical formulations, with results like those obtained using UV-Vis spectrophotometric method as reference (at 95% confidence level), as recommended by the Brazilian Pharmacopoeia.

Imipramine, IMI, which is also an example of an antidepressant in the tricyclic group, has been studied by two different research groups. In the electroanalytical methodology developed by Cinková and coauthors, a BDD electrode (4000 ppm) was applied.^[4bu] Cyclic and linear sweep voltammetric measurements revealed one distinct, irreversible and diffusion-controlled oxidation peak. Under optimized DPV conditions, the peak current of IMI was found to be linear function of the concentration from 1.5×10^{-6} – 1.94×10^{-5} mol L⁻¹ with the obtained detection limit of 5×10^{-7} mol L⁻¹. The practical usefulness of the developed method was successfully manifested on the analysis of pharmaceutical tablets with significant recoveries.

For the electroanalytical methodology of imipramine detection, proposed by Oliveira and coauthors,^[4cd] a BDD electrode (8000 ppm) with cathodic pre-treatment was applied. The voltammetric results showed two well-defined oxidation peaks with potentials of 0.04 V and 0.82 V vs. Ag/AgCl (3 mol L⁻¹ KCl) in 0.04 mol L⁻¹ BR buffer solution (pH 7.4). Under optimized SWV parameters, the analytical curves were obtained in the linear range of concentration 1.73×10^{-7} mol L⁻¹– 2.53×10^{-6} mol L⁻¹, with detection limit of 4.35×10^{-8} mol L⁻¹. The proposed method was applied with success in the determination of IMP in commercial pharmaceutical formulations and validated by comparison with standard method for determination of imipramine.

3.7. Other Pharmaceuticals

Levodropropizine (LDP), the enantiomer of dropropizine, is an anti-cough drug with an anti-tussive activity and a reduced sedative effect that may be attributed to the (+)-enantiomer. DPV and SWV methodologies were proposed by Agin and coauthors^[4a] for quantification to LDP in phosphate buffer pH 3.5 on BDD electrodes. The analytical curve was linear in the LDP concentration range from 2×10^{-7} to 1.0×10^{-4} mol L⁻¹ with

the values of the detection limit equals to 1.02×10^{-9} mol L⁻¹ (DPV) and 1.30×10^{-8} mol L⁻¹ (SWV). The developed methodology was successfully applied in the determination of LDP in syrup dosage forms (Levopront®, containing LDP as 30 mg/5 mL). The accuracy was proved by comparison to the detection results with the conventional HPLC-UV method.

Caffeine (CAF) and chlorogenic acid (CGA) are stimulant to the central nervous and cardiovascular systems and antioxidant and antiradical activity, respectively. SWV methodology was proposed by Yardim and coauthors^[4k] for quantification to CAF and CGA in binary mixtures by about 0.4 V (vs. Ag/AgCl/KCl_{sat}) in BR buffer (pH 1.0) on BDD electrodes. Working electrode was activated at the beginning of each working day in 0.5 mol L⁻¹ H₂SO₄ by applying a potential of 2.0 V for 180 s (between individual measurements it was applied 2.0 V for 30 s). The analytical curve was linear in the CAF and CGA concentration ranges from 4.12×10^{-6} to 2.88×10^{-5} mol L⁻¹ (CAF) and 5.64×10^{-6} – 1.47×10^{-4} (CGA) mol L⁻¹ with the values of the detection limit equal to 5.51×10^{-7} mol L⁻¹ and 1.26×10^{-6} mol L⁻¹, respectively. The practical applicability of this methodology was tested in coffee and energy drinks samples.

Tryptophan and tyrosine are amino acids and the simultaneous detection was achieved on BDD nanowire electrodes when the ratio of tryptophan/tyrosine was ≤ 0.5 . DPV methodology was proposed by Wang and coauthors^[4j] and it was used PBS buffer pH 7.4. The analytical curve was linear in the LDP concentration range from 5×10^{-6} to 5×10^{-4} mol L⁻¹ with the value of the detection limit equal to 5×10^{-6} mol L⁻¹. The developed methodology was successfully applied in the determination of these amino acids in lyophilized human serum samples.

Rutin has antioxidant activity and square-wave adsorptive stripping voltammetry methodology was proposed by Pinar and coauthors^[4g] for quantification of this molecule in BR buffer pH 4.0 at 0.48 V (vs. Ag/AgCl/KCl_{sat}) (after 60 s at 0.2 V) on BDD electrodes. The calibration curve was linear in the concentration range from 1.6×10^{-8} to 1.6×10^{-7} mol L⁻¹. A detection limit of 2.8×10^{-9} mol L⁻¹ was calculated. As an example, the practical applicability of boron-doped diamond electrode was tested with the measurement of rutin in rutin-containing dietary supplement samples (Solgar® tablets, containing rutin as 500 mg per tablet).

Bezafibrate is a drug of the biochemical fibrates class used as a hypolipidemic agent for treating disturbances in lipids levels and/or lipoproteins in the blood. The use of this drug helps to lower LDL cholesterol and triglycerides in the blood as well as raise HDL cholesterol. Ardila and coauthors^[4cw] used SWV to detect bezafibrate in pharmaceutical formulations. The authors used a 0.04 mol L⁻¹ BR buffer solution (pH 2.0) on BDD (8000 ppm) electrodes. Before the first use, the BDD electrode was electrochemically pretreated in a 0.5 mol L⁻¹ H₂SO₄ solution, either anodically by applying 0.5 A cm⁻² for 20 s, or cathodically by applying -0.5 A cm⁻² for 80 s. The calibration curve was linear in the concentration range from 1×10^{-7} to 9.1×10^{-6} mol L⁻¹ with detection limit of 9.8×10^{-8} mol L⁻¹.

Hydroquinone is the most skin depigmenting agent in the used topically in the treatment of hypermelanosis. Cunha and

coauthors^[40] used batch injection analysis with amperometric detection to quantify hydroquinones in pharmaceutical samples. The authors used $0.1 \text{ mol L}^{-1} \text{ H}_2\text{SO}_4$ as optimized electrolyte on BDD (8000 ppm) electrodes previously treated with two types of electrochemical activations, the anodic (+2.6 V, for 900 s in BR buffer medium) and subsequently cathodic (−3.0 V for 900 s in $0.2 \text{ mol L}^{-1} \text{ H}_2\text{SO}_4$) treatment. The calibration curve was linear in the concentration range from 1×10^{-5} to $2 \times 10^{-6} \text{ mol L}^{-1}$ with detection limits equal to $1.6 \times 10^{-8} \text{ mol L}^{-1}$. Satisfactory recovery values (91–96%) were obtained for pharmaceutical samples.

Ambroxol (AMB), a potential antioxidant drug belonging to the expectorant class, was quantified by square-wave adsorptive stripping voltammetry methodology proposed by Levent and coauthors.^[41] The authors used phosphate buffer pH 2.5 containing $4 \times 10^{-4} \text{ mol L}^{-1}$ sodium dodecylsulfate at 1.02 V (vs. Ag/AgCl/KCl_{sat}) (after 30 s at 0.50 V) on BDD electrodes. The calibration curve was linear in the concentration range from 5×10^{-8} to $7 \times 10^{-7} \text{ mol L}^{-1}$. A detection limit of $1 \times 10^{-8} \text{ mol L}^{-1}$ was calculated. The suggested method was successfully applied to Sekrol® tablets (containing AMB HCl 30 mg) and spiked human urine samples.

Ketoconazole and ciclopiroxolamine are synthetic, highly effective broad-spectrum antifungal agents. Mielech-Lukasiewicz and Roginska^[42] used BDD electrodes to quantify these pharmaceuticals by SWV methodology. BDD electrodes were cathodic conditioned from cycling from −2.9 V to 0.3 V (vs. saturated calomel electrode) at 500 mVs^{-1} . The authors used $\text{NH}_3\text{-NH}_4\text{Cl}$ buffer pH 9.42 for ketoconazole and McIlvaine buffer pH 7.0 for ciclopiroxolamine. The calibration curve was linear in the concentration range from 2.9×10^{-7} to $3.13 \times 10^{-6} \text{ mol L}^{-1}$ for ketoconazole and 25.3 to $419 \times 10^{-6} \text{ mol L}^{-1}$ for ciclopiroxolamine. The values of the detection limit were equal to $8.29 \times 10^{-8} \text{ mol L}^{-1}$ and $6.66 \times 10^{-6} \text{ mol L}^{-1}$ for ketoconazole and ciclopiroxolamine, respectively. The developed methodology was successfully applied in tablets, cream and shampoo (Ketokonazol® tablets as containing 200 mg of ketoconazole, Nizoral® cream and Nizoral® shampoo, both as containing 20 mg g^{-1} of ketoconazole, Stieprox® shampoo as containing 15 mg of ciclopiroxolamine per 1 mL of shampoo).

N-acetyl L-cysteine (NAC) is a mucolytic agent that was quantified by Nantaphol and coauthors using flow injection analysis with amperometric detection.^[43] The authors used 0.1 mol L^{-1} phosphate buffer pH 9.0 on BDD electrodes. The calibration curve was linear in the concentration range from 5.0×10^{-5} to $5 \times 10^{-4} \text{ mol L}^{-1}$. A detection limit of $1 \times 10^{-8} \text{ mol L}^{-1}$ was calculated. The suggested method was successfully applied in commercially available drug samples.

Dimenhydrinate (DIM), used to prevent motion sickness associated with nausea and vomiting, composed by the combination of two active pharmaceutical ingredients in equimolar ratio: diphenhydramine (DIP) and 8-chlorotheophylline (CTP). Freitas and coauthors^[45] used batch injection analysis with amperometric detection to quantify DIP (cation) and CTP (anion) simultaneously in pharmaceutical samples with a simple and fast injection procedure ($70 \text{ injections h}^{-1}$). The authors used 0.05 mol L^{-1} acid acetic/acetate buffer pH 4.7 on BDD

(doping level of ~8000 ppm) electrodes. Before the first use, the BDD was anodically pretreated by applying 0.01 A for 1000 s in 0.04 mol L^{-1} BR buffer solution and then cathodically pretreated by applying −0.01 A for 1000 s in a $0.1 \text{ mol L}^{-1} \text{ H}_2\text{SO}_4$ solution. The calibration curve was linear in the concentration range from 1×10^{-5} to $8 \times 10^{-5} \text{ mol L}^{-1}$ for DIP and from 1×10^{-5} to $6 \times 10^{-5} \text{ mol L}^{-1}$ for CTP. The values of the detection limits were $1.1 \times 10^{-7} \text{ mol L}^{-1}$ for CTP and $1.5 \times 10^{-7} \text{ mol L}^{-1}$ for DIP.

Hormones, including estrone, were quantified by Brocenschi and coauthors using DPV and SWV methodologies.^[44] The authors used $0.25 \text{ mol L}^{-1} \text{ H}_2\text{SO}_4$ on BDD electrodes (doping level of 8000 ppm). The BDD electrodes were electrochemically pretreated in $0.5 \text{ mol L}^{-1} \text{ H}_2\text{SO}_4$: anodic pretreatment 250 mA cm^{-2} for 60 s and cathodic pretreatment -250 mA cm^{-2} for 360 s. The calibration curve was linear in the concentration range from 2.0×10^{-7} to $2.0 \times 10^{-6} \text{ mol L}^{-1}$ (DPV) and from 1.0×10^{-7} to $2.0 \times 10^{-6} \text{ mol L}^{-1}$ (SWV). The values of the detection limits were calculated as 2.0×10^{-7} and $1.0 \times 10^{-7} \text{ mol L}^{-1}$ for DPV and SWV, respectively. The suggested method was successfully applied in ultrapure (Milli-Q), tap and lake water samples.

Coumarin, widely applied to the treatment of diseases as an anti-allergic, bronchodilator, anti-asthmatic and anti-inflammatory drug, was quantified by Miyano and coauthors using SWV methodology.^[46] The authors used 0.1 mol L^{-1} BR buffer (pH 8.0) on BDD electrodes (doping level of 8000 ppm). Before the use, BDD electrodes were submitted to anodic treatment (3.0 V vs. Ag/AgCl/KCl_{sat} for 10 min) and to a cathodic treatment (−3.0 V vs. Ag/AgCl/KCl_{sat} for 10 min). For electrode surface recovery, cathodic treatment was used for 30 s. The calibration curve was linear in the concentration range from 5×10^{-6} to $1 \times 10^{-4} \text{ mol L}^{-1}$. The detection limit was $1.5 \times 10^{-6} \text{ mol L}^{-1}$. The suggested method was successfully applied in an aqueous infusion of *Mikania glomerata*.

Methamphetamine, that has effect on brain and nervous system causing mental alertness and increase of energy, was quantified by Švorc and coauthors using DPV methodology.^[44b] The authors used BR buffer solution (pH 10.0) on BDD electrodes. Before the use, BDD electrodes were submitted to anodic treatment (2.0 V vs. Ag/AgCl/KCl_{sat} for 180 s) and to cathodic treatment was realized (−2.0 V vs. Ag/AgCl/KCl_{sat} for 180 s) in $1 \text{ mol L}^{-1} \text{ H}_2\text{SO}_4$. The calibration curve was linear in the concentration range from 7×10^{-8} to $8 \times 10^{-5} \text{ mol L}^{-1}$. The detection limit was $5 \times 10^{-8} \text{ mol L}^{-1}$. The suggested method was successfully applied in urine samples.

Yohimbine, an indole alkaloid, was quantified by Švorc and coauthors using DPV methodology.^[44a] The authors used BR buffer solution (pH 7.0) on BDD electrodes (doping level of 1000 ppm). Before the use, BDD electrodes were submitted to anodic treatment (2.0 V vs. Ag/AgCl/KCl_{sat} for 180 s) and to cathodic treatment was realized (−2.0 V vs. Ag/AgCl/KCl_{sat} for 180 s) in $1 \text{ mol L}^{-1} \text{ H}_2\text{SO}_4$. The calibration curve was linear in the concentration range from 2.50×10^{-4} to $9.10 \times 10^{-2} \text{ mol L}^{-1}$. The detection limit was $1.30 \times 10^{-4} \text{ mol L}^{-1}$. The suggested method was successfully applied in extracts of natural aphrodisiacs such as *Pausinystalia yohimbe* and *Rauvolfia serpentina*.

17 β -estradiol, natural estrogen excreted by humans and domestic animals, was quantified by Ke and coauthors using electrochemical impedance spectroscopy methodology.^[44p] The authors used 5 mmol L⁻¹ Fe(CN)₆³⁻/Fe(CN)₆⁴⁻ and 0.1 mol L⁻¹ KCl on hierarchical dendritic gold microstructure BDD electrodes. The calibration curve was linear in the concentration range from 1.0 \times 10⁻⁸ to 1.0 \times 10⁻³ mol L⁻¹. The detection limit was 5.0 \times 10⁻⁹ mol L⁻¹. The suggested method was successfully applied in real water samples. The accuracy was proved by comparison to the detection results with the conventional HPLC methodology.

HCTZ is a diuretic and valsartan (VAL) is an angiotensin II receptor antagonist, which the mixture of HCTZ and VAL in combined dosage forms is achieve better blood pressure control. These pharmaceuticals were quantified by Eisele and coauthors using SWV methodology.^[44n] The authors used BR buffer solution pH 5.0 on BDD electrodes (doping level of 8000 ppm). Before the experiments, the BDD electrode surface was electrochemically pretreated in a 0.5 mol L⁻¹ H₂SO₄ solution: firstly, an anodic pretreatment (0.5 A cm⁻², 30 s) and followed by a cathodic one (-0.5 A cm⁻², 150 s). The calibration curve was linear in the concentration range from 1.97 \times 10⁻⁶ to 8.81 \times 10⁻⁵ mol L⁻¹ (HCTZ) and 9.88 \times 10⁻⁶ to 2.20 \times 10⁻⁴ mol L⁻¹ (VAL). The values of the detection limits were equal to 6.39 \times 10⁻⁷ mol L⁻¹ (HCTZ) and 9.35 \times 10⁻⁷ mol L⁻¹ (VAL). HCTZ and VAL were determined in two different commercial pharmaceutical formulations and the accuracy was proved by comparison to the detection results with the conventional HPLC methodology.

Yohimbine, is an indole alkaloid, was quantified by Švorc and Kalcher using batch injection analysis with amperometric detection methodology.^[44y] The authors used BR buffer solution (pH 7.0) on BDD electrodes (doping level of 1000 ppm). Before the use, BDD electrodes were submitted to anodic treatment (2.0 V vs. Ag/AgCl/KCl_{sat} for 60 s) and to cathodic treatment (-2.0 V vs. Ag/AgCl/KCl_{sat} for 60 s) in 0.5 mol L⁻¹ H₂SO₄. The calibration curve was linear in the concentration range from 3 \times 10⁻⁷ to 1 \times 10⁻⁴ mol L⁻¹. The detection limit was 1.5 \times 10⁻⁷ mol L⁻¹. The developed methodology was successfully applied in extracts of natural aphrodisiacs such as *Pausinystalia yohimbe* and *Rauvolfia serpentina*.

Hydroxychloroquine, an antimalarial drug, was quantified by Decoro and coauthors using SWV.^[44da] The authors used 0.1 mol L⁻¹ H₂SO₄ on BDD electrodes (8000 ppm). Before the use, the BDD electrode was electrochemically pretreated in a 0.5 mol L⁻¹ H₂SO₄ solution: anodically by applying 1.0 A cm⁻² for 30 s and cathodically by applying -1.0 A cm⁻² for 120 s. The calibration curve was linear in the concentration range from 1 \times 10⁻⁷ to 1.9 \times 10⁻⁶ mol L⁻¹. The detection limit was 6 \times 10⁻⁸ mol L⁻¹. The suggested method was successfully applied in pharmaceutical samples and synthetic urine samples.

Pereira and coauthors developed a method for the simultaneous determination of promethazine and codeine based on batch injection analysis with multiple pulse amperometric detection using a BDD electrode.^[44dd] For this 0.1 mol L⁻¹ H₂SO₄ with 10% (v/v) ethanol was used as supporting electrolyte. Preceding the experiments, the BDD electrode was anodically pretreated by applying 0.01 A for 1000 s in a 0.04 mol L⁻¹ BR

buffer solution (pH 2.0) and then cathodically pretreated by applying -0.01 A for 1000 s in a 0.1 mol L⁻¹ H₂SO₄. For simultaneous detection, the BIA-MPA procedure provided linear range from 1.76 \times 10⁻⁵ to 8.79 \times 10⁻⁵ mol L⁻¹ and from 2.67 \times 10⁻⁵ to 1.34 \times 10⁻⁴ mol L⁻¹ for promethazine and codeine, respectively and limits of detection of 2.25 \times 10⁻⁷ for promethazine and 4.51 \times 10⁻⁷ for codeine.

Although nicotine is hardly used as a drug, it is present as the main component of tobacco derivatives, which makes its consumption widely diffused in the world. Švorc and coauthors developed a method based on DPV on a BDD electrode.^[44de] As electrolyte, BR buffer solution at pH 8 was used and at optimized experimental conditions, a linear range obtained for nicotine was found from 5 \times 10⁻⁷ to 2 \times 10⁻⁴ mol L⁻¹ with a detection limit of 3 \times 10⁻⁷ mol L⁻¹. In addition, the method proposed by the authors was subjected to recovery tests in different samples of tobacco products and anti-smoking pharmaceuticals with recovery rates between 91 and 105%.

Loratadine is a tricyclic antihistamine, which was quantified by Eisele and Sartoti using SWV methodology.^[44ae] The authors used 0.50 mol L⁻¹ HClO₄ solution on BDD electrodes. Before the use, electrode surface was submitted to anodic treatment (0.5 A cm⁻² for 30 s) and to cathodic treatment (-0.5 A cm⁻² for 120 s) in 0.5 mol L⁻¹ H₂SO₄. The calibration curve was linear in the concentration range from 9.8 \times 10⁻⁷ to 1.9 \times 10⁻⁵ mol L⁻¹. The detection limit was 7.8 \times 10⁻⁷ mol L⁻¹. The developed methodology was successfully applied in different commercial samples (tablets and liquid) and compared to the conventional spectrophotometric methodology.

Methotrexate, an antimetabolic agent, was quantified by Selesovská and coauthors using DPV methodology.^[44aq] The authors used 0.05 mol L⁻¹ H₂SO₄ solution on BDD electrodes (doping level of 1000 ppm). The calibration curve was linear in the concentration range from 5 \times 10⁻⁸ to 2.5 \times 10⁻⁵ mol L⁻¹. The detection limit was 1 \times 10⁻⁸ mol L⁻¹. The developed methodology was successfully applied in real drug preparations (tablets and injection solution) and spiked human urine.

Sulfamethoxazole (SMX), an antimicrobial agent, was quantified by Zhao and coauthors using SWV methodology.^[44au] The authors used PBS solution pH 7.0 on the MIP/BDD electrodes. The calibration curve was linear in the concentration range from 1 \times 10⁻⁷ to 1 \times 10⁻⁴ mol L⁻¹. The detection limit was 2.4 \times 10⁻⁸ mol L⁻¹. The suggested method was successfully applied in surface water samples.

Neuraminidase (NA) is an exosialidase enzyme that is present in many pathogenic microbes and viruses. Wahyuni and coauthors^[44at] characterized the electrochemical behavior of Zanamivir (a NA inhibitor), in the presence of NA and 0.33 mg mL⁻¹ of mucin *Bovine Submaxillary Glands* type I-S M3895, using CV in 0.1 mol L⁻¹ PBS (pH 5.5) at BDD electrodes modified with gold nanoparticles, the formation of Au microarray electrode at BDD electrode provides the more sensitive responses in comparison to that of gold bulk electrode. This modification was performed in 1 \times 10⁻³ mol L⁻¹ HAuCl₄·4H₂O solution in 5 \times 10⁻⁴ mol L⁻¹ H₂SO₄ solution by applying 200 mV during 100 s. The calibration curve was linear in the concentration range from 5 \times 10⁻⁶ to 1 \times 10⁻⁴ mol L⁻¹. The values of the

detection limits were equal to $1.53 \times 10^{-6} \text{ mol L}^{-1}$ for oxidation reaction and $1.53 \times 10^{-6} \text{ mol L}^{-1}$ for reduction reaction. The developed methodology was successfully applied in mucin as a real sample application, because NA can be found in the influenza virus.

Rosuvastatin calcium is an anti-lipid activity with pharmacological activity, reducing the blood cholesterol levels and the risks of cardiovascular diseases. This pharmaceutical was quantified by Silva and coauthors using SWV methodology.^[4ar] The authors used $0.1 \text{ mol L}^{-1} \text{ H}_2\text{SO}_4$ solution on BDD electrodes (doping level of 8000 ppm). Before the use, electrode surface was submitted to anodic treatment (3.0 V for 5.0 s) and to cathodic treatment (-3.0 V for 15.0 s) in $0.5 \text{ mol L}^{-1} \text{ H}_2\text{SO}_4$. The calibration curve was linear in the concentration range from 9.39×10^{-6} to $8.87 \times 10^{-5} \text{ mol L}^{-1}$. The detection limit was $1.04 \times 10^{-6} \text{ mol L}^{-1}$. The developed methodology was successfully applied in two different commercial samples (tablets) and biological fluid samples of urine and human serum. These results were in good agreement with those reached by the standard spectrophotometric methodology.

Trifluoperazine (TFP), a phenothiazine derivative with potent physiological activity, was quantified by Stankovic and coauthors using DPV methodology.^[4as] The authors used BR buffer solution at pH 6 on BDD electrodes (doping level of 1000 ppm) to quantify two oxidation peaks on higher potentials of TFP. Before the use, BDD electrodes were submitted to anodic treatment (2.0 V vs. Ag/AgCl/KCl_{sat} for 180 s) and to cathodic treatment (-2.0 V vs. Ag/AgCl/KCl_{sat} for 180 s) in $0.5 \text{ mol L}^{-1} \text{ H}_2\text{SO}_4$. The calibration curve was linear in the concentration range from 1.0×10^{-6} to $3.7 \times 10^{-5} \text{ mol L}^{-1}$. The values of the detection limits were equal to $7 \times 10^{-7} \text{ mol L}^{-1}$ and $6 \times 10^{-7} \text{ mol L}^{-1}$. The developed methodology was successfully applied in human urine samples.

Theophylline has a molecular structure similar to caffeine. Used as anti-asthmatic, is present in some soft drinks and food stuffs as well as in natural products. Cinková and coauthors developed methods for the detection of this pharmaceutical using DPV and SWV on BDD electrodes.^[4df] To activate the surface, 10 cyclic voltammograms in the potential range from -2.0 V to $+2.0 \text{ V}$ at 100 mVs^{-1} in $1 \text{ mol L}^{-1} \text{ H}_2\text{SO}_4$. Using $1 \text{ mol L}^{-1} \text{ H}_2\text{SO}_4$ as electrolyte, the same linear range obtained for DVP and SWV was equal to 2×10^{-6} to $3.80 \times 10^{-4} \text{ mol L}^{-1}$ with a detection limit of $9.1 \times 10^{-7} \text{ mol L}^{-1}$ using DPV and $1.45 \times 10^{-7} \text{ mol L}^{-1}$ using SWV. In addition, the method proposed by these authors was subjected to recovery tests in pharmaceutical dosages and human urine samples with accomplished recovery values of 93–103 %).

Dopamine (DA) in the presence of an excess of uric acid (UA), known as neurotransmitters, was quantified by May and coauthors using SWV methodology.^[4bd] The authors used 0.2 mol L^{-1} phosphate buffer solution pH 7.0 on the BDD-coated bSi long-needle electrode. The calibration curve was linear in the concentration range from 3.0×10^{-7} to $5.0 \times 10^{-7} \text{ mol L}^{-1}$. The detection limit was $2.7 \times 10^{-7} \text{ mol L}^{-1}$ for DA and $2.1 \times 10^{-6} \text{ mol L}^{-1}$ for UA. This system was used to generate a mechanical bactericidal effect, killing both Gram-negative and Gram-positive bacteria at high rates.

5-nitroquinoline, known as antileishmanial, was quantified by Vosáhlová and coauthors using DPV methodology.^[4bp] The authors used 0.1 mol L^{-1} acetate buffer (pH 5.0) on the BDD (doping levels ranging from 500 to 1000 ppm). Before the use, BDD electrodes were submitted to anodic treatment (2.4 V vs. Ag/AgCl/KCl_{sat} for 5 min) and to cathodic treatment (-2.4 V vs. Ag/AgCl/KCl_{sat} for 10 min) in $0.5 \text{ mol L}^{-1} \text{ H}_2\text{SO}_4$. The calibration curve was linear in the concentration range from 5×10^{-7} to $1 \times 10^{-4} \text{ mol L}^{-1}$. The detection limit was $2.9 \times 10^{-7} \text{ mol L}^{-1}$. The reduction of the quinoline skeleton is well observable only at the 2000 ppm electrode.

Ivermectin (IVM) and levamisole (LVM) is an anthelmintic drug that was quantified by Lourenção and coauthors using SWV methodology.^[4bc] The authors used $0.5 \text{ mol L}^{-1} \text{ H}_2\text{SO}_4$ solution and BDD electrodes (doping level of 8000 ppm). Before the use, electrode surface was submitted to cathodic treatment (-0.5 A cm^{-2} , 180/120 s) and to anodic treatment (0.5 A cm^{-2} , 30/60 s) in $0.5 \text{ mol L}^{-1} \text{ H}_2\text{SO}_4$. The calibration curves were linear in the concentration range from 6.0×10^{-7} to $5.0 \times 10^{-5} \text{ mol L}^{-1}$ (IVM) and from 1.0×10^{-8} to $5.0 \times 10^{-6} \text{ mol L}^{-1}$ (LVM). The values of the detection limits were equal to $3.0 \times 10^{-7} \text{ mol L}^{-1}$ (IVM) and $5.0 \times 10^{-6} \text{ mol L}^{-1}$ (LVM). The developed methodology was successfully applied in pharmaceutical formulations and in synthetic urine samples. These results were compared to the conventional methodologies (spectrophotometric absorption in the ultraviolet-visible region for IVM and potentiometric titration for LVM).

Furosemide (FUR), a diuretic used for the treatment of edematous conditions, was quantified by Medeiros and coauthors using SWV methodology.^[4be] The authors used 0.040 mol L^{-1} BR buffer pH 4.5 on BDD electrodes (doping level of 8000 ppm). Before the use, electrode surface was submitted to anodic treatment (3.0 mA cm^{-2} for 10 s) and to cathodic treatment (-3.0 mA cm^{-2} for 60 s) in $0.5 \text{ mol L}^{-1} \text{ H}_2\text{SO}_4$. The calibration curve was linear in the concentration range from 3×10^{-7} to $1.3 \times 10^{-5} \text{ mol L}^{-1}$. The value of the detection limit was $3 \times 10^{-7} \text{ mol L}^{-1}$. The developed methodology was successfully applied in pharmaceutical formulations (tablets) and in synthetic urine samples. These results were compared to the conventional spectrophotometric methodology.

Naphazoline (NPZ) is a sympathomimetic drug used in over-the-counter eye and nasal preparations. It was quantified by Oliveira and coauthors using batch-injection analysis system with square-wave voltammetry (BIA-SWV) methodology.^[4bg] The authors used 0.05 mol L^{-1} acetate buffer solution (pH 4.7) on BDD electrodes (doping level of 8000 ppm). Before the use, electrode surface was submitted to anodic treatment (0.01 A for 1000 s in 0.12 mol L^{-1} in BR buffer solution) and to cathodic treatment (-0.01 A for 1000 s in $0.1 \text{ mol L}^{-1} \text{ H}_2\text{SO}_4$ solution). The calibration curve was linear in the concentration range from 3×10^{-6} to $2.1 \times 10^{-5} \text{ mol L}^{-1}$. The value of the detection limit was $4 \times 10^{-8} \text{ mol L}^{-1}$. The electroanalytical features of the developed methodology for the simultaneous determination of naphazoline and zinc compared favorably of those of HPLC (naphazoline) and flame atomic absorption spectroscopy (zinc).

Imatinib (IMA), a new generation of anticancer drug, was quantified by Brycht and coauthors using DPV.^[4ax] The authors

used BR buffer pH 2.0 on BDD electrodes (doping level of 1000 ppm). Before the use, electrode surface was anodically pretreated in a stirred $0.1 \text{ mol L}^{-1} \text{ H}_2\text{SO}_4$ (2.0 V for 30 s). The calibration curve was linear in the concentration range from 3×10^{-8} to $2.5 \times 10^{-7} \text{ mol L}^{-1}$. The calculated detection limit was $6.3 \times 10^{-9} \text{ mol L}^{-1}$. The developed methodology was successfully applied in human urine samples.

Diphenhydramine, 8-chlorotheophylline and pyridoxine are usually used to avoid motion sickness associated with nausea and vomiting. Freitas and coauthors developed a method based on batch injection analysis with multiple pulse amperometric detection using a DDB electrode anodically pretreated by applying 0.01 A for 1000 s in 0.04 mol L^{-1} BR buffer and after a cathodic pre-treatment performed by applying -0.01 A for 1000 s in a $0.1 \text{ mol L}^{-1} \text{ H}_2\text{SO}_4$ solution.^[4dh] By using optimized conditions, a linear range equal to 1.0×10^{-5} to 3.0×10^{-5} for diphenhydramine and 2.0×10^{-5} to 6.0×10^{-5} for chlorotheophylline and pyridoxine were obtained. Besides a detection limits of $1.8 \times 10^{-7} \text{ mol L}^{-1}$ for diphenhydramine, $1.9 \times 10^{-7} \text{ mol L}^{-1}$ for chlorotheophylline and $5.4 \times 10^{-7} \text{ mol L}^{-1}$ for pyridoxine were also determined.

Bromazepam (BZ) and alprazolam (ALZ) have anticonvulsant, hypnotic, sedative and muscle-relaxant effects. These pharmaceuticals were quantified by Samiec and coauthors using DPV methodology.^[4ch] The authors used BR buffer (pH 11.0) on BDD electrodes (different doping levels of 1000, 2000, 4000 and 8000 ppm). Before the use, electrode surface was anodically pretreated in a stirred $1 \text{ mol L}^{-1} \text{ H}_2\text{SO}_4$ (2.0 V for 60 s). Subsequently, a cathodic pretreatment was carried out using -2.0 V for 30 s in the same medium. The calibration curves were linear in the concentration range from 1×10^{-6} to $1 \times 10^{-4} \text{ mol L}^{-1}$ (BZ) and 8×10^{-7} to $1 \times 10^{-4} \text{ mol L}^{-1}$ (ALZ). The values of the detection limits were $3.1 \times 10^{-7} \text{ mol L}^{-1}$ (BZ) and $6.4 \times 10^{-7} \text{ mol L}^{-1}$ (ALZ). The developed methodology was successfully applied in two different commercially available pharmaceuticals Lexaurin® (BZ) and Xanax® (ALZ).

Tadalafil (TDL) is used for treating benign prostatic hyperplasia. This pharmaceutical was quantified by Sartori and coauthors using SWV methodology.^[4ci] The authors used BR buffer (pH 4) on BDD electrodes (doping level of 8000 ppm). Before the use, electrode surface was cathodically pretreated in a stirred $0.5 \text{ mol L}^{-1} \text{ H}_2\text{SO}_4$ (-0.5 A cm^{-2} for 120 s). Subsequently, an anodic pretreatment using 0.5 A cm^{-2} for 30 s in the same medium. The calibration curves were linear in the concentration range from 1.5×10^{-7} to $1.28 \times 10^{-6} \text{ mol L}^{-1}$. The determined detection limit was $1.95 \times 10^{-8} \text{ mol L}^{-1}$. The developed methodology was successfully applied in pharmaceuticals (tablets). These results were compared to the conventional spectrophotometric methodology.

Caffeine (CAF) is a stimulant for central nervous system and vanillin (VAN) have is antioxidative activity. These pharmaceuticals were quantified by Ali and coauthors using square-wave adsorptive stripping voltammetry methodology.^[4bs] The authors applied the open circuit potential during 60 s in phosphate buffer pH 2.5 on BDD electrodes. Before the use, electrode surface was anodically pretreated in a stirred $0.5 \text{ mol L}^{-1} \text{ H}_2\text{SO}_4$ (1.8 V for 180 s). The calibration curves were linear in the

concentration range from 1.3×10^{-6} to $5.2 \times 10^{-4} \text{ mol L}^{-1}$ (CAF) and 6.6×10^{-6} to $6.6 \times 10^{-4} \text{ mol L}^{-1}$ (VAN). The values of the detection limits were $3.04 \times 10^{-7} \text{ mol L}^{-1}$ (CAF) and $1.47 \times 10^{-6} \text{ mol L}^{-1}$ (ALZ). The developed methodology was successfully applied in samples of commercially-available vanilla sugar, foamy instant coffee and cola soft drink.

Colchicine (COLC), a natural product used to treat gout, was quantified by Stankovic and coauthors using a DPV methodology.^[4cl] The authors used BR buffer at pH 7.5 on a bare BDD electrode. Before use, the electrode surface was anodically pretreated in a stirred solution of $1 \text{ mol L}^{-1} \text{ H}_2\text{SO}_4$ (2 V for 180 s). Subsequently, a cathodic pretreatment was performed using -2 V for 180 s in the same medium. The calibration curves were linear in the concentration range from 1×10^{-6} to $1 \times 10^{-4} \text{ mol L}^{-1}$. The value of the detection limit was $2.6 \times 10^{-7} \text{ mol L}^{-1}$. The developed methodology was successfully applied in tablets.

Flutamide (FLU), a non-steroidal androgen receptor antagonist primarily used in treatment of advanced prostate cancer, was quantified by Svrc and coauthors using DPV and SWV methodologies.^[4cn] The authors used $0.1 \text{ mol L}^{-1} \text{ H}_2\text{SO}_4$ on BDD electrodes (doping level of 1000 ppm). Before the use, electrode surface was cathodically pretreated (-2.5 V for 60 s) in a stirred $1 \text{ mol L}^{-1} \text{ H}_2\text{SO}_4$ solution. Subsequently, an anodic pretreatment was performed using 2.5 V for 60 s in the same medium. The calibration curves were linear in the concentration range from 9.9×10^{-7} to $3.5 \times 10^{-5} \text{ mol L}^{-1}$. The detection limit was $2.1 \times 10^{-7} \text{ mol L}^{-1}$. The developed methodology was successfully applied in human urine samples.

Warfarin is a blood anticoagulant used to reduce or prevent various cardiovascular and cerebro-vascular disorders. De Jesus and co-authors developed a method based on batch injection analysis with multiple pulse amperometric detection for Wardarin detection in pharmaceutical formulations.^[4di] The BDD electrode was cathodically pretreated by applying a current of 0.001 A during 120 s and, after that, by applying a current of -0.03 A during 360 s, and the contrary was performed for the anodic treatment. After optimizing all the necessary parameters, a linear range of $2 \times 10^{-6} \text{ mol L}^{-1}$ to $2 \times 10^{-4} \text{ mol L}^{-1}$ with detection limit of $1 \times 10^{-7} \text{ mol L}^{-1}$ was obtained. The proposed method presented recovery of 104–105% for pharmaceutical dosages.

Usually used to avoid motion sickness associated with nausea and vomiting. Freitas and coauthors developed a method based on batch injection analysis with multiple pulse amperometric detection using DDB electrode anodically pretreated by applying 0.01 A for 1000 s in 0.04 mol L^{-1} Britton-Robinson buffer solution and after a cathodic pretreatment was performed by applying -0.01 A for 1000 s in a $0.1 \text{ mol L}^{-1} \text{ H}_2\text{SO}_4$ solution.^[4dk] On optimized condition, a linear range equal to $1.0 \times 10^{-5} \text{ mol L}^{-1}$ to $1.0 \times 10^{-4} \text{ mol L}^{-1}$ for 8-chlorotheophylline, and $1.0 \times 10^{-5} \text{ mol L}^{-1}$ to $1.4 \times 10^{-4} \text{ mol L}^{-1}$ for caffeine and $1.0 \times 10^{-5} \text{ mol L}^{-1}$ to $1.0 \times 10^{-4} \text{ mol L}^{-1}$ for diphenhydramine with a detection limit of $3.1 \times 10^{-7} \text{ mol L}^{-1}$ for 8-chlorotheophylline, $4.9 \times 10^{-7} \text{ mol L}^{-1}$ for caffeine and $7.6 \times 10^{-7} \text{ mol L}^{-1}$ for diphenhydramine.

Cocaine is an alkaloid, stimulant, with anesthetic effects used primarily as a recreational drug. Freitas and co-authors developed a method based in batch-injection analysis system with square-wave voltammetric on BDD electrodes.^[4d] Prior the analyses, the BDD electrode was anodically pretreated by applying +0.01 A for 1000 s in 0.12 molL⁻¹ Britton-Robinson buffer solution (pH 1.6). Next, a cathodic pretreatment was carried out by applying -0.01 A for 1000 s in a 0.1 molL⁻¹ H₂SO₄ solution. As optimized electrolyte, the authors used 0.1 molL⁻¹ H₂SO₄. The linear range obtained is from 2.0 × 10⁻⁵ molL⁻¹ to 9.9 × 10⁻⁵ molL⁻¹ and 8.9 × 10⁻⁷ molL⁻¹ as detection limit. In addition, the authors verified the applicability of the method in the presence of the compounds used as adulterants, and it is important to note that seizing the presence of other compounds it was possible to detect cocaine in the seized cocaine samples.

Bromazepam and alprazolam belong to the class of benzodiazepines which are medicines used in the treatment of anxiety, insomnia, depression, psychiatric disorders and alcohol withdrawal syndromes. Samiec and coauthors developed a method using DPV on BDD electrodes.^[4dn] For BDD electrodes treatment the authors used an anodic pretreatment in 1 molL⁻¹ H₂SO₄ by applying 2.0 V for 60 s to get rid of any impurities on the BDDE surface. Subsequently, a cathodic pretreatment using -2.0 V for 30 s in the same medium was carried out. Using BR buffer, pH 11, as supporting electrolyte was obtained a linear range from 1 × 10⁻⁶ molL⁻¹ to 1 × 10⁻⁴ molL⁻¹ and 8 × 10⁻⁷ molL⁻¹ to 1 × 10⁻⁴ molL⁻¹ Bromazepam and alprazolam, respectively. With detection limit of 3.1 × 10⁻⁷ molL⁻¹ and 6.4 × 10⁻⁷ molL⁻¹ for bromazepam and alprazolam, respectively. For recovery analyzes in actual pharmaceutical samples values between 97 and 101% were obtained for both drugs. In addition, the method proved to be robust and indifferent to possible interferences.

Industrial foods may contain the most diverse compounds. In the work developed by Alpar and coauthors, a method was developed to detect 5-O-caffeoylquinic acid, vanillin and caffeine in commercial samples.^[4d] The authors used anodic and cathodic pretreatments of the BDD electrode were carried out in 0.5 molL⁻¹ H₂SO₄ for 180 s, by applying activation potential of 1.7 and -1.7 V, respectively. Using as supporting electrolyte 0.1 M HNO₃ solution a linear concentration ranges of 2.8 × 10⁻⁶ to 1.7 × 10⁻⁴, 3.3 × 10⁻⁶ to 3.3 × 10⁻⁴, and 5.2 × 10⁻⁷ to 2.1 × 10⁻⁴ molL⁻¹ for de 5-O-caffeoylquinic acid, vanillin and caffeine, respectively. With detection limits of 4.0 × 10⁻⁷, 3.8 × 10⁻⁷, and 1.5 × 10⁻⁷ molL⁻¹, for de 5-O-caffeoylquinic acid, vanillin and caffeine, respectively. In order to evaluate the validity and the practical feasibility of the proposed method samples of vanilla sugar, cola soft drink and foamy instant coffee enriched with vanilla were analyzed where it was possible to obtain recovery percentages of 91 to 105%.

Cetirizine dihydrochloride is carboxylated metabolite of hydroxyzine and belongs to the second-generation class of antihistamines based on piperazine. Culkova and coauthors developed a simple method for cetirizine detection in different samples based in differential pulse voltammetry.^[4dp] Using 0.1 molL⁻¹ phosphate buffer solution (pH 8.0) and a cathodi-

cally pretreated using the potential of -3 V during 300 s in 0.6 molL⁻¹ H₂SO₄, it was obtained a linear range equal to 6.7 × 10⁻⁸ to 5.4 × 10⁻⁷ molL⁻¹ and detection limit to 1.6 × 10⁻⁸ molL⁻¹. The applicability of method was confirmed by analysis of pharmaceutical formulations and human urine as typical real samples.

Oxcarbazepine is an anticonvulsant or antiepileptic drug used in the treatment of partial and generalized seizures. Lima and coauthors develop a method based on flow injection analysis system coupled to multiple-pulse amperometric detection on BDD electrodes.^[4dq] As supporting electrolyte, the 0.1 molL⁻¹ acetate buffer pH 4.0 was used and the BDD electrodes was cathodically pretreated in a 0.5 molL⁻¹ H₂SO₄ solution by applying 0.03 A during 360 s. The anodic pretreatment was carried out by applying 0.001 A during 120 s using the same solution. A linear range from 2.0 × 10⁻⁶ to 8.0 × 10⁻⁵ molL⁻¹ with a limit of detection of 4.2 × 10⁻⁷ molL⁻¹ under optimized flow injection analysis conditions and recovery values close to 100% in analyses in tablets and urine.

Antihistamines such as pheniramine or chlorpheniramine are commonly associated with naphazoline (NPZ) in eye drops and nasal decongestants. Oliveira and coauthors develop a method for simultaneous detection of those compounds using batch-injection analysis system with multiple pulse amperometric.^[4dr] BDD electrode was anodically pretreated by applying 0.01 A for 1000 s in 0.12 molL⁻¹ BR buffer solution and then cathodically pretreated by applying -0.01 A for 1000 s in a 0.1 molL⁻¹ H₂SO₄ solution. A linear range from 1.6 × 10⁻⁵ to 1.6 × 10⁻⁴ molL⁻¹ for pheniramine and chlorpheniramine and 2.0 × 10⁻⁶ to 1.5 × 10⁻⁵ molL⁻¹ for naphazoline with a limit of detection of 6.4 × 10⁻⁷ molL⁻¹, 4.7 × 10⁻⁷ molL⁻¹ and 1.1 × 10⁻⁷ molL⁻¹ for pheniramine, chlorpheniramine and naphazoline, respectively.

Wong and coauthors developed a method based in flow injection analysis system with multiple pulse amperometric detection for the simultaneous determination of dopamine (DOP) and cysteamine (CYS) using BDD electrodes. The BDD electrode was submitted to anodic and cathodic pretreatment in a 0.5 molL⁻¹ H₂SO₄ solution by applying 0.04 Acm⁻² for 30 s and -0.04 Acm⁻² for 180 s, respectively. The analytical curves were linear in the concentration range from 5.0 × 10⁻⁷ to 1.3 × 10⁻⁴ molL⁻¹ for dopamine and from 5.0 × 10⁻⁷ to 1.5 × 10⁻⁴ molL⁻¹ for cysteamine, with detection limits of 1.1 × 10⁻⁸ and 1.3 × 10⁻⁸ molL⁻¹, respectively. The developed method were applied to analysis of serum and water river samples with the recoveries ranging from 92 to 110%.

Benzocaine is a local anesthetic presents in different aerosol sprays. Pysarevska and coauthors developed a miniaturized thick-film BDD electrode that was applied as electrochemical sensor for simple quantification of this local anesthetic agent. The cathodic and anodic pretreatment of the working electrode were carried out in the presence of 1 molL⁻¹ HNO₃ applying either -2.0 or 2.0 V (both for period of 40 s). In optimized parameters, the linear concentration range of 0.1-400 × 10⁻⁶ molL⁻¹ and 0.4-200 × 10⁻⁶ molL⁻¹. The limit of detection of 80 × 10⁻⁹ molL⁻¹ and 100 × 10⁻⁹ molL⁻¹ for DPV and SWV, respectively. The developed protocols were applied to analysis of the commercial pharmaceuticals with the recoveries ranging

from 97 to 105% and from 97 to 103% for DPV and SWV procedures as well as model human urine samples with recoveries from 96 to 104% and from 99 to 101%.

4. Conclusions and Future Perspectives

Bare and modified BDD electrodes have been effectively employed in voltammetric or flow injection methods for electroanalysis of the most commercially relevant classes of pharmaceutical compounds in numerous biological and environmental matrices. BDD electrodes exhibit a plethora of favorable properties, being their chemical stability, low tendency for adsorption of the reaction products on their surface, and huge potential window, the most relevant ones, when compared to most of solid electrodes. This literature review indicated that the most electrochemically characterized drugs have been antihypertensives, analgesics, antipyretics, and antibiotics, while application to other bioactive compounds (hormones, etc.) are still scarce, which can lead to further developments and achievements. In general, the described figures of merit (accuracy, calibration range, limit of detection, reproducibility and precision) for the electroanalytically characterized drugs compare favorably with those reached by the standard techniques (mainly gas or liquid chromatography with different detectors and spectrophotometry). Authors are unanimous on recognizing that the responses of BDD electrode are extremely influenced by the type of applied electrochemical pretreatment and that the H-terminated BDD surfaces usually originate the best electroanalytical performances. Moreover, studies that explore the combination of the inherent benefits of BDD electrode with the usage of nanomaterials in order to specifically tailor the BDD electrode surface properties are also very limited and, thus, exciting progresses are envisaged in this field. In this context, bare or modified BDD electrodes can open up new opportunities for the development of electrochemical sensors for real time on-line or in-line monitoring applications, in particular, for those occurring under harsh conditions.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: boron-doped diamond · electrodes · electroanalysis · electrochemical sensor · pharmaceuticals

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