

# Bioelectroanalysis of pharmaceutical compounds

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**Abstract** Recent developments in the bioelectroanalysis of pharmaceutical compounds are reviewed, concentrating particularly on the development of electrode materials and measurement strategies and on their application. The advantages of electroanalytical techniques as alternatives to other analytical procedures such as rapid response, sensitivity and low detection limits are highlighted and illustrated. Particular emphasis is given to carbon-based materials for voltammetric electroanalysis; new potentiometric sensors and electrochemical biosensors are also reviewed.

**Keywords** Electroanalysis · Pharmaceutical compounds · Electrode materials

## Introduction

Electroanalysis offers the possibility of determining an analyte concentration directly in a sample without any pre-treatment or chemical separation, in situations where matrix

effects are small, as well as of analysing coloured materials and samples with dispersed solid particles. Additionally, simultaneous and fast determination of a mixture of substances may be possible, with high sensitivity and low cost. There exist thousands of published articles involving electroanalytical methods for determining pharmaceutical products. In this review, we will not provide a comprehensive survey of all these articles but will highlight those which illustrate the approaches employed and show innovative aspects with respect to the type of electrode material or electroanalytical technique used.

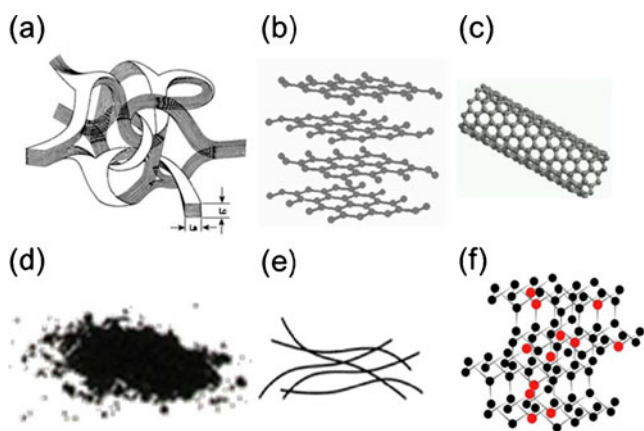
Most of the research undertaken has used electrodes of different forms of carbon. The reason for the use of carbon is the fact that it exists in many different forms which can be adapted to the necessity of the experiment—some of these will be described below—and that it is easily used in the positive potential region (most pharmaceutical compounds are determined by oxidation). Electroanalytical techniques employed are usually cyclic voltammetry (CV) and differential pulse or square-wave voltammetry, the last to increase sensitivity and decrease detection limits. One of the main difficulties with the electroanalysis of organic compounds in general is adsorption of the compound itself or of its oxidation products on the electrode surface. Some of the new materials and strategies developed have been precisely to reduce these effects and enable series of analyses to be undertaken with high reproducibility and/or repeatability. A number of different types of carbon electrode material used for pharmaceutical analysis are shown in Fig. 1. Different types of carbon electrode will now be addressed in turn followed by novel electrode materials for voltammetric and potentiometric sensing strategies and electrochemical biosensors.

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**Fig. 1** Structures of **a** glassy carbon, **b** graphite, **c** carbon nanotubes, **d** graphite powder, **e** carbon fibres, and **f** boron-doped diamond

### Glassy carbon electrodes

Glassy carbon was first described as a crystallite growth in non-graphitizing carbons, following an investigation of the structure of carbons of different origin treated at very high temperatures which has shown that the graphitizing and non-graphitizing carbons form two distinct and well-defined classes [1]. The differences in structure were apparent from the earliest stages of carbonization and were attributed mainly to the formation at low temperatures, in the non-graphitizing carbons, of a strong system of cross-linking uniting the crystallites. This leads to a random orientation of the crystallites in a rigid, finely porous mass. In the graphitizing carbons, the cross-linking is much weaker, the structure is more compact and neighbouring crystallites have a strong tendency to lie in a nearly parallel orientation. It was shown that crystallite growth occurs by the gradual displacement of whole layer planes or even of groups of layer planes. The pre-orientation existing in the graphitizing carbons facilitates this process, enabling the rearrangement of the layer planes to take place by small stages, and is the principal factor favouring crystallite growth in the graphitizing carbons. In the non-graphitizing carbons, crystallite growth is impeded both by the strong cross-linking between neighbouring crystallites and by their random orientation [1].

The structure of glassy carbon continued to be the subject of research, and it was found that “when many polymers are pyrolysed, they change directly into a form of carbon which retains the original morphology without passing through a plastic phase. This type of carbon has a glass-like appearance and is referred to as a glassy carbon. It is hard and brittle, unlike the soft graphitic forms of carbon, and does not revert to these forms at high temperatures and is called “glassy carbon” [2]. The manufacture of glassy carbon consists in carbonization by heating phenol/formaldehyde

polymers or polyacrylonitrile between 1,000 °C and 3,000 °C under pressure [1, 3].

Glassy carbon is, structurally, a  $sp^2$  carbon, characterised by the length of microcrystallites,  $La$ , in the graphite lattice plane ( $a$ -axis) and the thickness of the microcrystallites perpendicular to the graphite planes ( $c$ -axis),  $Lc$ . This structure is responsible for its amorphous characteristics, isotropy and possible lack of homogeneity.

Glassy carbon has been used as electrode material due to its excellent electrical and mechanical properties, wide potential range, extreme chemical inertness, being highly resistant to acid attack, impermeable to gases and has relatively reproducible performance. Glassy carbon electrodes can be polished using small alumina particles or diamond paste (0.05–1.0  $\mu\text{m}$ ) on a smooth polishing cloth, followed by rinsing with ultrapure water. Surface electrochemical pre-treatment, by cycling between +1.0 and –1.0 V, is also usually employed to create an active and reproducible glassy carbon electrode surface and to enhance its analytical performance [4, 5].

Glassy carbon electrodes have been widely used for mechanistic and electroanalytical evaluation of pharmaceuticals. A comprehensive list of medicinal drugs investigated is presented in Table 1, which includes [6–131]. An example of the use of glassy carbon electrodes is in the mechanistic evaluation and quantitative measurement of the cancer treatment drug glivec [57], shown in Fig. 2.

The oxidation mechanisms of drugs of abuse have also been studied using glassy carbon electrodes [132–135]. The importance of antioxidants to human health, namely from the polyphenol family of phytochemical antioxidants, to protect from the damage caused by oxidative stress, is documented in several studies undertaken on the electrochemical mechanisms of antioxidants [136–141]. Almost all antioxidants can be found in essential nutrients, and the understanding of the redox mechanisms is of foremost importance in the aim of developing new compounds from medicinal plants that are potentially therapeutically active.

A number of excellent reviews has been recently published [142–146] describing applications using chromatographic separation before electrochemical detection or of electroanalytical stripping techniques for the determination of pharmaceutically active compounds in dosage forms and biological samples, such as serum or urine.

### Boron-doped diamond electrodes

Boron-doped diamond (BDD) electrodes have been used as excellent materials for electroanalytical applications, due to their outstanding properties, which are significantly different from those of other conventional  $sp^2$  carbon electrodes, such as glassy carbon, pyrolytic graphite or carbon paste

**Table 1** Determination of pharmaceutical compounds using a glassy carbon electrode

Analyte	Technique	Medium	Potential/V	LOD	Ref.
Abacavir	DPV SWV	pH 2.0 BRb	1.07	$2.2 \times 10^{-7}$ M	[6]
Acetaminophen	CV/FIA	pH 5.5 acetate buffer	0.27	$1.7 \times 10^{-6}$ M	[7]
Adriamycin	CV DPV SWV	pH 4.5 acetate buffer	0.45	$7.9 \times 10^{-11}$ M	[8–10]
Alfuzosin	DPV SWV	pH 6.0 phosphate buffer	0.85	$1.610^{-7}$ M	[11]
Ambroxol	DPV	0.2 M H <sub>2</sub> SO <sub>4</sub>	1.05	$9.410^{-7}$ M	[12]
Amisulpride	DPV SWV	pH 7.0 BRb, pH 3.0 BRb	0.80–1.25	$2.2 \times 10^{-8}$ M	[13]
Amlodipine besylate	AdSSWV	pH 11.0 BRb	0.51	$1.4 \times 10^{-8}$ M	[14]
Amlodipine besylate	CV DPV SWV	pH 5.0 BRb	0.85	$8.0 \times 10^{-7}$ M	[15]
Apomorphine	DPV	pH 9 borate buffer	0.8	$5.0 \times 10^{-7}$ M	[16, 17]
Ascorbic acid	CV DPV SWV	–	0.40	$7.0 \times 10^{-7}$ M	[18]
Atenolol	DPV	–	1.04	$1.6 \times 10^{-4}$ M	[19]
Atomoxetine	CV DPV	pH 5.0 BRb	1.46	$6.9 \times 10^{-5}$ M	[20]
Atorvastatin	DPV SWV	0.1 M H <sub>2</sub> SO <sub>4</sub> , pH 3.0 BRb	1.02	$2.1 \times 10^{-7}$ M	[21]
Atorvastatin	CV DPV SWV	pH 5.0 BRb	0.92	$6.0 \times 10^{-7}$ M	[15]
Azithromycin	DPV	pH 7.0 phosphate buffer	0.700	$9.2 \times 10^{-7}$ M	[22, 23]
Benperidol	CV	0.1 M H <sub>2</sub> SO <sub>4</sub>	1.45	$8.0 \times 10^{-4}$ M	[24]
Benznidazole	CV DPV	pH 7.5 phosphate buffer	–0.46	$1.0 \times 10^{-5}$ M	[25]
Berberine	CV DPV SWV	pH 3.3 acetate buffer	1.17	$1.0 \times 10^{-5}$ M	[26]
Bromhexine	CV DPV	pH 2.5 BRb (methanol)	1.01	$1.4 \times 10^{-5}$ M	[27]
Bromocriptine	DPV	pH 5.0 BRb	0.70	0.01 mg/L	[28]
Buprenorphine	AdSV	pH 9.0 phosphate buffer	0.32	$2.0 \times 10^{-7}$ M	[29]
Candesartan cilexetil	AdSDPV AdSSWV	pH 5.0 phosphate buffer	1.60	$9.2 \times 10^{-7}$ M	[30]
Carvedilol	DPV SWV	0.2 M H <sub>2</sub> SO <sub>4</sub>	1.22	$2.1 \times 10^{-9}$ M	[31]
Catecholamines	CV coulometry	Acidic media	0.58	–	[32]
Cefadroxil monohydrate	DPV	pH 7.0 phosphate buffer	1.15	–	[33]
Cefixime	DPV SWV	pH 4.5 acetate buffer	0.90	$6.4 \times 10^{-7}$ M	[34]
Cefoperazone	DPV SWV	pH 2.0 phosphate buffer	0.87	$2.9 \times 10^{-7}$ M	[35]
Cefotaxime	DPV SWV	pH 2.0 phosphate buffer	0.87	$2.8 \times 10^{-7}$ M	[36]
Ceftazidime	DPSV OSWSV	pH 2.7 phosphate buffer	–1.0	$2.0 \times 10^{-10}$ M	[37]
Ciprofloxacin	Amperometric biosensor	pH 7.0 phosphate buffer	–0.20	$4.0 \times 10^{-8}$ M	[38]
Cinnarizine	Cv CAdSV	pH 3.7 acetate buffer	0.44	$9.0 \times 10^{-9}$ M	[39]
Cisapride	DPV SWV	pH 3.5 acetate buffer	1.02	$1.9 \times 10^{-7}$ M	[40]
Citalopram	CV DPV SWV	pH 8.2 phosphate buffer	0.85	$9.5 \times 10^{-6}$ M	[41]
Codeine	DPV SWV	pH 3.0 acetate buffer	1.2	$3.0 \times 10^{-6}$ M	[42]
Dihydrocodeine	SWV	pH 3.0 acetate buffer	1.2	$1.4 \times 10^{-5}$ M	[43]
Dopamine	FIA/amperometry		0.1	$1.5 \times 10^{-4}$ M	[44]
Disopyramide	CV DPV SWV	pH 7.0 phosphate buffer	0.7	$1.3 \times 10^{-6}$ M	[45]
Dopamine	CV DPV SWV	–	0.40	$7.0 \times 10^{-7}$ M	[18]
Doxycycline	Potentiometry		–	$4.0 \times 10^{-5}$ M	[46]
Droperidol	CV	0.1 M H <sub>2</sub> SO <sub>4</sub>	1.45	$8.0 \times 10^{-4}$ M	[24]
Enrofloxacin	AdSDPV	pH 7.0 BRb	–1.60	1.3 µg/L	[47]
Etodolac	DPV SWV	pH 2.2 BRb	0.70	$6.8 \times 10^{-7}$ M	[48]
β-Estradiol	DPV	0.05 M H <sub>2</sub> SO <sub>4</sub>	1.00	$4.0 \times 10^{-5}$ M	[49]
Fexofenadine HCl	DPV SWV	pH 7.0 BRb	0.86	$6.6 \times 10^{-9}$ M	[50]
Flunarizine	CV	0.5 M H <sub>2</sub> SO <sub>4</sub> (20% methanol)	1.27	$6.0 \times 10^{-6}$ M	[51]
Flupentixol	DPV SWV	pH 7.0 BRb	0.75	$1.2 \times 10^{-7}$ M	[52]
Fluphenazine	CV	0.1 M H <sub>2</sub> SO <sub>4</sub>	1.35	–	[53]
Fluvastatin sodium	DPV SWV	pH 10.0 BRb	0.80	$1.1 \times 10^{-6}$ M	[54]
Formoterol fumarate	LSV, DPV, SWV	–	–	$8.0 \times 10^{-6}$ M	[55]

**Table 1** (continued)

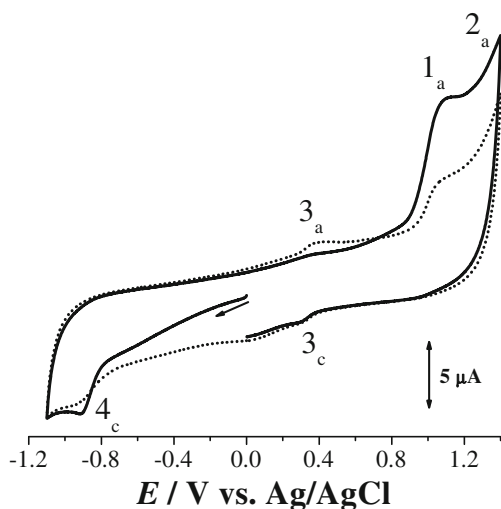
Analyte	Technique	Medium	Potential/V	LOD	Ref.
Ganciclovir	DPV SWV	pH 2.0 BRb	1.15	$8.1 \times 10^{-8}$ M	[56]
Glivec	CV DPV SWV	–	–	–	[57–59]
Hydrochlorothiazide	DPV	pH 3.3 BRb	1.040	5.0 µg/L	[60]
Hydroxychloroquine	DPV	pH 4.0 BRb	1.40	11.2 mg/L	[61]
Imipramine	CV	0.1 M H <sub>2</sub> SO <sub>4</sub>	1.15	–	[62]
Indinavir	DPV SWV	pH 10.0 BRb	0.75	$1.3 \times 10^{-7}$ M	[63]
Indole-3-propionamide	CV DPV	pH 2.0 BRb	0.78	$1.0 \times 10^{-5}$ M	[64]
5-(3'-Indolyl)-2-thiohydantoin derivatives	CV DPV	pH 1.0–pH 4.71	0.46–0.90	$1.0 \times 10^{-6}$ M	[65]
Isoniazid	CV	pH 9.0 NH <sub>3</sub> /NH <sub>4</sub> Cl buffer	0.1	$3.2 \times 10^{-6}$ M	[66–68]
Lacidipine	DPV SWV	0.1 M H <sub>2</sub> SO <sub>4</sub>	0.85	$1.4 \times 10^{-7}$ M	[68]
Lamivudine	DPV SWV	pH 4.5 acetate buffer	–1.26	$6.3 \times 10^{-8}$ M	[69]
Levofloxacin	CV	pH 5.0 acetate buffer	0.80	$1.0 \times 10^{-7}$ M	[70, 71]
Levodopa Carbidopa	DPV	0.1 M HClO <sub>4</sub>	0.58–1.02	$4.2 \times 10^{-8}$ M	[72]
α-Lipoic acid	CV DPV SWV	pH 6.9 phosphate buffer	0.76	$1.8 \times 10^{-6}$ M	[73]
Loracarbef	DPV SWV	0.1 M H <sub>2</sub> SO <sub>4</sub>	1.28	$2.4 \times 10^{-7}$ M	[74]
Mefloquine	DPV SWV	pH 11.1 BRb	–1.21	$4.5 \times 10^{-7}$ M	[75]
Melatonin and pyridoxine	DPV	0.5 M H <sub>2</sub> SO <sub>4</sub>	0.72–1.29	$5.9 \times 10^{-6}$ M	[76]
Metolazone	CV DPV SWV	pH 7.0 phosphate buffer	0.82	–	[77]
Metronidazole	DPV	pH 9.0 BRb	–0.71	$2.0 \times 10^{-8}$ M	[78–83]
Mitoxantrone	CV DPV SWV	pH 2.1 BRb	0.65	$1.9 \times 10^{-7}$ M	[84, 85]
Navelbine	CV DPV	pH 9.3 borax buffer	0.60	$1.0 \times 10^{-5}$ M	[86]
Nefazodone	DPV SWV	0.1 M H <sub>2</sub> SO <sub>4</sub>	1.00	$2.1 \times 10^{-7}$ M	[88]
Niclosamide	CV DPV SWV	pH 4.5 acetate buffer	–0.06	$1.0 \times 10^{-5}$ M	[89]
Nifedipine	CV	0.2 M H <sub>2</sub> SO <sub>4</sub> (20% methanol)	1.0	$1.1 \times 10^{-5}$ M	[90]
Norfloxacin enoxacin	Cathodic stripping voltammetry	DMF and HCl	–1.0	10 mg/L	[91]
Olsalazine sodium	DPV	pH 7.0 phosphate buffer	0.50	$5.8 \times 10^{-7}$ M	[92]
Omeprazole	CV DPV SWV	pH 7.0 phosphate buffer	0.8	$1.0 \times 10^{-6}$ M	[93]
Opipramol	DPV	pH 3.70 acetate buffer	0.82	$2.7 \times 10^{-7}$ M	[94]
Omidazole	CV	pH 4.7 acetate buffer	–0.350.65	$6.0 \times 10^{-6}$ M	[95]
Paracetamol	DPSV	pH 5.7 BRb	0.75	0.042 mg/L	[96]
Pefloxacin	CV DPV	pH 5.7 acetate buffer	0.85	$1.0 \times 10^{-6}$ M	[97]
Pentoxifylline	CV DPV	pH 3.0 phosphate buffer	1.35	$4.4 \times 10^{-10}$ M	[98]
Phenobarbital	DPSV	pH 5.7 BRb	0.75	0.042 mg/L	[96]
Phenothiazine derivatives	DPV SWV	pH 2.0 phosphate buffer	0.55–0.75	$6.0–7.5 \times 10^{-7}$ M	[99]
2-Phenylindole	CV	–	–	–	[100]
Pimozide	DPV	pH 2.1 BRb	1.10	$6.0 \times 10^{-7}$ M	[101]
Piribedil	DPV SWV	0.1 M H <sub>2</sub> SO <sub>4</sub> , pH 5.7 acetate buffer	1.27–1.29	$5.6 \times 10^{-7}$ M	[102]
Prednisolone	SWV	0.5 M H <sub>2</sub> SO <sub>4</sub>	0.59	$3.4 \times 10^{-7}$ M	[103]
Promethazine	CV	pH 4.7 acetate buffer	0.8	$2.0 \times 10^{-5}$ M	[104]
Repaglinide	CV DPV	pH 7.0 BRb	0.75	$1.1 \times 10^{-7}$ M	[105]
Quetiapine	DPV SWV	pH 3.5 acetate buffer	1.00	$4.0 \times 10^{-8}$ M	[106]
S-Adenosyl-methionine	DPV SWV	pH 2.0 phosphate buffer	1.50	$2.6 \times 10^{-6}$ M	[107]
Salbutamol	BIA/amperometry	–	0.9	$2.5 \times 10^{-7}$ M	[108]
Salicylic acid	DPV	pH 2.4 BRb	1.09	1.04 mg/L	[109]
Sanguinarine	CV DPV SWV	pH 7.0 phosphate buffer	0.6	$1.0 \times 10^{-5}$ M	[110]
Sertindole	CV DPV SWV	pH 3.5 acetate buffer	1.08	$1.9 \times 10^{-7}$ M	[111]

**Table 1** (continued)

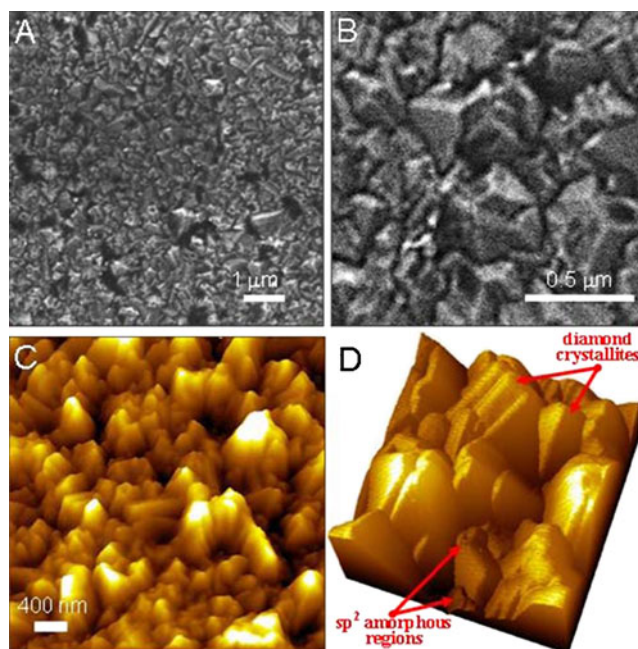
Analyte	Technique	Medium	Potential/V	LOD	Ref.
Sildenafil citrate	CV DPV SWV	pH 2.0 phosphate buffer	1.36	$5.7 \times 10^{-6}$ M	[112]
Simvastatin	DPV SWV	0.1 M H <sub>2</sub> SO <sub>4</sub>	1.10	$2.7 \times 10^{-7}$ M	[113]
Sparfloxacin	DPV	–	–	–	[114]
Tamsulosin	DPV SWV	pH 4.5 acetate buffer	1.15	$3.3 \times 10^{-7}$ M	[115]
Tegaserod	DPV	pH 9.0 BRb	0.16	$3.0 \times 10^{-10}$ M	[116]
Terbutaline	CV	pH 6.0 phosphate buffer	0.80	$8.0 \times 10^{-6}$ M	[117]
Thalidomide	CV DPV SWV	pH 7.0 phosphate buffer	0.74–1.10	–	[118, 119]
Tinidazole	CV	–	–1.0	$2.0 \times 10^{-6}$ M	[120]
Tramadol	CV DPV	pH 9.3	–	$2.2 \times 10^{-6}$ M	[121]
Trimebutine	DPV	Acetonitrile/0.1 M LiClO <sub>4</sub>	1.32	0.3 mg/L	[122]
Trimetazidine	AdSSWV	pH 5.0 acetate buffer	0.75	$2.0 \times 10^{-8}$ M	[123]
Tropolone	CV	–	–0.014	$1.0 \times 10^{-7}$ M	[124]
Valacyclovir	DPV SWV	pH 10.0 BRb	0.90	$1.0 \times 10^{-7}$ M	[125]
Verapamil	DPV SWV	pH 3.7 acetate buffer	0.94	$1.6 \times 10^{-7}$ M	[126]
Vardenafil	DPV SWV	pH 2.0 phosphate buffer	1.35	$2.3 \times 10^{-8}$ M	[127]
Vincristine, vindesine, vinblastine	CV DPV	pH 9.3 borax buffer	0.6	$1.0 \times 10^{-5}$ M	[87]
Vitamin C	Amperometry	–	–	–	[128]
Zolpidem	DPV	pH 8.0 BRb	0.889	$2.0 \times 10^{-7}$ M	[129]
Zuclopenthixol	DPV	pH 5.2 phosphate buffer	0.82	$2.2 \times 10^{-7}$ M	[130]
Ziprasidone	CV	0.1 M H <sub>2</sub> SO <sub>4</sub>	1.0	$1.0 \times 10^{-4}$ M	[131]

DPV differential pulse voltammetry, FIA flow injection analysis, SWV square-wave voltammetry, CV cyclic voltammetry, LSV linear sweep voltammetry, CA chronoamperometry, AdSSWV adsorptive stripping square wave voltammetry, AdSDPV adsorptive stripping differential pulse voltammetry, OSWSV Osteryoung square-wave stripping voltammetry, CAdSV catalytic adsorptive stripping voltammetry, DPSV differential pulse stripping voltammetry

[147–149]. Figure 3 shows scanning electron microscopy and atomic force microscopy imaging of the BDD surface. BDD is stable toward corrosion in very aggressive media,



**Fig. 2** Redox processes of glivec. CV obtained with a GCE in a solution of 50 μM glivec in pH 4.5 0.1 M acetate buffer saturated with N<sub>2</sub>; (solid line) first and (dotted line) second scan at  $\nu=500$  mV s<sup>-1</sup>. Reproduced with permission from [57]



**Fig. 3** BDD electrode surface. SEM images: **a** 10,000 and **b** 50,000 times. AFM images: **c**  $4,000 \times 4,000 \times 150$  nm<sup>3</sup> and **d**  $1,000 \times 1,000 \times 150$  nm<sup>3</sup>. Reproduced with permission from [149]

has a very low and stable voltammetric or amperometric background current and an extremely good electrochemical stability in both alkaline and acidic media. It also manifests a high sensitivity response, weak adsorption of polar surface contaminants and low sensitivity to the presence of dissolved oxygen in aqueous solutions. Figure 4 shows the approximate potential ranges of three commonly used electrode materials (Pt, Hg and C) and BDD. As can be observed, BDD presents a very wide working potential window, which can be larger than 3.5 V. As a consequence, the best electroanalytical performance is generally observed for high-quality films (i.e. negligible  $sp^2$ -bonded carbon impurity and a low fraction of secondary growths) in terms of linear dynamic range, limit of detection (LOD), response time, response precision and response stability. Analytical curves obtained using BDD electrodes often present a linear response over many orders of magnitude of concentration. The response time, i.e. the time for the analytical signal, reaches a maximum magnitude and decay back to the baseline. This response time for BDD electrodes is often much less than for other  $sp^2$  carbon electrodes. Good response precision and response stability are obtained using BDD electrodes because  $sp^2$  carbon electrodes are instable over the time resulting in potential changes due surface changes and adsorption of analyte and/or reaction products [147–149].

The electrochemical behaviour of BDD electrodes depends on their physical, chemical and electronic properties, which can be significantly affected by the surface termination such as hydrogen, oxygen and others. Hydrogen termination (HT-) and oxygen termination (OT-) are generated by electrochemical methods involving hydrogen evolution ( $H_2$ ) and oxygen evolution ( $O_2$ ), respectively, or by r. f. plasma treatment (HT- and OT-) amongst others. H-terminated surfaces are hydrophobic with high conductivity (negative electron affinity), whereas O-terminated surfaces are hydrophilic with low conductivity (positive electron

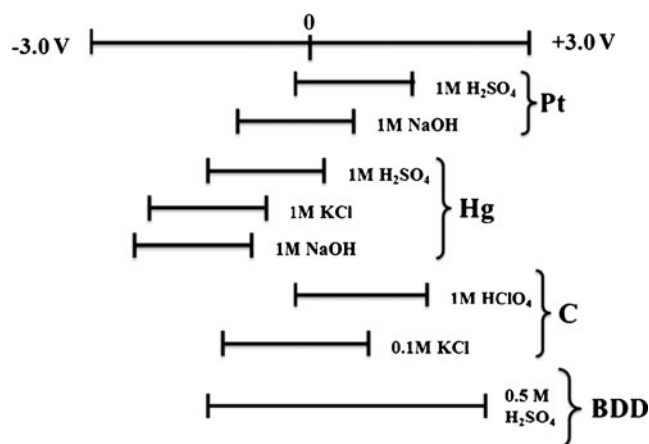
affinity) and the former present relatively high electron transfer rates as pointed out by Suffredini et al. [150]. The electrochemical behaviour of BDD electrodes also depends on the dopant concentration (B concentration), structural defects in the diamond film, non-diamond carbon impurity concentration ( $sp^2$  inclusions), grain boundary size (micro and nanodiamond), amongst others [147–152].

A comparison of the effect of anodic and cathodic electrochemical pre-treatments [applying  $\pm 3.0$  V vs. Ag/AgCl (3.0 M KCl), for 30 min, in 0.5 M  $H_2SO_4$ ] on the electrochemical response for some redox couples shows that for all redox couples studied, the electroanalytical response was significantly enhanced at the cathodically pre-treated BDD electrode [148, 153]. Figure 5 shows (a) cathodic and (b) anodic electrochemical pre-treatments of BDD electrodes and the surface termination with hydrogen-terminated BDD (HT-BDD) and oxygen-terminated BDD (OT-BDD).

It has been shown that, for many analytes, the combination of a cathodically pre-treated (hydrogen-terminated) BDD electrode with electrochemical techniques becomes a very powerful analytical tool. Hence, applications of cathodically pre-treated BDD electrodes in the amperometric and/or voltammetric determinations of various pharmaceutical products in different matrixes are presented hereinafter.

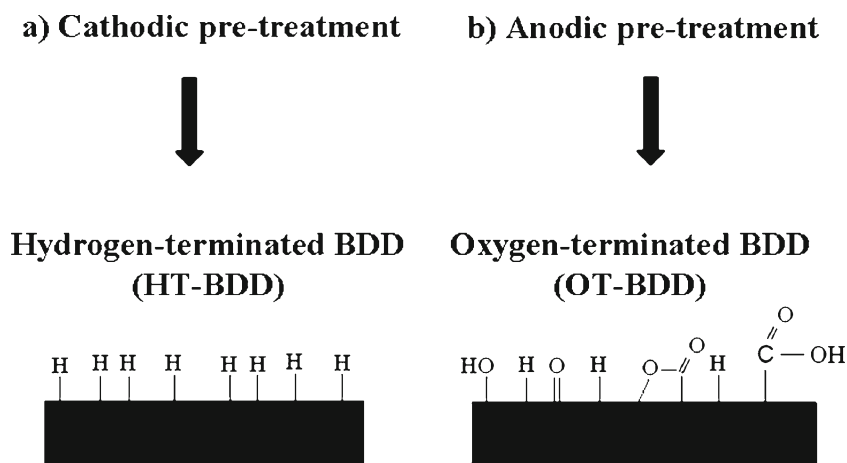
Acetylsalicylic acid (ASA), trade name aspirin, was determined in pharmaceutical formulations using square-wave voltammetry (SWV) at a cathodically pre-treated BDD electrode [154]. In this proposed electroanalytical method, ASA can be directly determined in a 0.01 M  $H_2SO_4$  solution without the need of a previous time-consuming alkaline hydrolysis step. A single oxidation peak at a potential of +1.97 V vs. Ag/AgCl (3.0 M KCl) with the characteristics of an irreversible reaction was obtained. The analytical curve was linear in the ASA concentration range  $2.50 \times 10^{-6}$ – $1.05 \times 10^{-4}$  M, with a LOD of 2.0  $\mu$ M. The proposed method was applied with success in the determination of ASA in several pharmaceutical formulations; the results were in close agreement, at a 95% confidence level, with those obtained using an official method of the British Pharmacopoeia.

The same research group simultaneously determined ascorbic acid (2-(1,2-dihydroxyethyl)-4,5-dihydroxyfuran-3-one) (AA) and caffeine (1,3,7-trimethyl-purine-2,6-dione) (CAF) by differential pulse voltammetry (DPV) using a cathodically pre-treated boron-doped diamond electrode as working electrode [155]. Linear analytical curves ( $r=0.999$ ) were obtained from  $1.9 \times 10^{-5}$  to  $2.1 \times 10^{-4}$  M for AA and from  $9.7 \times 10^{-6}$  to  $1.1 \times 10^{-4}$  M for CAF, with detection limits of 19  $\mu$ M and 7.0  $\mu$ M, respectively. This method was successfully applied for the determination of AA and CAF in pharmaceutical formulations, with results equal to those obtained using a HPLC reference method. In another work [156], paracetamol (*N*-acetyl-*p*-aminophenol, acetaminophen)



**Fig. 4** Supporting electrolyte approximate potential ranges for platinum, mercury, carbon and boron-doped diamond electrodes

**Fig. 5** Surface termination after boron-doped diamond electrode **a** cathodic and **b** anodic pre-treatments



and CAF were determined simultaneously and individually using a cathodically pre-treated BDD electrode. This was achieved using (a) SWV for paracetamol and (b) DPV for caffeine individually and for both drugs simultaneously. In the binary mixtures, a separation of 0.55 V between the oxidation peak potentials of paracetamol and caffeine was obtained. The corresponding analytical curve was linear in the range from 0.50 to 83  $\mu\text{M}$  for both compounds. The LOD values for the simultaneous determination of paracetamol and caffeine were 0.49 and 0.035  $\mu\text{M}$ , respectively, and the method was successfully applied to the simultaneous determination of paracetamol and caffeine in several pharmaceutical formulations.

The electrochemical behaviour of triflusal (TRF) and aspirin, before and after hydrolysis in water and in alkaline medium using two different electrode surfaces, glassy carbon and BDD, was studied by DPV over a wide pH range [157]. The hydrolysis products were 2-(hydroxyl)-4-(trifluoromethyl)-benzoic acid (HTB) for triflusal and salicylic acid (SA) for aspirin, which in vivo represent their main metabolites. Glassy carbon electrodes enable only indirect determination of TRF and aspirin through the electrochemical detection of their hydrolysis products HTB and SA, respectively. The oxidation processes of HTB and SA are pH dependent and involve different numbers of electrons and protons. Moreover, the difference between the oxidation peak potential of SA and HTB was equal to 100 mV in the studied pH range from 1 to 8 due to the  $\text{CF}_3$  of the aromatic ring of the HTB molecule. Due to its wider oxidation potential range, the boron-doped diamond electrode was used to study the direct oxidation of TRF and aspirin, as well as of their respective metabolites HTB and SA.

Estriol (1,3,5,(10)-estratriene-3,16 $\alpha$ ,17 $\beta$ -triol) is one of the three main estrogens produced by the human body. Estriol is only produced in significant amounts during pregnancy as it is made by the placenta and the control of its concentration gives a good indication of the general health of the foetus. A square-wave voltammetric method using a cathodically pre-treated BDD electrode for the

determination of estriol hormone in a pharmaceutical product and in a urine sample taken during pregnancy was described by Santos et al. [158]. The analytical curve obtained in the optimized experimental conditions was linear in the concentration range from  $2.0 \times 10^{-7}$  to  $2.0 \times 10^{-5}$  M ( $r=0.9994$ ), with a detection limit of  $1.7 \times 10^{-7}$  M and a quantification limit of  $8.5 \times 10^{-7}$  M. Recoveries of estriol were in the range of 98.6–101%, for the pharmaceutical sample, and 100–103% for the urine sample, indicating no significant matrix interference effects on the analytical results. The voltammetric method was applied with success to the determination of estriol in the commercial products and urine sample taken during pregnancy and could be an interesting alternative to the radioimmunoassay method.

Lidocaine (2-(diethylamino)-*N*-(2,6-dimethylphenyl)acetamide) is a local anaesthetic commonly used to relieve pain related to surgical, dental and gynaecological procedures. A SWV method was proposed by Oliveira et al. [159] using a cathodically pre-treated BDD electrode. Thus, before each determination, the BDD electrode was pre-treated in a 0.1 M  $\text{HClO}_4$  solution by applying +3.2 V vs. Ag/AgCl (3.0 M KCl) for 30 s (to clean the electrode surface), followed by  $-2.8$  V vs. Ag/AgCl (3.0 M KCl) for 30 s. The analytical curve was linear in the lidocaine concentration range from  $2.42 \times 10^{-5}$  to  $1.14 \times 10^{-4}$  M with recoveries ranged from 97.7% to 99.2% for three commercial pharmaceutical products (gels). The proposed method was successfully applied in the determination of lidocaine in the presence of propyleneglycol in three different commercial gel formulations. In those determinations, the presence of propyleneglycol had no influence on the square-wave voltammetric responses.

Propranolol (PROP) (1-isopropylamino-3-(1-naphthyl-oxo)-2-propranolol) and atenolol (ATN) (4-(2-hydroxy-3-isopropylaminopropoxy) phenylacetamide) are cardioselective  $\beta$ -adrenergic receptor blocking agents. These  $\beta$ -blocker agents are most frequently prescribed to treat tremors, high

blood pressure (hypertension), angina pectoris, cardiac arrhythmias and myocardial infarction. The independent determination of the two  $\beta$ -blocker agents in pharmaceutical formulations using square-wave voltammetry and a cathodically pre-treated boron-doped diamond electrode was also proposed [160]. The SWV determination of propranolol or atenolol was carried out in 0.1 M  $\text{H}_2\text{SO}_4$  or 0.5 M  $\text{NaNO}_3$  (pH 1.0, adjusted with concentrated  $\text{HNO}_3$ ), respectively. The analytical curves obtained ranging from 0.20 to 9.0  $\mu\text{M}$  for PROP and from 2.0 to 41  $\mu\text{M}$  for ATN, with detection limits of 0.18 and 0.93  $\mu\text{M}$ , respectively. The recoveries found ranged from 93.9% to 105%, for PROP, and from 92.5% to 106%, for ATN, and the method was successfully applied in the determination of both  $\beta$ -blockers in several pharmaceutical formulations.

Sildenafil citrate (1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1-H-pyrazolo[4,3-d]pyridin-5-yl)-4-ethoxyphenyl]sulphonyl]-4-methylpiperazine citrate), commonly known under trade name Viagra<sup>®</sup>, is a drug widely used as oral therapy for erectile dysfunction. Sartori et al. [161] proposed the use of DPV in conjunction with a cathodically ( $-1.0 \text{ A cm}^{-2}$  for 240 s in 0.5 M  $\text{H}_2\text{SO}_4$ ) pre-treated BDD electrode for the determination of Viagra<sup>®</sup> in pharmaceutical products. According to the authors, the HT-BDD electrode presented a better peak definition and a higher current magnitude, indicating that the cathodic pre-treatment of the electrode led to a larger oxidation wave for Viagra<sup>®</sup>. Cyclic voltammetric studies show that sildenafil presents two irreversible oxidation peaks, at  $\sim 1.5$  and  $\sim 2.0$  V vs. Ag/AgCl (3.0 M KCl). In order to avoid interference from the oxygen evolution reaction, only the first peak was considered for the development of the electroanalytical method. The analytical curve was linear in the sildenafil concentration interval from  $7.3 \times 10^{-7}$  to  $7.3 \times 10^{-6}$  M with a limit of detection of  $6.4 \times 10^{-7}$  M. The recoveries ranged from 91.5% to 101%, and the DPV method was applied with success in three commercial products.

Sulphamethoxazole (SMX), a sulphamide indicated primarily to treat urinary infections, is found in pharmaceutical products with another drug that increases its power. When SMX is combined with trimethoprim (TMP), they are used for the treatment of bronchitis, sinusitis, ear infections and pneumocystis pneumonia. A simultaneous DPV determination of SMX and TMP using a cathodically (HT<sup>-</sup>) or an anodically (OT<sup>-</sup>) pre-treated BDD electrode has been reported by Andrade et al. [162]. The cathodic or anodic pre-treatment was carried out by applying  $-0.5$  or  $0.5 \text{ A cm}^{-2}$ , respectively, during 60 s, in a 0.5 M  $\text{H}_2\text{SO}_4$  solution. Cyclic voltammetric studies, at pH 7 (0.2 M Britton–Robinson buffer), show that on a HT-BDD electrode, both SMX and TMP voltammograms presented well-defined irreversible oxidations peak at 0.92 and 1.1 V vs. Ag/AgCl (3.0 M KCl), respectively. When an OT-BDD electrode was used,

in the same experimental conditions described, the magnitude of these oxidation peaks decreased, more so for SMX oxidation. The analytical curves were linear in the concentrations range 1.0–10 and 0.2–2.0  $\text{mg L}^{-1}$  for SMX and TMP, respectively. The calculated values for the LOD and the limit of quantification were  $3.65 \mu\text{g L}^{-1}$  (14.4 nM) and  $12.2 \mu\text{g L}^{-1}$  (48.2 nM) for SMX and  $3.92 \mu\text{g L}^{-1}$  (13.5 nM) and  $13.1 \mu\text{g L}^{-1}$  (45.1 nM) for TMP. Besides this, repeatability tests carried out by successive measurements ( $n=10$ ) in the same solution (10  $\text{mg L}^{-1}$  SMX and 2.0  $\text{mg L}^{-1}$  TMP) showed relative standard deviation values of 0.3% and 0.1%, respectively. The proposed method was applied successfully to determine SMX and TMP by the standard addition method in three different commercial formulations.

Sulphadiazine and sulphamethoxazole were determined independently in pharmaceutical formulations employing a cathodically pre-treated BDD electrode and SWV at an irreversible oxidation peak at +1.1 V [163]. In this work, a BDD electrode was pre-treated in 0.5 M  $\text{H}_2\text{SO}_4$  [164], in which it was first anodically pre-treated (+3.0 V vs. SCE for 30 min) to clean its surface, followed by a cathodic pre-treatment ( $-3.0$  V vs. SCE for 30 min). Additionally, before each measurement, the electrode was conditioned at  $-3.0$  V vs SCE for 30 s, the first pre-treatment each day being done for 30 s at  $-2.0$  V vs. SCE. The analytical curves were linear in the concentration ranges from  $8.01 \times 10^{-6}$  to  $1.19 \times 10^{-4}$  M ( $r=0.9995$ ) for sulphadiazine and from  $6.10 \times 10^{-6}$  to  $6.01 \times 10^{-5}$  M ( $r=0.9995$ ) with limits of detection of 2.19 and 1.15  $\mu\text{M}$  for sulphadiazine and sulphamethoxazole, respectively. The recoveries ranged from 95% to 104%, and the method was successfully applied to the determination of sulphadiazine and sulphamethoxazole in pharmaceutical formulations.

### Carbon composite electrodes

Solid electrodes were the first used in electrochemistry [165, 166]. Solid carbon electrodes can be prepared from a number of available carbon types grouped by McCreery and Cline [167] as pyrolytic graphite, polycrystalline graphite, glassy carbon and carbon fibres. Each type presents its own advantages and limitations that define the electrode applicability and uses. Kinoshita also presents a detailed description of electrochemical and physicochemical properties of carbon [168].

Since Adams described the preparation of an electrode in which graphite was agglutinated by bromoform in 1958 [169], the search for new strategies for preparation of graphite electrode materials became a prolific branch of research into alternatives to mercury and noble metal electrodes to determine organic compounds in the positive potential range with less need of surface renewal. The strategy of



agglutinating graphite with an inner liquid or a solid polymer leads to the preparation of composite electrodes, defined by Tallman and Petersen as a material prepared by mixing at least one insulating phase with at least one conductor phase, resulting in a new material with properties that differ from those of the starting ones [170]. They also classified the composite electrodes, prepared with graphite as a conductor, as *solid*, when the insulating phase is a polymer or *paste*, when oils or paraffin are used.

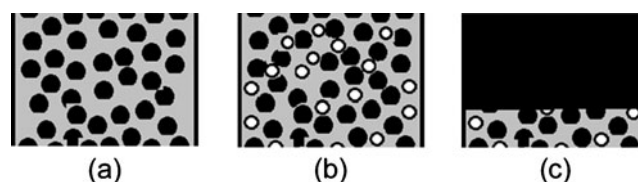
Due to its extensive use in many electrochemical and electroanalytical studies, the preparation and use of carbon paste electrodes (CPE), invented by Adams [169, 171], have been frequently reviewed. Kalcher et al. presented an extensive review covering the period 1990–1993 [172], in which they presented previous reports on CPE uses and preparation [173–175]. Among these, one is specifically directed to pharmaceutical analysis [176] and others to modified pastes [177–179]. The use of carbon pastes modified with enzymes was reviewed by Gorton [180].

More recently, Crespilho and Resende [181] reviewed the use of humic acids as the CPE modifier and finally, celebrating the 50th anniversary of this kind of electrode material. Svancara et al. [182, 183] reviewed the electrochemistry and electroanalytical applications of CPE electrodes.

Reviews on the preparation and uses of solid carbon-based electrodes have also been presented, starting with Tallman and Petersen [170] followed by Céspedes and co-workers [184]. Alegret [185] reported on graphite–polymer composites and biocomposites for electrochemical sensing, and Pividori and Alegret [186] reviewed the use of rigid carbon composites in genosensing.

Strategies for the preparation and use of solid carbon electrodes are also discussed by Uslu and Oskan [144, 145]. Preparation of electrodes modified with carbon nanotubes (CNT) is of growing interest as presented by Wang et al. [187], Dumitrescu et al. [188] and Ahammad et al. [189]. Surface modifications, films and nanotubes deposited on the electrode surface will be considered separately below. Another topic that is of recent interest in the literature is the use of ionic liquids in the preparation of sensors as presented by Wei and Ivaska [190]. The most recent general review paper on the preparation and uses of rigid carbon electrodes was presented by Navratil and Barek [191].

Many recent applications of solid (also called rigid) composite electrodes involve preparation by agglutinating graphite with a polymer in order to prepare a rigid electrode body. The main advantage is that the whole electrode body is prepared, and if surface renewal is needed, the composite material (bulk modified or not) is not loosened, as occurs when only the surface is modified. Figure 6 illustrates the possibilities of preparation of unmodified composites, bulk modified composites and composites prepared on top of an electrode substrate surface.



**Fig. 6** Representation of composite electrodes: **a** unmodified, **b** body modified and **c** modified composite deposited on a substrate electrode surface. In these representations, the *grey phase* represents the agglutinant, the *black circles* the graphite and the *hollow circles* represent the modifier; the *black strip* in **c** represents the substrate electrode

These composites are classified according to the way in which the conductor phase (in this case graphite) is dispersed in the agglutinant (a polymer or an inner oil), as *dispersed* when the conductor is randomly distributed in the composite matrix or *consolidated* when the conductor is present in defined areas of the material as in arrays [170]. The advantages in preparing such kinds of electrodes are mainly related to the ease of construction, possibility of being constructed in many different shapes, physical characteristics, mechanical resistance, robustness for flow applications, low cost, simplicity of surface renewal and improvements in signal to noise ratio [170, 192]. Additionally, there is the possibility of modifier incorporation, and there is good reproducibility and repeatability of (electro)active area.

In the development of these electrode materials is very important to find an appropriate conductor/agglutinant ratio. Trijueque et al. [193] reached this relation theoretically using the percolation theory for a graphite/epoxy composite with conductor particles size <50  $\mu\text{m}$ . According to the theory, the current suddenly increases for a certain minimum threshold amount of conductor and then assumes an almost constant value. The resistance of the composite follows an inverse behaviour, and when the material becomes conductive, Navarro-Laboulais et al. [194] consider that the graphite particles act as an array of ultramicroelectrodes. In particular, if the conducting particles are sufficiently close to each other then, besides the good conduction within the composite, on the surface, the diffusion fields overlap sufficiently such that the behaviour is similar to that of a bulk solid electrode of the same geometric area.

Concerning the insulating (agglutinant) phase, there are many described in the literature. Examples are polyvinyl chloride (PVC) [195], epoxy resin [196], Kel-F [197], wax [198], ceramics [199], silicone rubber [200], amongst others.

Depending on the materials used in the preparation of the composite, procedures involved in the electrode material preparation can be (1) graphite mixed with a thermoplastic polymer followed by thermosetting of the mixture; (2) compression of polymer powder and graphite; (3) in situ polymerization of monomer mixed with graphite; (4) melting,

homogenization and cooling of paraffin (or other melting inner substance) mixed with graphite and (5) dissolution of the polymer in a volatile solvent, mixing with graphite and evaporation of the solvent [192, 201].

Some recent advances in preparing these electrodes and their use in pharmaceutical analysis are presented next. Table 2 summarises most of the analytical characteristics, analytes and techniques involved in each case.

#### Graphite/castor oil polyurethane composite electrodes

The advantages of using castor oil derived polyurethane were first described in 2002 by Mendes et al. [201]. After optimizing the building parameters, the authors proposed a 60% in graphite composition (*m/m*), as the best regarding mechanical resistance and response when one considers the voltammetric profile and current intensity. Since the

**Table 2** Determination of pharmaceutical compounds using solid carbon composite electrodes

Analyte	Technique	Medium	LDR/M	LOD/M	Ref
<b>GPUE</b>					
Atenolol	DPV	Universal buffer pH 10	$4 \times 10^{-6}$ – $100 \times 10^{-6}$	$3.16 \times 10^{-6}$	[206]
Atenolol	FIA	Universal buffer pH 10	$0.2 \times 10^{-3}$ – $3 \times 10^{-3}$	$18.1 \times 10^{-6}$	[207]
Dopamine	SWV	BR buffer pH 7.4	$6.6 \times 10^{-6}$ – $24.1 \times 10^{-6}$	$6.4 \times 10^{-8}$	[203]
Furosemide	DPV	Acetate, phosphate or borax	$0.75 \times 10^{-6}$ – $6.5 \times 10^{-6}$	$0.15 \times 10^{-6}$	[211]
	SWV	buffer solutions pH 1.2 to 13	$3 \times 10^{-6}$ – $9 \times 10^{-6}$	$0.96 \times 10^{-6}$	
Imipramine	SWV	BR buffer pH 7.0	$3.04 \times 10^{-7}$ – $30.4 \times 10^{-7}$	$4.6 \times 10^{-9}$	[208]
Nortriptyline	CV	BR buffer pH 7.4	$1.66 \times 10^{-5}$ – $17.3610^{-5}$	–	[211]
Paracetamol	SWV	Universal buffer pH 8	$1.0 \times 10^{-7}$ – $1.0 \times 10^{-5}$	$6.7 \times 10^{-8}$	[210]
Rutin	SWV	BR buffer pH 5.0	$1.1 \times 10^{-6}$ to $3.1 \times 10^{-6}$	$7.1 \times 10^{-9}$	[205]
Verapamil	DPV	Acetate buffer pH 5.3	$2 \times 10^{-6}$ – $30 \times 10^{-6}$	$0.7 \times 10^{-6}$	[209]
	SWV	Acetate buffer pH 5.3	$2 \times 10^{-6}$ – $14 \times 10^{-6}$	$0.7 \times 10^{-6}$	
<b>GEE</b>					
2-Aminonaphtalene	DPV	BR buffer pH 8	$2 \times 10^{-6}$ – $10 \times 10^{-6}$	$0.92 \times 10^{-6}$	[215]
Adenine, guanine	DPV	Phosphate buffer pH 7	$1 \times 10^{-4}$ – $2.5 \times 10^{-4}$	–	[215]
Ascorbic acid	Amperometry	Phosphate buffer pH 5	$9.93 \times 10^{-7}$ – $2.85 \times 10^{-4}$	$0.65 \text{ ng mL}^{-1}$	[214]
Ascorbic acid	CV	0.1 M phosphate buffer/0.1 M KCl pH 7 and 2	–	–	[216]
		0.1 M H <sub>2</sub> SO <sub>4</sub>	–	–	
<b>GSRE</b>					
Propranolol	DPV	BR buffer pH 7.4	$5$ – $80.6 \times 10^{-6}$	$1.1 \times 10^{-6}$	[224]
Rutin	DPV	BR buffer pH 4	$5$ – $50 \times 10^{-8}$	$1.8 \times 10^{-8}$	[223]
<b>Other composites</b>					
Ascorbate	Amperometric	0.1 M Sodium phosphate buffer pH 7	–	$7.7 \times 10^{-6}$	[227]
Ascorbic acid	FIA	0.1 M KBr	$5 \times 10^{-5}$ – $1 \times 10^{-3}$	$1.51 \times 10^{-5}$	[227]
Benzhexol	CV	0.1 M phosphate buffer pH 8	$3.5 \times 10^{-5}$ – $2 \times 10^{-6}$	$3 \times 10^{-7}$	[233]
Procyclidine		0.1 M phosphate buffer pH 8.5	$2.5 \times 10^{-4}$ – $3 \times 10^{-6}$	$4 \times 10^{-7}$	
Diclofenac	DPV	0.1 M HClO <sub>4</sub>	$6 \times 10^{-8}$ – $10^{-6}$	$5 \times 10^{-8}$	[228]
	SWV		$5 \times 10^{-9}$ – $6 \times 10^{-7}$	$5 \times 10^{-9}$	
Folic acid	DPASV	0.1 M phosphate buffer pH 7.8	$9.1 \times 10^{-12}$ – $3.4 \times 10^{-8}$	$0.034$ – $0.038 \text{ ng mL}^{-1}$	[234]
L-Tryptophan	DPASV	0.1 M phosphate buffer pH 2	$4.4 \times 10^{-9}$ – $9.1 \times 10^{-8}$	$0.24 \text{ ng mL}^{-1}$	[235]
Acetylsalicylic acid	FIA	Phosphate buffer pH 7	$1 \times 10^{-3}$ – $5 \times 10^{-3}$	$1.1 \times 10^{-5}$	[225]
Kaempferol	DPV	Methanol–NaClO <sub>4</sub>	$2.4 \times 10^{-7}$ – $3.4 \times 10^{-6}$	$6 \text{ ng mL}^{-1}$	[229]
Oxalic acid	DPV, LSV, CA	Na <sub>2</sub> SO <sub>4</sub>	$0.5$ – $3 \times 10^{-3}$	$0.05 \times 10^{-3}$	[230]
Quercetin	DPV	Methanol–NaClO <sub>4</sub>	$3.2 \times 10^{-7}$ – $9.9 \times 10^{-7}$	$6 \text{ ng mL}^{-1}$	[229]
Rutin	LSV	0.1 M KNO <sub>3</sub> /10 <sup>-6</sup> M HNO <sub>3</sub> pH 6	$9.9 \times 10^{-7}$ – $8.07 \times 10^{-6}$	$2.65 \times 10^{-8}$	[226]
Rutin	DPV	0.1 M phosphate buffer pH 7	$2 \times 10^{-8}$ – $1.0 \times 10^{-6}$	$1.5 \times 10^{-8}$	[232]
Salicylic acid	FIA	Phosphate buffer pH 7	$1 \times 10^{-5}$ – $5 \times 10^{-5}$	$3.5 \times 10^{-6}$	[225]

GPUE graphite/castor oil polyurethane composite electrodes, GEE graphite/epoxy composite electrodes, GSRE graphite–silicone rubber composite electrode, DPV differential pulse voltammetry, FIA flow injection analysis, SWV square-wave voltammetry, CV cyclic voltammetry, DPASV differential pulse anodic stripping voltammetry, LSV linear sweep voltammetry, CA chronoamperometry

polymer presents an oily nature, it can prevent swelling of the electrode material during its use in aqueous media, and its resistance to most organic solvents allows it to be used in non-aqueous media [202].

Using a device prepared with this material, de-Toledo et al. [203] determined dopamine in a synthetic cerebrospinal fluid at pH 7.4 in Britton–Robinson buffer in a DPV procedure without interference of ascorbic acid at 0.20 V (vs. Ag/AgCl). The same authors used the device to investigate the oxidation mechanism of the tricyclic antidepressant imipramine using electrochemical and quantum chemical studies. Following this, a new electroanalytical determination procedure was developed based on SWV measurements and applied in pharmaceutical formulations in good agreement with the official spectrophotometric method [204]. The electrochemical oxidation of the flavonoid rutin was used for its determination in green tea infusion samples using SWV at graphite/castor oil polyurethane composite electrodes (GPUE) [205], with detection limits at the nanomolar level and which was shown to be ten times more sensitive than glassy carbon under the same conditions.

The anti-hypertensive atenolol was determined in pharmaceutical formulations using a DPV procedure, being much more sensitive than the GC [206]. The results agreed with those from an official HPLC method at the micromolar level. The analyte is oxidized in basic medium (pH=10.0, universal buffer), with an oxidation peak at 760 mV (vs. SCE). Interference from other analytes was noticed, but no effect from the constituents of the pharmaceutical formulations was observed. The determination of the same analyte was also performed in a flow injection procedure in which the atenolol signal was detected in an amperometric procedure at the GPUE. The procedure was additionally successfully applied in the determination of the analyte in pharmaceutical formulations with 90 determinations per hour [207].

The GPUE was also used in the determination of furosemide, another anti-hypertensive and diuretic pharmaceutical, at the GPUE. The oxidation process at +1.0 V (vs. SCE) was investigated by CV and electrochemical impedance spectroscopy (EIS) methods, over a wide pH range [208]. The quantification of furosemide was carried out using CV, DPV and SWV, with the best detection limit obtained in DPV as 0.15  $\mu\text{M}$  without need of surface renewal. The method was applied to pharmaceutical formulation analysis with results that agreed with those from a spectrophotometric procedure.

The release profiles of verapamil, a calcium-channel blocker class anti-hypertensive, from commercial tablets was studied using the GPUE, after developing the DPV and SWV conditions for the drug determination. Detection limits at the sub-micromolar level were achieved and EIS suggested that any adsorption of the analyte on the electrode

surface occurred during measurements [209]. This was attributed to a very thin nanometre-thick film of polyurethane on the top of surface-“exposed” graphite particles, protecting them from adsorption whilst being so thin as to allow electron transfer to occur.

In order to improve selectivity and sensitivity of the GPUE, the potentiality of inserting molecularly imprinted polymers (MIPs) in the electrode body was investigated [210]. Thus, a paracetamol-modified methacrylate matrix was first prepared and the analyte removed by solvent extraction. The resulting MIPs were inserted into the composite electrode matrix, and parameters such as particle size and MIP content were evaluated. The MIP-modified electrode was shown to be more sensitive than the non-imprinted modified GPUE and the interference of phenacetin decreased remarkably when the paracetamol MIP was used in the electrode modification. Figure 7 shows the process of preparing the MIP and its insertion into the graphite–polyurethane composite.

Finally, a study on the possible sites of oxidation and epoxidation of the antidepressant nortriptyline using electrochemical and quantum chemistry methods has been presented [211]. The authors suggested that the proposed method could be used to quantify the analyte in pharmaceutical and biological fluids using CV with advantages in relation to the boron-doped diamond and the GC electrodes. EIS was also used to evaluate the behaviour of nortriptyline on the GPUE surface.

#### Graphite/epoxy composite electrodes

Epoxides have long been used in the preparation of carbon composite electrodes. This strategy for preparing solid carbon electrodes was probably initiated by Swofford and Carman in 1966 [212], using the electrode as a stationary and rotating sensor for  $[\text{Fe}(\text{CN})_6]^{3-}$  as an electrochemical probe. Reviews [172, 191] have also resumed the uses and applications of such devices. From these reviews, one can see that the groups of Alegret et al. in Spain and Navratil et al. in the Czech Republic have presented much work in this field. Although many kinds of epoxy resin formulation can be used in the preparation of the electrodes, they appear not to have a significant effect on the final result. Recently, an education paper has been presented concerning the preparation and applications of graphite–epoxy composite electrodes [213].

Since the earlier 1990s, epoxy composites have been successfully used as modified electrodes as amperometric detectors for multivitamin preparations [214]. However, they are still being used without modification in the determination of 2-aminonaphthalene, adenine, guanine and manganese in DPV procedures [215]. Also, using an unmodified electrode material, the evaluation of the oxidation potential

of hydroquinone and ascorbic acid has been described in weakly acidic and neutral media [216]. The results were compared with thermodynamic data and the effect of ageing of the electrode material was also evaluated.

#### Graphite/silicone rubber composite electrodes

Pungor et al. first described the preparation and use of the graphite–silicone rubber composite electrode (GSRE) [217]. The authors presented a short review on the development of many types of carbon-based electrodes and considered the use of GSRE in voltammetry. The magnitude of the residual current, the relation between the electroactive species concentration and the peak current, as well as reproducibility, was investigated. The electrochemical behaviour of some organic and inorganic compounds was also studied.

The Hungarian group then presented some research on the use of these composites as voltammetric working electrodes [217–222]. However, surprisingly, the use of this interesting composite material was interrupted, and only potentiometric studies were subsequently carried out. It may be that the negative potential range limitations of the electrode material led to it being neglected.

In a recent paper, Santos et al. [223] determined rutin using a GSRE and a DPV procedure. At the GSRE, rutin presented a reversible redox pair of peaks at 0.411 and 0.390 V (vs. SCE) in Britton–Robinson buffer (pH 4.0). Using optimized parameters rutin could be determined at  $10^{-8}$  M level, with need of surface renewing after each determination. The repeatability of the electrode between successive resurfacing steps was  $1.09 \pm 0.06 \mu\text{A}$  ( $n=10$ ).

The GSRE was also used in the determination of the anti-hypertensive propranolol in a DPV procedure in BR buffer (pH 7.4). Optimized parameters led to detection at the micromolar level, but with need of surface renewal, with peak current repeatability of  $4.5 \pm 0.1 \mu\text{A}$  ( $n=10$ ) for the same propranolol solution [224].

#### Other composite electrodes

An amperometric multisite detection flow injection system was developed using a tubular graphite paraffin wax composite electrode. Initially, the system was optimized with  $[\text{Fe}(\text{CN})_6]^{4-}$  as probe, and the system was then used for the sequential determination of salicylic and acetylsalicylic acids at a fixed potential of 0.98 V (vs. Ag/AgCl). Detection limits of  $10^{-5}$  and  $10^{-3}$  M were found, respectively, for salicylic and acetylsalicylic acids [225].

The determination of rutin in a graphite–paraffin composite electrode modified with Cu(II) immobilised in ion-exchange resin was carried out. Many parameters were optimized concerning the content of copper in the resin as

well as the content of Cu-resin in the paraffin electrode. Sub-micromolar amounts of rutin could be determined with this device in a  $\text{KNO}_3/\text{HNO}_3$  solution (pH 6.0) supporting electrolyte [226].

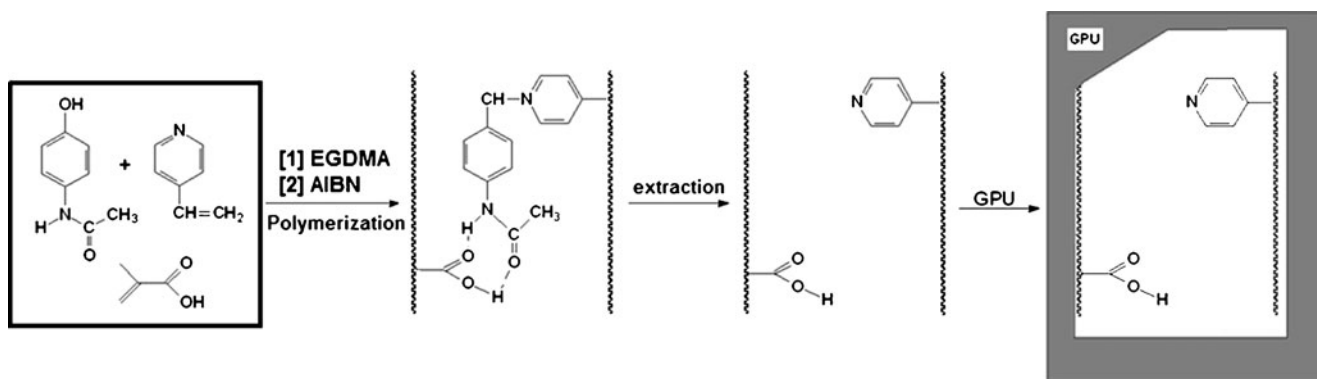
A graphite–PVC/tetrathiafulvalene–tetracyanoquinodimethane composite electrode was prepared and used as a detector in a wall-jet electrochemical cell for a flow system. The proportions of the components of the sensor were optimized and allowed the determination of ascorbic acid with good reproducibility, good electron transfer kinetics and low background current [227]. Detection at the  $10^{-5}$ -M level is just a little better than at the graphite–PVC composite electrode also used by the authors.

The electrochemical behaviour of diclofenac at graphite–Teflon<sup>®</sup>, graphite–epoxy and carbon black–epoxy electrodes was investigated, presenting a similar behaviour at all three electrodes, with an irreversible peak at 0.84 V (vs. Ag/AgCl), giving rise to products that are electroactive and present reversible redox processes at 0.39 and 0.63 V. However, graphite was preferable to carbon black whilst both epoxy and Teflon<sup>®</sup> gave a similar response [228]. The authors pointed out the possibility of using MIP's in the modification of the electrodes and found that incubation of the electrodes in a diclofenac solution in acetonitrile increases the signal even at non-imprinted electrodes containing acrylic polymers, suggesting the presence of interactions between the polymer and the analyte.

In other comparative study, carbon fibre, carbon fibre coated with Nafion and graphite–PVC electrodes were used in the determination of the flavonoids quercetin and kampferol from Ginkgo Biloba phytopharmaceutical samples. The electrodes were used in DPV in two different media: (a) polar solution consisting of methanol–acetonitrile– $\text{NaClO}_4$  (0.1 M) (30:30:40, v/v/v) and (b) non-polar medium composed of dioxane–hexane– $[\text{LiCl}/\text{methanol}$  (10%, m/v)] (40:40:20, v/v/v). The performance of the sensors as liquid chromatographic electrochemical detectors was evaluated, and the composite electrode was shown to be more sensitive than the others in a comparison presented in [229]. Chromatographic procedures using other detectors were also evaluated.

An exfoliated graphite–polystyrene composite electrode was used in the determination of oxalic acid in DPV, linear sweep voltammetry and chronoamperometry procedures [230]. Oxalic acid voltammograms were obtained in 0.1 M  $\text{Na}_2\text{SO}_4$ , appropriate conditions for each technique. Limits of detection of  $10^{-5}$  M were found with the voltammetric techniques without need of surface renewal, and the results found in spiked in the electrolyte agreed with the classical titration procedure using  $\text{KMnO}_4$ .

A flexible composite material prepared with graphite and cellulose acetate polymer was described [231]. The new electrode was characterised using CV and EIS as well as



**Fig. 7** Steps of the GPUE paracetamol MIP-modified composite electrode preparation: **a** a mixture of methacrylic acid, 4-vinylpyridine and paracetamol is polymerized in the presence of azobis-isobutyronitrile (AIBN) and ethylene glycol dimethacrylate (EGDMA) in acetonitrile at

65 °C for 24 h; **b** polymethacrylate containing the paracetamol is formed; **c** the paracetamol is extracted generating the imprinted polymer with coordination sites, and finally, **d** the imprinted polymer is inserted into the graphite-polyurethane composite

SEM. The electrode was successfully applied to the determination of ascorbate in vitamin C tablets with amperometric detection at 0.0 V (vs. SCE), with a detection limit in the micromolar range. Electropolymerization of neutral red on the electrode surface was performed as a promising strategy for future use as a redox mediator in biosensors.

Nanostructures of MCM-41 silica were prepared and used to modify a carbon paste electrode for the determination of rutin with enhanced current compared with the GC electrode. The improvement was attributed to the larger electrode area, high sorption capacity and specific mesopores. Using the new electrode, rutin was determined with a sub-micromolar detection limit and the procedure applied in traditional Chinese medicines [232].

Benzhexol and procyclidine were determined using an electrochemiluminescence-based sensor, prepared by placing a graphite composite containing tris(bipyridine)ruthenium(II). After characterisation of the sensor response, it was used for the determination of the pharmaceuticals with a detection limit at the  $10^{-7}$ -M level [233].

A new approach to prepare composite electrodes involves the preparation of molecularly imprinted polymeric fibres (monoliths) for direct use in the sensing devices, in which polymeric fibres containing graphite as a conducting phase are incorporated into polymers imprinted with the desired analyte. The procedure was used in folic acid analysis using differential pulse anodic stripping voltammetry after accumulation of the analyte at 1.2 V (vs. Ag/AgCl) during 180 s in phosphate buffer (pH 7.8). The procedure was applied to blood and pharmaceutical samples with a detection limit around  $0.034$ – $0.038$  ng mL<sup>-1</sup> [234]. The same kind of sensor was used in the determination of the amino acid *L*-tryptophan, presenting enantioselectivity. Determination of the amino acid in aqueous, biological and pharmaceutical samples was achieved with a detection limit of  $0.24$  ng mL<sup>-1</sup> [235].

Normally, graphite or even glassy carbon [236] microparticles are used as conducting phase. More recently, the use of multiwalled carbon nanotubes (MWCNT) has been investigated either as full or as partial replacement for graphite [237, 238] to explore possible electrocatalytic effects and will be discussed further in the next section on CNT.

Other types of bulk modification have been researched with success. The incorporation of a zinc metalloporphyrin enabled enhancement of the signal corresponding to the reduction process of metronidazole benzoate [239] and of iron tetrapyrroline porphyrin for the selective measurement of estradiol valerate [240]. In [241], a bienzymatic biosensor based on creatinase and sarcosine oxidase was used for the assay of creatine, and a trienzymatic biosensor based on creatinase, sarcosine oxidase and creatininase was proposed for the assay of creatinine all the enzymatic elements being incorporated into a diamond paste electrode. A novel insulating phase based on the mixture of cellulose acetate with ionic liquid was developed in [242], was used for immobilising laccase and incorporated into a carbon paste electrode for successful functioning as demonstrated by the analysis of methyl dopa,

Carbon composite electrodes can be used as substrates for modification in the same way as bulk solid electrodes, for example [243–245]; whereas [243] concerns colloidal-gold cysteamine modification, [244] employs MWCNT and [245] a film of non-ionic poly(2-amino-5-mercapto-thiadiazole).

### New electrode materials for bioelectroanalysis of pharmaceuticals

In this section, new and recently developed electrode and modified electrode materials that have been used for the

analysis of pharmaceutical compounds will be introduced and applications described. Emphasis will be given to those developed within the last 5 years. During this period, two review papers have appeared on different aspects of the application of modified electrodes to pharmaceutical analysis [145, 246]. Interestingly, new materials for potentiometric analysis have played quite a large role as well as bulk- or surface-modified electrodes for voltammetric or amperometric analysis, and there are some reports of electrochemical biosensors.

#### Screen-printed electrodes

Screen-printed electrodes have found increasing use as single-use, disposable electrochemical sensors or in situations where low cost is important [247]. For this reason, they have also been investigated for the electroanalysis of pharmaceutical compounds in complex media. Many of the electrode materials tested with bulk carbon electrodes have also been tested at carbon screen-printed electrodes.

Recent examples can be found where the carbon electrode has been modified with another component, usually to confer or enhance electrocatalytic properties. Thus poly(L-histidine) modification was successfully used for isoniazid [248], poly(3,4-ethylenedioxythiophene) for acetaminophen [249] and cobalt phthalocyanine for citric acid in pharmaceutical formulations [250]. Silver nanoparticles were incorporated into the carbon layer and showed a catalytic effect towards oxcarbazepine [251].

A CNT-containing screen-printed carbon electrode was used for silybin determination following heating of the electrode up to 50 °C in order to enhance the adsorptive accumulation of the analyte increasing the signal by up to two orders of magnitude [252].

#### Carbon nanotube electrodes

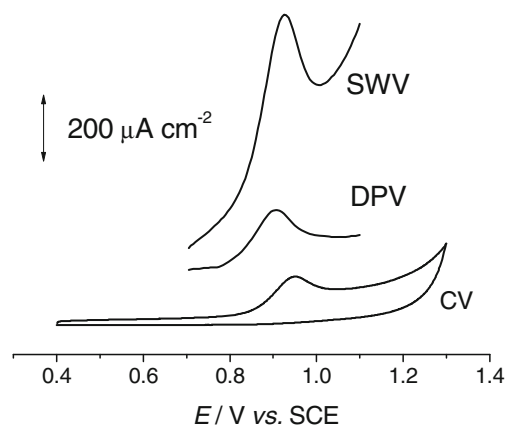
CNT have been used in many different types of sensors as a way of increasing the analytical signal and investigating possible electrocatalytic properties, exploiting the fact that the reaction sites on the carbon nanotube surface are, in principle, different from those at a macroscopic glassy carbon or carbon paste electrode, e.g. [253]. There is always an increase in current due to the higher surface area but not as much as would be calculated—this is because some of the surface is not active and because access of the analyte to the reaction sites may be difficult. The fact that the first is the case was recently illustrated in a study comparing three different brands of carbon nanotube where evident differences were encountered [254]. Some of the research has involved immobilising carbon nanotubes on the surface of a substrate electrode, others co-immobilising it with other

components, and in a third strategy it is incorporated into a paste/composite matrix.

As examples of the first strategy, CNT were immobilised using Nafion and used to determine venlafaxine and desvenlafaxine [255]. Poly(4-amino-benzoic acid) was used instead of Nafion to measure doxepin [256], polycysteic acid for sinomenine [257] and chitosan matrices either to measure acetaminophen and mefenamic acid simultaneously [258] or dipyrone [259]; in this latter case, the CNTs are covalently bound to the matrix [259]. Single-walled carbon nanotube (SWCNT)- and MWCNT-modified carbon ceramic electrodes were compared for nanomolar detection of acetaminophen [260], it being found that the current enhancement and electrocatalytic effects were better using SWCNT.

MWCNTs have been mixed with silver [261] or cobalt [262] nanoparticles to measure sumatriptan and thioridazine, respectively. Mixtures with cerium dioxide [263] and silica [264] have also been investigated. Finally, poly(Nile blue) has been employed with CNT to measure carbidopa and benserazide [265], the phenazine acting as redox mediator to enhance the signal and providing a more highly conducting matrix.

Carbon paste/composite electrodes have been devised with CNT as conducting phase instead of graphite microparticles; detailed studies suggest that it is the density of edges that determines the performance [266]. For pharmaceutical applications, a CNT/silicone rubber composite electrode was developed for propranolol [237]; Fig. 8 shows a comparison of determination of propranolol by oxidation using cyclic, differential pulse and square-wave voltammetry and clearly demonstrates the higher sensitivity of SWV. In another example, thionine was immobilised on CNT before preparing a carbon paste electrode to measure



**Fig. 8** Voltammograms of 50  $\mu\text{mol L}^{-1}$  propranolol in B-R buffer pH 7.0 at MWCNT/silicone rubber composite electrode using the techniques SWV, DPV and CV. Conditions—SWV: pulse amplitude=50 mV, frequency=25 Hz and step potential  $\Delta E=5$  mV. DPV: scan rate=25  $\text{mV s}^{-1}$  and pulse amplitude=50 mV. CV: scan rate=50  $\text{mV s}^{-1}$ . Reproduced with permission from [237]

ascorbic acid, acetaminophen and isoniazid simultaneously [238]. In these cases, it is necessary to circumvent the increased tendency for adsorption of organic compounds on the electrode surface. Use of ionic liquids to form the paste, as investigated for dextromethorphan [267], is another strategy for this purpose which can be expected to have some success in the future owing to the hydrophobic nature of many ionic liquids.

#### Fullerene electrodes

Fullerenes have been suggested for use in electrochemistry owing to their conducting properties and possible electrocatalytic effects. In pharmaceutical voltammetric studies, they have been studied as alternatives for carbon nanotubes, etc. to modify carbon electrodes. Examples are fullerene-modified glassy carbon electrodes for the determination of atenolol [19], methylprednisolone [268] and cefitizoxime [269], graphite electrodes for dexamethasone [270] and graphite electrodes together with CNT for triamcinolone [271]. Fullerene-modified gold electrodes have been employed for prednisolone [272] and for dopamine in the presence of ascorbic acid [273].

#### Potentiometric sensors containing new ion-exchange components

The determination of pharmaceutical compounds using ion-selective electrodes has been important for many years. The strategy usually involves incorporating a component in the membrane which is selective for the molecule in question, usually through formation of an association complex. The matrix materials has usually been PVC.

In one of the early papers of this series [274], low-cost ion-selective electrodes with a membrane consisting of PVC with poly(ester-urethane) plus drug–tetraphenylborate and drug–phosphotungstate ion pairs as electroactive materials were developed for the determination of the 1,4-benzodiazepines bromazepam, clonazepam and diazepam in pharmaceutical preparations as well as in biological fluids. The poly(ester-urethane)s were used successfully to avoid complications encountered in the usage of PVC-based electrodes in complex matrices such as urine. Electrode fouling was prevented due to their higher hydrophobic nature and lower tendency for adsorption of endogenous cations and proteins than PVC.

Another report, several years later [275], concerns ion-selective electrodes based on PVC membranes, again doped with drug–tetraphenylborate or drug–phosphotungstic acid ion-pair complexes as molecular recognition materials, but without poly(urethane), applied to the measurement of antiepileptic drugs in pharmaceuticals, plasma and urine.

A similar type of membrane material was used for Pioglitazone (an oral antidiabetic agent that acts primarily by decreasing insulin resistance) use ion association complexes based on a PVC membrane sensor with electroactive materials of tetraphenylborate, phosphomolybdate or phosphotungstate [276]. Tetraphenylborate was the electroactive material in an ISE made with a screen-printed electrode and *o*-nitrophenyloctylether plasticizing agent [277, 278].

A PVC matrix was used for sodium tetraphenyl phthalate as an electroactive material and dibutyl phthalate as an anion excluder to form ion pairs with amiloride (a potassium-conserving relatively weak natriuretic diuretic with anti-hypertensive activity) [279].

Several papers use reineckate salts as electroactive agents. These include sensors for dextromethorphan, a highly effective non-opioid antitussive drug (reineckate salt or phosphomolybdate electroactive agents) [280], for oxybutynin hydrochloride and flavoxate hydrochloride urogenital system drugs (reineckate salt or tungstophosphate) [281] or antidiabetic drugs were also determined by carbon paste-based and PVC membrane-based ISEs (reineckate salt or tungstophosphate) [282].

Different approaches were taken for the analysis of *S*-ketoprofen, a nonsteroidal anti-inflammatory drug. Maltodextrins with different dextrose equivalents were used to design three enantioselective ISEs and were shown to be highly effective for the envisaged purpose [283]. Enantioselective potentiometric membranes in carbon paste membranes were also developed containing fullerenes for the assay of (*L*)-histidine [284] and ibuprofen [285] or *S*-deprenyl [286]. In [287], a PVC membrane incorporating bismuth tetraiodate was found to be excellent association agent for the determination of melatonin and oxomemazine in urine and pharmaceutical preparations without interferences.

Finally, in [288], an approach based on host–guest interaction in molecularly imprinted materials was developed, characterised and successfully applied to the sensing of norflaxin. Polymers were used made from methacrylic acid and/or 2-vinyl pyridine.

#### Electrochemical biosensors

The development of voltammetric biosensors for pharmaceutical compounds has increased in recent years. Carbon and gold screen-printed electrodes, together with the addition of gold nanoparticles, were used as substrates for cytochrome biosensors, using cytochrome P450B4 covalently linked to the substrate, application being illustrated by the determination of phenobarbital in pharmaceutical drugs [289]. Gold chips were also employed as substrates for such CYP450 biosensors [290].

In [291], horseradish peroxidase (HRP) was immobilised in a polypyrrole matrix, formed in situ by electropolymerisation to measure levetiracetam (a novel antiepileptic); a strategy of covalent grafting of HRP was employed in [292]. Finally, HRP was immobilised within a zirconium alkoxide–polyethyleneimine film and applied to acetaminophen [293]. An amperometric immunosensor was developed for the anti-HIV agent dideoxyinosine based on carbon paste impregnated with solubilized antidideoxyinosine [294].

## Conclusions

This review of recent developments in the bioelectroanalysis of pharmaceutical compounds has demonstrated that the field is thriving. It can be expected to continue to find wide application, particularly given the manifest advantages of electrochemistry in relation to other analytical techniques. The search for new materials in order to avoid adsorption problems or electrode surface changes, an issue already partially solved, can be expected to continue and lead to further successes in the future.

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## References

- Franklin RE (1951) Crystallite growth in graphitizing and non-graphitizing carbons. *Proc R Soc Lond A* 209:196–218
- Jenkins GM, Kawamura K (1971) Structure of glassy carbon. *Nature* 231:175–176
- Harris PJF (2004) Fullerene-related structure of commercial glassy carbons. *Phil Mag* 84:3159–3167
- McCreery RL (1991) Carbon electrodes: structural effects on electron transfer kinetics. In: Bard AJ (ed) *Electroanalytical chemistry*, vol 17. Dekker, New York, pp 221–274
- Brett CMA, Oliveira-Brett AM (1993) *Electrochemistry, principles, methods and applications*. Oxford University Press, UK
- Uslu B, Ozkan SA (2004) Anodic voltammetry of abacavir and its determination in pharmaceuticals and biological fluids. *Electrochim Acta* 49:4321–4329
- Silva MLS, Garcia MBQ, Lima JLFC, Barrado E (2006) Modified tubular electrode in a multi-commutated flow system: determination of acetaminophen in blood serum and pharmaceutical formulations. *Anal Chim Acta* 573–574:383–390
- Piedade JA, Fernandes IR, Oliveira-Brett AM (2002) Electrochemical sensing of DNA–adriamycin interactions. *Bioelectrochemistry* 56:81–83
- Oliveira-Brett AM, Vivan M, Fernandes IR, Piedade JAP (2002) Electrochemical detection of in situ adriamycin oxidative damage to DNA. *Talanta* 56:959–970
- Oliveira-Brett AM, Piedade JAP, Chiorcea A-M (2002) Anodic voltammetry and AFM imaging of picomoles of adriamycin adsorbed onto carbon surfaces. *J Electroanal Chem* 538–539: 267–276
- Uslu B (2002) Voltammetric analysis of alfuzosin HCl in pharmaceuticals, human serum and simulated gastric juice. *Electroanalysis* 14:866–870
- Demircigil BT, Uslu B, Ozkan Y, Ozkan SA, Senturk Z (2003) Voltammetric oxidation of ambroxol and application to its determination in pharmaceutical and in drug dissolution studies. *Electroanalysis* 15:481–489
- Ozkan SA, Uslu B, Senturk Z (2004) Electroanalytical characteristics of amisulpride and voltammetric determination of the drug in pharmaceuticals and biological media. *Electroanalysis* 16:231–237
- Gazy AAK (2004) Determination of amlodipine besylate by adsorptive square wave anodic stripping voltammetry on glassy carbon electrode in tablets and biological fluids. *Talanta* 62:575–582
- Dogan-Topal B, Bozal B, Demircigil BT, Uslu B, Ozkan SA (2009) Electroanalytical studies and simultaneous determination of amlodipine besylate and atorvastatin calcium in binary mixtures using first derivative of radio-voltammetric methods. *Electroanalysis* 21:2427–2439
- Garrido JMPJ, Delerue-Matos C, Borges MFM, Macedo TRA, Oliveira-Brett AM (2002) Oxidative behaviour of apomorphine and its metabolites. *Bioelectrochemistry* 55:113–114
- Garrido JMPJ, Delerue-Matos C, Borges F, Macedo TRA, Oliveira-Brett AM (2003) Flow injection electrochemical determination of apomorphine. *Anal Lett* 36:2199–2210
- Erdurak-Kiliç CS, Uslu B, Dogan B, Ozgen U, Ozkan SA, Coskun M (2006) Anodic voltammetric behavior of ascorbic acid and its selective determination in pharmaceutical dosage forms and some *Rosa* species of Turkey. *J Anal Chem* 61:1113–1120
- Goyal RN, Singh SP (2006) Voltammetric determination of atenolol at C<sub>60</sub>-modified glassy carbon electrodes. *Talanta* 69:932–937
- Pérez-Ortiz M, Munõz C, Zapata-Urzuá C, Álvarez-Lueje A (2010) Electrochemical behavior of atomoxetine and its voltammetric determination in capsules. *Talanta* 82:398–403
- Dogan-Topal B, Uslu B, Ozkan SA (2007) Investigation of electrochemical behavior of lipid lowering agent atorvastatin calcium in aqueous media and its determination from pharmaceutical dosage forms and biological fluids using boron-doped diamond and glassy carbon electrodes. *Comb Chem High T Scr* 10:571–582
- Nigovi B, Simunic B (2003) Voltammetric assay of azithromycin in pharmaceutical dosage forms. *J Pharm Biomed Anal* 32:197–202
- Palomeque ME, Ortiz PI (2007) New automatized method with amperometric detection for the determination of azithromycin. *Talanta* 72:101–105
- Biryol I, Ozkan SA (1997) Voltammetric determination of droperidol and benperidol. *J Pharm Biomed Anal* 15:1695–1701
- La-Scalea MA, Serrano SHP, Ferreira EI, Oliveira-Brett AM (2002) Voltammetric behavior of benzimidazole at a DNA-electrochemical biosensor. *J Pharm Biomed Anal* 29:561–568
- Diculescu VC, Enache TA, Oliveira PJ, Oliveira-Brett AM (2009) Electrochemical oxidation of berberine and of its oxidation products at a glassy carbon electrode. *Electroanalysis* 21:1027–1034
- Turchán M, Jara-Ulloa P, Bollo S, Nuñez-Vergara LJ, Sequella JA, Álvarez-Lueje A (2007) Voltammetric behaviour of bromhexine and its determination in pharmaceuticals. *Talanta* 73:913–919
- Radi A, El-Shahawi MS, Elmogy T (2005) Differential pulse voltammetric determination of the dopaminergic agonist bromocriptine at glassy carbon electrode. *J Pharm Biomed Anal* 37:195–198
- García-Fernández MA, Fernández-Abedul MT, Costa-García A (2000) Determination of buprenorphine in pharmaceuticals and human urine by adsorptive stripping voltammetry in batch and flow systems. *Electroanalysis* 12:483–489



30. Dogan B, Uslu B, Ozkan SA (2004) Anodic stripping voltammetry of the hypertensive drug candesartan cilexetil at the glassy carbon electrode. *Pharmazie* 11:840–844
31. Dogan B, Ozkan SA (2005) Electrochemical behavior of carvedilol and its adsorptive stripping determination in dosage forms and biological fluids. *Electroanalysis* 17:2074–2083
32. Ziyatdinova GK, Budnikov GK (2005) Determination of some catecholamines by coulometric titration and cyclic voltammetry. *J Anal Chem* 60:673–677
33. Ozkan SA, Erk N, Uslu B, Yılmaz N, Biryol I (2000) Study on electrooxidation of cefadroxil monohydrate and its determination by differential pulse voltammetry. *J Pharm Biomed Anal* 23:263–273
34. Golcu A, Dogan B, Ozkan SA (2005) Anodic voltammetric behavior and determination of cefixime in pharmaceutical dosage forms and biological fluids. *Talanta* 67:703–712
35. Dogan B, Golcu A, Ozkan SA (2009) Electrochemical behavior of the bactericidal cefoperazone and its selective voltammetric determination in pharmaceutical dosage forms and human serum. *Curr Pharm Anal* 5:179–189
36. Dogan B, Golcu A, Dolaz M, Ozkan SA (2009) Anodic oxidation of antibacterial drug cefotaxime sodium and its square wave and differential pulse determination in pharmaceuticals and human serum. *Curr Pharm Anal* 5:197–207
37. El-Maali NA (2000) Voltammetric analysis of ceftazidime after preconcentration at various mercury and carbon electrodes: application to sub-ppb level determination in urine samples. *Talanta* 51:957–968
38. Torriero AAJ, Ruiz-Diaz JJJ, Salinas E, Marcevsky EJ, Sanz MI, Raba J (2006) Enzymatic rotating biosensor for ciprofloxacin determination. *Talanta* 69:691–699
39. El-Sayed GO, Yasin SA, El-Badawy AA (2008) Voltammetric behavior and determination of cinnarizine in pharmaceutical formulations and serum. *Anal Lett* 41:3021–3033
40. Satana E, Uslu B, Ozkan SA (2002) Differential pulse and square wave voltammetric determination of cisapride in tablet dosage form. *Pharmazie* 57:501–503
41. Nouws HPA, Delerue-Matos C, Barros AA, Maesen E, Moreira SCPA, Neves MMPS (2008) Static and hydrodynamic monitoring of citalopram based on its electro-oxidation behavior at a glassy-carbon surface. *Anal Lett* 41:2171–2185
42. Garrido JMPJ, Delerue-Matos C, Borges F, Macedo TRA, Oliveira-Brett AM (2002) Electroanalytical determination of codeine in pharmaceutical preparation. *Anal Lett* 35:2487–2498
43. Garrido JMPJ, Delerue-Matos C, Borges F, Macedo TRA, Oliveira-Brett AM (2003) Electrochemical determination of dihydrocodeine in pharmaceuticals. *Anal Lett* 36:577–590
44. Bezerra VS, Lima Filho JL, Montenegro MCBSM, Araujo AN, Silva VL (2003) Flow-injection amperometric determination of dopamine in pharmaceuticals using a polyphenol oxidase biosensor obtained from soursop pulp. *J Pharm Biomed Anal* 33:1025–1031
45. Diculescu VC, Enache TA, Oliveira-Brett AM (2007) Electrochemical oxidation at a glassy carbon electrode of the anti-arrhythmia drug disopyramide. *Anal Lett* 40:2860–2871
46. Sun XX, Aboul-Enein HY (2002) Internal solid contact sensor for the determination of doxycycline hydrochloride in pharmaceutical formulation. *Talanta* 58:387–396
47. Navalon A, Blanc R, Reyes L, Navas N, Vilchez JL (2002) Determination of the antibacterial enrofloxacin by differential pulse adsorptive stripping voltammetry. *Anal Chim Acta* 454: 83–91
48. Yılmaz S, Uslu B, Ozkan SA (2001) Anodic oxidation of etodolac and its square wave and differential pulse voltammetric determination in pharmaceutical and human serum. *Talanta* 54:351–360
49. Salcı B, Biryol I (2002) Voltammetric investigation of  $\beta$ -estradiol. *J Pharm Biomed Anal* 28:753–759
50. Golcu A, Dogan B, Ozkan SA (2005) Anodic voltammetric behavior and determination of antihistaminic agent: fexofenadine HCl. *Anal Lett* 38:1913–1931
51. Uslu B, Yılmaz N, Erk N, Ozkan SA, Senturk Z, Biryol I (1999) The study of the voltammetric behavior of flunarizine. *J Pharm Biomed Anal* 21:215–220
52. Dogan B, Ozkan SA, Uslu B (2005) Electrochemical characterization of flupenthixol and rapid determination of the drug in human serum and pharmaceuticals by voltammetry. *Anal Lett* 38:641–656
53. Senturk Z, Ozkan SA, Uslu B, Biryol I (1996) Anodic voltammetry of fluphenazine at different solid electrodes. *J Pharm Biomed Anal* 15:365–370
54. Ozkan SA, Uslu B (2002) Electrochemical study of fluvastatin sodium analytical application to pharmaceutical dosage forms, human serum, and simulated gastric juice. *Anal Bioanal Chem* 372:582–586
55. Demircigil BT, Ozkan SA, Coruh O, Yılmaz S (2002) Electrochemical behavior of formoterol fumarate and its determination in capsules for inhalation and human serum using differential-pulse and square-wave voltammetry. *Electroanalysis* 14:122–127
56. Uslu B, Dogan B, Ozkan SA (2005) Electrochemical studies of ganciclovir at glassy carbon electrodes and its direct determination in serum and pharmaceuticals by square wave and differential pulse voltammetry. *Anal Chim Acta* 537:307–313
57. Diculescu VC, Vivan M, Oliveira-Brett AM (2006) Voltammetric behaviour of anti-leukemia drug glivec. Part I—electrochemical study of glivec. *Electroanalysis* 18:1800–1807
58. Diculescu VC, Vivan M, Oliveira-Brett AM (2006) Voltammetric behaviour of anti-leukemia drug glivec. Part II—redox processes of glivec electrochemical metabolite. *Electroanalysis* 18:1808–1814
59. Diculescu VC, Vivan M, Oliveira-Brett AM (2006) Voltammetric behaviour of anti-leukemia drug glivec. Part III—in situ DNA oxidative damage by the glivec electrochemical metabolite. *Electroanalysis* 18:1963–1970
60. Razak OA (2004) Electrochemical study of hydrochlorothiazide and its determination in urine and tablets. *J Pharm Biomed Anal* 34:433–440
61. Arguelho MLPM, Andrade JF, Stradiotto NR (2003) Electrochemical study of hydroxychloroquine and its determination in plaquenil by differential pulse voltammetry. *J Pharm Biomed Anal* 32:269–275
62. Uslu B, Biryol I (1997) Determination of imipramine hydrochloride in drugs based on voltammetric oxidation at platinum and activated glassy carbon electrodes. *STP Pharma Sci* 7:248–253
63. Dogan B, Canbaz D, Ozkan SA, Uslu B (2006) Electrochemical methods for determination of protease inhibitor indinavir sulfate in pharmaceuticals and human serum. *Pharmazie* 61:409–413
64. Süzen S, Ates-Alagöz Z, Demircigil BT, Ozkan SA (2001) Synthesis and analytical evaluation by voltammetric studies of some new indole-3-propionamide derivatives. *II Farmaco* 56:835–840
65. Süzen S, Demircigil BT, Buyukbingol E, Ozkan SA (2003) Electroanalytical evaluation and determination of derivatives by voltammetric studies: possible relevance to in vitro metabolism. *New J Chem* 27:1007–1011
66. Majidi MR, Jouyban A, Asadpour-Zeynali K (2006) Voltammetric behavior and determination of isoniazid in pharmaceuticals by using overoxidized polypyrrole glassy carbon modified electrode. *J Electroanal Chem* 589:32–37
67. Quintino MSM, Angnes L (2006) Fast BIA-amperometric determination of isoniazid in tablets. *J Pharm Biomed Anal* 42:400–404

68. Ozkan SA (2002) Determination of the antihypertensive drug lacidipine in pharmaceuticals using by differential pulse and square wave voltammetry. *Pharmazie* 57:503–505
69. Dogan B, Uslu B, Suzen S, Ozkan SA (2005) Electrochemical evaluation of nucleoside analogue lamivudine in pharmaceutical dosage forms and human serum. *Electroanalysis* 17:1886–1894
70. Radi A, El-Sherif Z (2002) Determination of levofloxacin in human urine by adsorptive square-wave anodic stripping voltammetry on a glassy carbon electrode. *Talanta* 58:319–324
71. Radi A, El Ries MA, Kandil S (2003) Electrochemical study of the interaction of levofloxacin with DNA. *Anal Chim Acta* 495:61–67
72. Quintino MSM, Yamashita M, Angnes L (2006) Voltammetric studies and determination of levodopa and carbidopa in pharmaceutical products. *Electroanalysis* 18:655–661
73. Corduneanu O, Garnett M, Oliveira-Brett AM (2007) Anodic oxidation of  $\alpha$ -lipoic acid at a glassy carbon electrode and its determination in dietary supplements. *Anal Lett* 40:1763–1778
74. Dogan-Topal B, Golcu A, Ozkan SA (2009) Electrochemical investigation and determination of the bacterial loracarbet by voltammetric methods. *Anal Lett* 42:689–705
75. Uslu B, Dogan B, Ozkan SA, Aboul-Enein HY (2005) Voltammetric investigation and determination of mefloquine. *Electroanalysis* 17:1563–1570
76. Uslu B, Demircigil BT, Ozkan SA, Senturk Z, Aboul-Enein HY (2001) Simultaneous voltammetric determination of melatonin and pyridoxine HCl in pharmaceutical dosage forms. *Pharmazie* 56:938–942
77. Pontinha ADR, Oliveira SCB, Oliveira-Brett AM (2008) Electrochemical oxidation of metolazone at a glassy carbon electrode. *Electroanalysis* 20:2531–2536
78. Lu SF, Wu KB, Dang XP, Hu SS (2004) Electrochemical reduction and voltammetric determination of metronidazole at a nanomaterial thin film coated glassy carbon electrode. *Talanta* 63:653–657
79. Jiang XH, Lin XQ (2006) Voltammetry of the interaction of metronidazole with DNA and its analytical application. *Bioelectrochemistry* 68:206–212
80. Ozkan SA, Ozkan Y, Sentürk Z (1998) Electrochemical reduction of metronidazole at activated glassy carbon electrode and its determination in pharmaceutical dosage forms. *J Pharm Biomed Anal* 17:299–305
81. Oliveira-Brett AM, Serrano SHP, Gutz I, La-Scalea MA, Cruz ML (1997) Voltammetric behaviour of nitroimidazoles at a DNA-biosensor. *Electroanalysis* 9:1132–1137
82. Oliveira-Brett AM, Serrano SHP, Gutz I, La-Scalea MA (1997) Electrochemical reduction of metronidazole at a DNA-modified glassy carbon electrode. *Bioelectrochem Bioenerg* 42:175–178
83. Oliveira-Brett AM, Serrano SHP, Gutz I, La-Scalea MA (1997) Comparison of the voltammetric behaviour of metronidazole at a DNA-modified glassy carbon electrode, a mercury film electrode and a glassy carbon electrode. *Electroanalysis* 9:110–114
84. Oliveira-Brett AM, Macedo TRA, Raimundo D, Marques MH, Serrano SHP (1998) Voltammetric behaviour of mitoxantrone at a DNA-biosensor. *Biosens Bioelectron* 13:861–867
85. Oliveira-Brett AM, Macedo TRA, Raimundo D, Marques MH, Serrano SHP (1999) Electrochemical oxidation of mitoxantrone at a glassy carbon electrode. *Anal Chim Acta* 385:401–408
86. Oliveira-Brett AM, Grazina MMM, Macedo TRA, Oliveira C, Raimundo D (1993) A study of the electrochemical oxidation of Navelbine. *J Pharm Biomed Anal* 11:203–206
87. Oliveira-Brett AM, Grazina MMM, Macedo TRA, Raimundo D (1994) Anodic behavior of some *Vinca* alkaloids with cytostatic activity: effect of pH. *Electroanalysis* 6:57–61
88. Uslu B, Ozkan SA (2002) Electroanalytical characteristics of nefazodone hydrochloride and their application from pharmaceuticals and human serum. *Anal Chim Acta* 462:49–57
89. Abreu FC, Goulart MOF, Oliveira Brett AM (2002) Detection of the damage caused to DNA by niclosamide using an electrochemical DNA-biosensor. *Biosens Bioelectron* 17:913–919
90. Sentürk Z, Ozkan SA, Ozkan Y (1998) Electroanalytical study of nifedipine using activated glassy carbon electrode. *J Pharm Biomed Anal* 16:801–807
91. Solangi AR, Khuhawar MY, Bhangar MI (2005) Adsorptive stripping voltammetric determination of fluoroquinolones in pharmaceuticals. *J Food Drug Anal* 13:201–204
92. Uslu B, Yilmaz S, Ozkan SA (2001) Determination of olsalazine sodium in pharmaceuticals by differential pulse voltammetry. *Pharmazie* 56:629–632
93. Jorge SMA, Pontinha ADR, Oliveira-Brett AM (2010) Electrochemical redox behaviour of omeprazole using a glassy carbon electrode. *Electroanalysis* 22:625–631
94. Turhan E, Uslu B (2008) Electroanalytical determination of opi-pramol in pharmaceutical preparations and biological fluids. *Anal Lett* 41:2013–2032
95. Ozkan SA, Sentürk Z, Biryol I (1997) Determination of ornidazole in pharmaceutical dosage forms based on reduction at an activated glassy carbon electrode. *Int J Pharm* 157:137–144
96. Ni YN, Wang YR, Kokot S (2004) Differential pulse stripping voltammetric determination of paracetamol and phenobarbital in pharmaceuticals assisted by chemometrics. *Anal Lett* 37:3219–3235
97. Uslu B, Dogan-Topal B, Ozkan SA (2008) Electroanalytical investigation and determination of pefloxacin in pharmaceuticals and serum at boron-doped diamond and glassy carbon electrodes. *Talanta* 74:1191–1220
98. Hegde RN, Nandibewoor ST (2008) Electrochemical oxidation of pentoxifylline and its analysis in pure and pharmaceutical formulations at a glassy carbon electrode. *Anal Lett* 41:977–991
99. Mielech-Lukasiewicz K, Puzanowska-Tarasiewicz H, Panuszko A (2008) Electrochemical oxidation of phenothiazine derivatives at glassy carbon electrodes and their differential pulse and square-wave voltammetric determination in pharmaceuticals. *Anal Lett* 41:789–805
100. Bozkaya P, Dogan B, Suzen S, Nebioglu D, Ozkan SA (2006) Determination and investigation of electrochemical behavior of 2-phenylindole derivatives: discussion on possible mechanistic pathways. *Can J Anal Sci Spect* 51:125–139
101. Ozkan SA, Ozkan Y, Senturk Z (2002) Electrooxidation of pimo-zide and its differential pulse voltammetric and HPLC-EC determination. *Anal Chim Acta* 453:221–229
102. Uslu B, Ozkan SA (2003) Electroanalytical characteristics of pibedil and its differential pulse and square wave voltammetric determination in pharmaceuticals and human serum. *J Pharm Biomed Anal* 31:481–489
103. Yilmaz S, Skrzypek S, Dilgin Y, Yagmur S, Coskun M (2007) Electrochemical oxidation of prednisolone at glassy carbon electrode and its quantitative determination in human serum and tablets by Osteryoung square wave voltammetry. *Curr Anal Chem* 3:41–46
104. Uslu B, Biryol I, Ozkan SA, Senturk Z (1996) Voltammetric determination of promethazine by platinum and glassy carbon electrodes. *Tr J Chem* 20:323–328
105. El-Ries MAN, Mohamed GG, Attia AK (2008) Electrochemical determination of the antidiabetic drug repaglinide. *Yakugaku Zasshi* 128:171–177
106. Ozkan SA, Dogan B, Uslu B (2006) Voltammetric analysis of the novel antipsychotic drug quetiapine in human serum and urine. *Microchim Acta* 153:27–35
107. Uslu B, Ozkan SA, Aboul-Enein HY (2002) Electrochemical study of S-adenosyl-methionine and its differential pulse and

- square wave voltammetric determination. *Electroanalysis* 14:736–740
108. Quintino MSM, Angnes L (2004) Bia-amperometric quantification of salbutamol in pharmaceutical products. *Talanta* 62: 231–236
  109. Torriero AAJ, Luco JM, Serono L, Raba J (2004) Voltammetric determination of salicylic acid in pharmaceuticals formulations of acetylsalicylic acid. *Talanta* 62:247–254
  110. Diculescu VC, Enache TA, Oliveira PJ, Oliveira-Brett AM (2010) Electrochemical oxidation of sanguinarine and of its oxidation products at a glassy carbon electrode—relevance to intracellular effects. *Electroanalysis* 22:113–120
  111. Altun Y, Dogan B, Uslu B, Ozkan SA (2009) Anodic behavior of sertindole and its voltammetric determination in pharmaceuticals and human serum using glassy carbon and boron-doped diamond electrodes. *Electrochim Acta* 54:1893–1903
  112. Ozkan SA, Uslu B, Zuman P (2004) Electroanalytical oxidation of sildenafil citrate (Viagra) on carbon electrodes. *Anal Chim Acta* 501:227–233
  113. Coruh O, Ozkan SA (2006) Determination of the anti hyperlipidemic simvastatin by various voltammetric techniques in tablets and serum samples. *Pharmazie* 61:285–290
  114. Kumar KG, Augustine P, Poduval R, John S (2006) Voltammetric studies of sparfloxacin and application to its determination in pharmaceuticals. *Pharmazie* 61:291–292
  115. Ozkan SA, Uslu B (2003) Voltammetric investigation of tamsulosin. *Talanta* 61:147–156
  116. Radi A (2004) Preconcentration and differential pulse voltammetry of tegaserod at a glassy carbon electrode. *Anal Lett* 37:1103–1113
  117. Yılmaz N, Ozkan SA, Uslu B, Senturk Z, Biryol I (1998) Determination of terbutaline based on oxidation by voltammetry. *J Pharm Biomed Anal* 17:349–355
  118. Oliveira SCB, Vivan M, Oliveira-Brett AM (2008) Electrochemical behavior of thalidomide at a glassy carbon electrode. *Electroanalysis* 20:429–2434
  119. Oliveira SCB, Chiorcea-Paquim AM, Ribeiro SM, Melo ATP, Vivan M, Oliveira-Brett AM (2009) In situ electrochemical and AFM study of thalidomide–DNA interaction. *Bioelectrochemistry* 76:201–207
  120. Ozkan SA (1997) Voltammetric determination of tinidazole in tablets. *Analisis* 25:130–131
  121. Garrido EMPJ, Garrido JMPJ, Borges F, Delerue-Matos C (2003) Development of electrochemical methods for determination of tramadol—analytical application to pharmaceutical dosage forms. *J Pharm Biomed Anal* 32:975–981
  122. Adhoum N, Monser L (2005) Determination of trimebutine in pharmaceuticals by differential pulse voltammetry at a glassy carbon electrode. *J Pharm Biomed Anal* 38:619–623
  123. Ghoneim MM, Khashaba PY, Beltagi AM (2002) Determination of trimetazidine HCl by adsorptive stripping square wave voltammetry at a glassy carbon electrode. *J Pharm Biomed Anal* 27:235–241
  124. Boutakhrif K, Quarin G, Ozkan SA, Kauffmann J-M (1996) Determination of tin(II) in pharmaceuticals by amperometric oxidation after complexation with tropolone. *Electroanalysis* 8:89–794
  125. Uslu B, Ozkan SA, Senturk Z (2006) Electrooxidation of the antiviral drug valacyclovir and its square-wave and differential pulse voltammetric determination in pharmaceuticals and human biological fluids. *Anal Chim Acta* 555:341–347
  126. Demircan S, Kir S, Ozkan SA (2007) Electroanalytical characterization of verapamil and its voltammetric determination in pharmaceuticals and human serum. *Anal Lett* 40:1177–1195
  127. Uslu B, Dogan B, Ozkan SA, Aboul-Enein HY (2005) Electrochemical behavior of vardenafil on glassy carbon electrode: determination in tablets and human serum. *Anal Chim Acta* 552:127–134
  128. Thangamutlu R, Kumar SMS, Pillai KC (2007) Direct amperometric determination of L-ascorbic acid (vitamin C) at octacyanomolybdate-doped-poly(4-vinylpyridine) modified electrode in fruit juice and pharmaceuticals. *Sens Actuators B* 120:745–753
  129. Radi A, Bechiet G, Wahdan T (2004) Electrochemical study of zolpidem at glassy carbon electrode and its determination in a tablet dosage form by differential pulse voltammetry. *Chem Pharm Bull* 52:1063–1065
  130. Senturk Z, Ozkan SA, Ozkan Y, Aboul-Enein HY (2000) Voltammetric investigation of oxidation of zuclopenthixol and application to its determination in dosage forms and drug dissolution studies. *J Pharm Biomed Anal* 22:315–323
  131. Kul D, Gumustas M, Uslu B, Ozkan SA (2010) Electroanalytical characteristics of antipsychotic drug ziprasidone and its determination in pharmaceuticals and serum samples on solid electrodes. *Talanta* 82:286–295
  132. Garrido JMPJ, Delerue-Matos C, Borges F, Macedo TRA, Oliveira-Brett AM (2004) Electrochemical analysis of opiates—an overview. *Anal Lett* 37:845–858
  133. Garrido JMPJ, Delerue-Matos C, Borges F, Macedo TRA, Oliveira-Brett AM (2004) Voltammetric oxidation of drugs of abuse III. Heroin and metabolites. *Electroanalysis* 16:1497–1502
  134. Garrido JMPJ, Delerue-Matos C, Borges F, Macedo TRA, Oliveira-Brett AM (2004) Voltammetric oxidation of drugs of abuse II. Codeine and metabolites. *Electroanalysis* 16:1427–1433
  135. Garrido JMPJ, Delerue-Matos C, Borges F, Macedo TRA, Oliveira-Brett AM (2004) Voltammetric oxidation of drugs of abuse I. Morphine and metabolites. *Electroanalysis* 16:1419–1426
  136. Oliveira-Brett AM, Ghica M-E (2003) Electrochemical oxidation of quercetin. *Electroanalysis* 15:1745–1750
  137. Janeiro P, Oliveira-Brett AM (2004) Catechin electrochemical oxidation mechanisms. *Anal Chim Acta* 518:109–115
  138. Janeiro P, Oliveira-Brett AM (2005) Solid state electrochemical oxidation mechanism of morin in aqueous media. *Electroanalysis* 17:733–738
  139. Ghica M-E, Oliveira-Brett AM (2005) Electrochemical oxidation of rutin. *Electroanalysis* 17:313–318
  140. Corduneanu O, Janeiro P, Oliveira-Brett AM (2006) On the electrochemical oxidation of resveratrol. *Electroanalysis* 18:757–762
  141. Janeiro P, Corduneanu O, Oliveira-Brett AM (2005) Chrysin and (±)-taxifolin electrochemical oxidation mechanisms. *Electroanalysis* 38:1059–1064
  142. Ozkan SA, Uslu B, Aboul-Enein HY (2003) Analysis of pharmaceuticals and biological fluids using modern electroanalytical techniques. *Crit Rev Anal Chem* 33:155–181
  143. Ozkan SA (2007) LC with electrochemical detection. Recent application to pharmaceuticals and biological fluids. *Chromatographia* 66:S3–S13
  144. Uslu B, Ozkan SA (2007) Solid electrodes in electroanalytical chemistry: present applications and prospects for high throughput screening of drug compounds. *Comb Chem High T Scr* 10:495–513
  145. Uslu B, Ozkan SA (2007) Electroanalytical application of carbon based electrodes to the pharmaceuticals. *Anal Lett* 40:817–853
  146. Ozkan SA (2009) Principles and techniques of electroanalytical stripping methods for pharmaceutical active compounds in dosage forms and biological samples. *Curr Pharm Anal* 5:127–143
  147. Swain GM (2004) Electroanalytical applications of diamond electrodes. In: Nebel CE, Ristein J (eds) *Semiconductors and*

- semimetals: thin-film diamond II. Elsevier, San Diego, pp 121–145
148. Sarada BV et al (2005) Electroanalytical applications of highly boron-doped diamond electrode. In: Fujishima A et al (eds) *Diamond electrochemistry*. Elsevier, Tokyo, pp 261–286
  149. Enache TA, Chiorcea-Paquim A-M, Fatibello-Filho O et al (2009) Hydroxyl radicals electrochemically generated in situ on a boron-doped diamond electrode. *Electrochem Commun* 11: 1342–1345
  150. Suffredini HB, Pedrosa VA, Codognoto L et al (2004) Enhanced electrochemical response of boron-doped diamond electrodes brought on by a cathodic surface pre-treatment. *Electrochim Acta* 49:4021–4026
  151. Oliveira SCB, Oliveira-Brett AM (2010) Voltammetric and electrochemical impedance spectroscopy characterization of a cathodic and anodic pre-treated boron doped diamond electrode. *Electrochim Acta* 55:4599–4605
  152. Jolley S, Koppang M, Jackson T, Swain GM (1997) Flow injection analysis with diamond thin-film detectors. *Anal Chem* 69:4099–4107
  153. Codognoto L, Machado SAS, Avaca LA (2002) Square wave voltammetry on boron-doped diamond electrodes for analytical determination. *Diam Relat Mater* 11:1670–1675
  154. Sartori ER, Medeiros RA, Rocha-Filho RC, Fatibello-Filho O (2009) Square-wave voltammetric determination of acetylsalicylic acid in pharmaceutical formulations using a boron-doped diamond electrode without the need of previous alkaline hydrolysis step. *J Braz Chem Soc* 20:360–366
  155. Lourenção BC, Medeiros RA, Rocha-Filho RC, Fatibello-Filho O (2010) Simultaneous differential pulse voltammetric determination of ascorbic acid and caffeine in pharmaceutical formulations using a boron-doped diamond electrode. *Electroanalysis* 22:1717–1723
  156. Lourenção BC, Medeiros RA, Rocha-Filho RC, Mazo LH, Fatibello-Filho O (2009) Simultaneous voltammetric determination of paracetamol and caffeine in pharmaceutical formulations using a boron-doped diamond electrode. *Talanta* 78:748–752
  157. Enache TA, Fatibello-Filho O, Oliveira-Brett AM (2010) Electrochemical behavior of triflusal, aspirin and their metabolites at glassy carbon and boron doped diamond electrodes. *Comb Chem High T Scr* 13:569–577
  158. Santos KD, Braga OC, Vieira IC, Spinelli A (2010) Electroanalytical determination of estriol hormone using a boron-doped diamond electrode. *Talanta* 80:1999–2006
  159. Oliveira RTS, Salazar-Banda GR, Ferreira VS, Oliveira SC, Avaca LA (2007) Electroanalytical determination of lidocaine in pharmaceuticals preparations using boron-doped diamond electrodes. *Electroanalysis* 19:1189–1194
  160. Sartori ER, Medeiros RA, Rocha-Filho RC, Fatibello-Filho O (2010) Square-wave voltammetric determination of propranolol and atenolol in pharmaceuticals using a boron-doped diamond electrode. *Talanta* 81:1418–1424
  161. Sartori ER, Batista EF, Rocha-Filho RC, Fatibello-Filho O (2010) Differential pulse voltammetric determination of sildenafil citrate (Viagra) in pharmaceutical formulations using a boron-doped diamond electrode. *Anal Lett* 43:1046–1054
  162. Andrade LS, Rocha-Filho RC, Cass QB, Fatibello-Filho O (2009) Simultaneous differential pulse voltammetric determination of sulfamethoxazole and trimethoprim on a boron doped diamond electrode. *Electroanalysis* 21:1475–1480
  163. Souza CD, Braga OC, Vieira IC, Spinelli A (2008) Electroanalytical determination of sulfadiazine and sulfamethoxazole in pharmaceuticals using a boron-doped diamond electrode. *Sens Actuators B* 135:66–73
  164. Salazar-Banda GR, Andrade LS, Nascente PAP, Pizani PS, Rocha SC, Avaca LA (2006) On the changing electrochemical behaviour of boron-doped diamond surfaces with time after cathodic pre-treatments. *Electrochim Acta* 51:4612–4619
  165. Delahay P (1954) *New instrumental methods in electrochemistry*. Interscience, New York
  166. Adams RN (1969) *Electrochemistry at solid electrodes*. Marcel Dekker, New York
  167. McCreery RL, Cline KK (1996) Carbon electrodes. In: Kissinger PT, Heineman WR (eds) *Laboratory techniques in electroanalytical chemistry*, 2nd edn. Marcel Dekker, New York, pp 293–330, Ch. 10
  168. Kinoshita K (1988) *Carbon: electrochemical and physicochemical properties*. Wiley, New York
  169. Adams RN (1958) Carbon paste electrodes. *Anal Chem* 30:1576
  170. Tallman DE, Petersen SL (1990) Composite electrodes for electroanalysis—principles and applications. *Electroanalysis* 2:499–510
  171. Adams RN (1963) Carbon paste electrodes. *Rev Polarog* 11:71–78
  172. Kalcher K, Kauffmann JM, Wang J, Svancara I, Vytras K, Neuhold C, Yang Z (1995) Sensors based on carbon-paste in electrochemical analysis—a review with particular emphasis on the period 1990–1993. *Electroanalysis* 7:5–22
  173. Stulikova M, Stulik K (1974) Utilization of hydrocarbon materials in electroanalytical chemistry. *Chem Listy* 68:800–835
  174. Stulik K, Pacáková V (1981) Electrochemical detection techniques in high-performance liquid-chromatography. *J Electroanal Chem* 129:1–24
  175. Wang J (1990) Modified electrodes for electrochemical detection in flowing streams. *Anal Chim Acta* 234:41–48
  176. Patriarche GJ, Viré JC (1987) Applications of polarography and voltammetry in analysis for drugs. *Anal Chim Acta* 196:193–204
  177. Kalcher K (1990) Chemically modified carbon paste electrodes in voltammetric analysis. *Electroanalysis* 2:419–433
  178. Ulakhovich NA, Medyantseva EP, Budnikov GK (1993) Carbon paste electrodes as chemical sensors in voltammetric analysis. *Zh Anal Khim* 48:980–998
  179. Kalcher K, Cai X, Kölbl G, Svancara I, Vytras K (1994) New trends in voltammetric analysis: modified carbon paste electrodes. *Sb Ved Pr Vys Sk Chem Technol Pardubice* 57:5–27
  180. Gorton L (1995) Carbon-paste electrodes modified with enzymes, tissues, and cells. *Electroanalysis* 7:23–45
  181. Crespilho FN, Rezende MOO (2004) Carbon paste electrodes modified with humic acids: study and determination of metals in aqueous solution. *Quím Nova* 27:964–969
  182. Svancara I, Vytras K, Kalcher K, Walcarius A, Wang J (2009) Carbon paste electrodes in facts, numbers, and notes: a review on the occasion of the 50-years jubilee of carbon paste in electrochemistry and electroanalysis. *Electroanalysis* 21:7–28
  183. Svancara I, Walcarius A, Kalcher K, Vytras K (2009) Carbon paste electrodes in the new millennium. *Cent Eur J Chem* 7:598–656
  184. Céspedes F, Martínez-Fabregas E, Alegret S (1996) New materials for electrochemical sensing I. Rigid conducting composites. *Trends Anal Chem* 15:296–304
  185. Alegret S (1996) Rigid carbon—polymer biocomposites for electrochemical sensing—a review. *Analyst* 121:1751–1758
  186. Pividori MI, Alegret S (2005) Electrochemical genosensing based on rigid carbon composites. A review. *Anal Lett* 38:2541–2565
  187. Wang YR, Hu P, Liang QL, Luo GA, Wang YM (2008) Application of carbon nanotube modified electrode in bioelectroanalysis. *Chin J Anal Chem* 36:1011–1016
  188. Dumitrescu I, Unwin PR, Macpherson JV (2009) Electrochemistry at carbon nanotubes: perspective and issues. *Chem Commun* 45:6886–6901
  189. Ahammad AJS, Lee JJ, Rahman MA (2009) Electrochemical sensors based on carbon nanotubes. *Sensors* 9:2289–2319
  190. Wei D, Ivaska A (2008) Applications of ionic liquids in electrochemical sensors. *Anal Chim Acta* 607:126–135

191. Navratil T, Berek J (2009) Analytical applications of composite solid electrodes. *Crit Rev Anal Chem* 39:131–147
192. Cervini P (2006) Aplicação de eletrodos compostos a base de poliuretano-graphite. 2006, 185f. Tese (Doutorado em Ciências—Química Analítica)—Instituto de Química de São Carlos, Universidade de São Paulo, São Carlos. <http://www.teses.usp.br/teses/disponiveis/75/75132/tde-12042007-095708/>. Accessed 5 Sep 2011
193. Trijueque J, García-Jareño JJ, Navarro-Laboulais J, Sanmantías A, Vicente F (1999) Ohmic drop of Prussian-blue/graphite+epoxy electrodes. *Electrochim Acta* 45:789–795
194. Navarro-Laboulais J, Trijueque J, Vicente F, Scholl H (1994) Voltammetric determination of optimal conductive load proportion in graphite-epoxy composite electrodes. *J Electroanal Chem* 379:159–163
195. Albertús F, Llerena A, Alpizar J, Cerda V, Luque M, Rios A, Valcárcel M (1997) A PVC-graphite composite electrode for electroanalytical use. *Anal Chim Acta* 355:23–32
196. Wang J, Golden T, Varughese K, El-Rayes I (1989) Polishable and robust modified graphite epoxy electrodes. *Anal Chem* 61:508–512
197. Anderson J, Tallman DE, Chesney DJ, Anderson JL (1978) Fabrication and characterization of a Kel-F-graphite composition electrode for a general voltammetric applications. *Anal Chem* 50:1051–1056
198. Elvin PJ, Krivis AF (1958) Voltammetric studies with the graphite indicating electrode. *Anal Chem* 30:1645–1648
199. Gun G, Tsionsky M, Lev O (1994) Voltammetric studies of composite ceramic carbon working electrodes. *Anal Chim Acta* 294:261–270
200. Pungor E, Szepesváry E (1968) Voltammetric studies with silicone rubber-based graphite electrodes. *Anal Chim Acta* 43:289–296
201. Mendes RK, Claro-Neto S, Cavalheiro ETG (2002) Evaluation of a new rigid carbon-castor oil polyurethane composite as an electrode material. *Talanta* 57:909–917
202. Cesarino I, Marino G, Cavalheiro ETG (2010) A novel graphite-polyurethane composite electrode modified with thiol-organofunctionalized silica for the determination of copper ions in ethanol fuel. *Fuel* 89:1883–1888
203. de-Toledo RA, Santos MC, Cavalheiro ETG, Mazo LH (2005) Determination of dopamine in synthetic cerebrospinal fluid by SWV with graphite polyurethane composite electrode. *Anal Bioanal Chem* 381:1161–1166
204. de-Toledo RA, Santos MC, Honório KM, da-Silva ABF, Cavalheiro ETG, Mazo LH (2006) Use of graphite polyurethane composite electrode for imipramine oxidation—mechanism proposal and electroanalytical determination. *Anal Lett* 39:507–520
205. Malagutti AR, Zuin VG, Cavalheiro ETG, Mazo LH (2006) Determination of rutin in green tea infusions using square-wave voltammetry with a rigid carbon-polyurethane composite electrode. *Electroanalysis* 18:1028–1034
206. Cervini P, Ramos LA, Cavalheiro ETG (2007) Determination of atenolol at a graphite-polyurethane composite electrode. *Talanta* 72:206–209
207. Cervini P, Cavalheiro ETG (2008) Graphite-polyurethane composite electrode as an amperometric flow detector in the determination of atenolol. *Anal Lett* 41:1867–1877
208. Semaan FS, Pinto EM, Cavalheiro ETG, Brett CMA (2008) A graphite-polyurethane composite electrode for the analysis of furosemide. *Electroanalysis* 20:2287–2293
209. Semaan FS, Cavalheiro ETG, Brett CMA (2009) Electrochemical behavior of verapamil at graphite-polyurethane composite electrodes: determination of release profiles in pharmaceutical samples. *Anal Lett* 42:1119–1135
210. Cervini P, Cavalheiro ETG (2009) Evaluation of the analytical potentialities of a composite electrode modified with molecularly imprinted polymers. *Anal Lett* 42:1940–1957
211. de-Toledo RA, Santos MC, Suffredini HB, Homem-de-Mello P, Honório KM, Mazo LH (2009) DFT and electrochemical studies on nortriptyline oxidation sites. *J Mol Model* 15:945–952
212. Swofford HS, Carman RL (1966) Voltammetric applications of rotating and stationary carbon-epoxy electrodes. *Anal Chem* 38:966–969
213. Calixto CMF, Cervini P, Cavalheiro ETG (2008) Eletrodo composto à base de graphite-Araldite®: aplicações didáticas. *Quím Nova* 31:2194–2198
214. Wring SA, Hart JP, Birch BJ (1990) Voltammetric behavior of ascorbic-acid at a graphite epoxy composite electrode chemically modified with cobalt phthalocyanine and its amperometric determination in multivitamin preparations. *Anal Chim Acta* 229:63–70
215. Sebkova S, Navratil T, Kopanica M (2005) Graphite composite electrode in voltammetry. *Anal Lett* 38:1747–1758
216. Kiryushov VN, Skvortsova LI, Aleksandrova TP (2007) Voltammetric studies of the activity of an electrode made of a graphite-epoxy composite in redox reactions of ascorbic acid and hydroquinone. *J Anal Chem* 62:161–167
217. Pungor E, Szepesváry E, Havas J (1968) Voltammetric studies on graphite impregnated silicone rubber electrodes. *Anal Lett* 1:213–220
218. Pungor E, Feher Z, Nagy G (1971) Voltammetric determinations of some drugs using silicone rubber-based electrodes. *Magy Kem Foly* 77:298–302
219. Pungor E, Nagy G, Feher Z (1971) Use of silicone rubber-based graphite in flowing media. II. Voltammetric determination of electroactive materials injected into a flowing supporting electrolyte. *Magy Kem Foly* 77:294–298
220. Feher Z, Nagy G, Toth K, Pungor E (1974) The use of precipitate based silicone rubber ion-selective electrodes and silicone rubber based graphite voltammetric electrodes in continuous analysis. A review. *Analyst* 99:699–708
221. Pungor E, Feher Z, Nagy G (1975) The voltammetric application of silicone rubber based graphite electrodes with special regard to flowing systems. *Pure Appl Chem* 44:595–612
222. Niegreis Z, Horvai G, Toth K, Pungor E (1986) Silicone rubber wall-jet electrode in hydrodynamic voltammetry. *Symp Biol Hung* 31:83–95
223. Santos SX, Mazo LH, Cavalheiro ETG (2008) The use of a graphite-silicone rubber composite electrode in the determination of rutin in pharmaceutical formulation. *J Braz Chem Soc* 19:1600–1606
224. Santos SX, Cavalheiro ETG (2011) The potentialities of using a graphite-silicone rubber composite electrode in the determination of propranolol. *Anal Lett* 44:850–862
225. Catarino RIL, Garcia MBQ, Lapa RAS, Lima JLFC, Barrado E (2002) Sequential determination of salicylic and acetylsalicylic acids by amperometric multisite detection flow injection analysis. *J AOAC Int* 85:1253–1259
226. Freitas KHG, Medeiros RA, Fatibello-Filho O (2009) Voltammetric determination of rutin using a carbon composite electrode modified with copper(II)-resin. *Anal Lett* 42:881–897
227. Cano M, Palenzuela B, Rodriguez-Amaro R (2006) A PVC/TTF-TCNQ composite electrode for use as a detector in flow injection analysis. *Electroanalysis* 18:1727–1729
228. Blanco-Lopez MC, Fernandez-Llano L, Lobo-Castanon MJ, Miranda-Ordieres AJ, Tunon-Blanco P (2004) Voltammetry of diclofenac at graphite, carbon composites, and molecularly imprinted polymer-composite electrodes. *Anal Lett* 37:915–927

229. Aguilar-Sanchez R, Ahuatl-Garcia F, Davila-Jimenez MM, Elizalde-González MP, Guevara-Villa MR (2005) Chromatographic and electrochemical determination of quercetin and kaempferol in phytopharmaceuticals. *J Pharm Biomed Anal* 38:239–249
230. Manea F, Radovan C, Corb I, Pop A, Burtica G, Malchev P, Picken S, Schoonman J (2007) Electrochemical oxidation and determination of oxalic acid at an exfoliated graphite–polystyrene composite electrode. *Sensors* 7:615–627
231. Barsan MM, Pinto EM, Florescu M, Brett CMA (2009) Development and characterization of a new conducting carbon composite electrode. *Anal Chim Acta* 635:71–78
232. Xie XF, Zhou DZ, Zheng XJ, Huang WS, Wu KB (2009) Electrochemical sensing of rutin using an MCM-41 modified electrode. *Anal Lett* 42:678–688
233. Qi B, Du Y, Yang XR (2008) Determination of benzhexol and procyclidine using an electrochemiluminescence-based sensor constructed by a screen-print technique. *Microchim Acta* 162:211–217
234. Prasad BB, Tiwari MP, Madhuri R, Sharma PS (2010) Development of a highly sensitive and selective hyphenated technique (molecularly imprinted micro-solid phase extraction fiber-molecularly imprinted polymer fiber sensor) for ultratrace analysis of folic acid. *Anal Chim Acta* 662:14–22
235. Prasad BB, Madhuri R, Tiwari MP, Sharma PS (2010) Enantioselective recognition of *D*- and *L*-tryptophan by imprinted polymer-carbon composite fiber sensor. *Talanta* 81:187–196
236. Rodriguez MC, Rivas GA (2002) Glassy carbon paste electrodes modified with polyphenol oxidase. Analytical applications. *Anal Chim Acta* 459:43–51
237. dos-Santos SX, Cavalheiro ETG, Brett CMA (2010) Analytical potentialities of carbon nanotube/silicone rubber composite electrodes: the determination of propranolol. *Electroanalysis* 22:2776–2783
238. Shahrokhian S, Asafian E (2010) Simultaneous voltammetric determination of ascorbic acid, acetaminophen and isoniazid using thionine immobilized multi-walled carbon nanotube modified carbon paste electrode. *Electrochim Acta* 55:666–672
239. Joseph R, Kumar KG (2009) Electrochemical reduction and voltammetric determination of metronidazole benzoate at modified carbon paste electrode. *Anal Lett* 42:2309–2321
240. Batista IV, Lanza MRV, Dias ILT, Tanaka SMCN, Tanaka AA, Sotomayor MDPT (2008) Electrochemical sensor highly selective for estradiol valerate determination based on a modified carbon paste with iron tetrapyrrolineporphyrine. *Analyst* 133:1692–1699
241. Stefan-van Staden RI, Bokretson RG (2006) Simultaneous determination of creatine and creatinine using monocrystalline diamond paste-based amperometric biosensors. *Anal Lett* 39:2227–2233
242. Moccelini SK, Franzoi AC, Vieira IC, Dupont J, Scheeren CW (2011) A novel support for laccase immobilization: cellulose acetate modified with ionic liquid and application in biosensor for methyl dopa detection. *Biosens Bioelectron* 26:3549–3554
243. Agüi L, Manso J, Yáñez-Sedeño P, Pingarrón JM (2004) Colloidal-gold cysteamine-modified carbon paste electrodes as suitable electrode materials for the electrochemical determination of sulphur-containing compounds. Application to the determination of methionine. *Talanta* 64:1041–1047
244. Pauliukaite R, Ghica ME, Fatibello-Filho O, Brett CMA (2010) Graphite–epoxy electrodes modified with functionalised carbon nanotubes and chitosan for the rapid electrochemical determination of dipyrone. *Comb Chem High T Scr* 13:590–598
245. Wei JA, He JB, Cao SQ, Zhu YW, Wang Y, Hang GP (2010) Enhanced sensing of ascorbic acid, dopamine and serotonin at solid carbon paste electrode with a nonionic polymer film. *Talanta* 83:190–196
246. Radi A (2010) Recent updates of chemically modified electrodes in pharmaceutical analysis. *Comb Chem High T Scr* 13:728–752
247. Renedo OD, Alonso-Lomillo MA, Martinez MJA (2007) Recent developments in the field of screen-printed electrodes and their related applications. *Talanta* 73:202–219
248. Bergamini MF, Santos DP, Zononi MVB (2010) Determination of isoniazid in human urine using screen-printed carbon electrode modified with poly-L-histidine. *Bioelectrochemistry* 77:133–138
249. Su W, Cheng SH (2010) Electrochemical oxidation and sensitive determination of acetaminophen in pharmaceuticals at poly(3,4-ethylenedioxythiophene)-modified screen-printed electrodes. *Electroanalysis* 22:707–714
250. Honeychurch KC, Gilbert L, Hart JP (2010) Electrocatalytic behaviour of citric acid at a cobalt phthalocyanine-modified screen-printed carbon electrode and its application in pharmaceutical and food analysis. *Anal Bioanal Chem* 396:3103–3111
251. Dominguez-Renedo O, Calvo MEB, Alonso-Lomillo MA (2010) Oxcarbazepine analysis by adsorptive stripping voltammetry using silver nanoparticle-modified carbon screen-printed electrodes. *Sens Lett* 8:268–272
252. Wu SH, Nie FH, Chen QZ, Sun JJ (2011) Highly sensitive detection of silybin based on adsorptive stripping analysis at single-sided heated screen-printed carbon electrodes modified with multi-walled carbon nanotubes with direct current heating. *Anal Chim Acta* 687:43–49
253. Jacobs CB, Peairs MJ, Venton BJ (2010) Carbon nanotube based electrochemical sensors for biomolecules. *Anal Chim Acta* 662:105–127
254. Carvalho RC, Gouveia-Caridade C, Brett CMA (2010) Glassy carbon electrodes modified by multiwalled carbon nanotubes and poly(neutral red). A comparative study of different brands and application to electrocatalytic ascorbate determination. *Anal Bioanal Chem* 398:1675–1685
255. Sanghavi BJ, Srivastava AK (2011) Adsorptive stripping differential pulse voltammetric determination of venlafaxine and desvenlafaxine employing Nafion–carbon nanotube composite glassy carbon electrode. *Electrochim Acta* 56:4188–4196
256. Xu XL, Huang F, Zhou GL, Zhang S, Kong JL (2010) A novel electrochemical sensor for probing doxepin created on a glassy carbon electrode modified with poly(4-amino-benzoic acid)/multi-walled carbon nanotubes composite film. *Sensing* 10:8398–8410
257. Wang CY, Guan J, Qu QS, Yang GJ, Hu XY (2007) Voltammetric determination of sinomenine in biological fluid using a glassy carbon electrode modified by a composite film of polycysteic acid and carbon nanotubes. *Comb Chem High T Scr* 10:595–603
258. Babaei A, Afrasiabi M, Babazadeh M (2010) A glassy carbon electrode modified with multiwalled carbon nanotube/chitosan composite as a new sensor for simultaneous determination of acetaminophen and mefenamic acid in pharmaceutical preparations and biological samples. *Electroanalysis* 22:1743–1749
259. Pauliukaite R, Ghica ME, Fatibello-Filho O, Brett CMA (2009) A comparative study of different crosslinking agents for the immobilization of functionalized carbon nanotubes within a chitosan film supported on a graphite–epoxy composite electrode. *Anal Chem* 81:5364–5372
260. Habibi B, Jahanbakhshi M, Pournaghiazar MH (2011) Electrochemical oxidation and nanomolar detection of acetaminophen at a carbon-ceramic electrode modified by carbon nanotubes: a comparison between multi walled and single walled carbon nanotubes. *Microchim Acta* 172:147–154
261. Ghalkhani M, Shahrokhian S, Ghorbani-Bidkorbeh F (2009) Voltammetric studies of sumatriptan on the surface of pyrolytic

- graphite electrode modified with multi-walled carbon nanotubes decorated with silver nanoparticles. *Talanta* 80:31–38
262. Shahrokian S, Ghalkhani M, Adeli M, Amini MK (2009) Multi-walled carbon nanotubes with immobilised cobalt nanoparticle for modification of glassy carbon electrode: application to sensitive voltammetric determination of thioridazine. *Biosens Bioelectron* 24:3235–3241
263. Ji YL, Wang GF, Zhang CH, Fang B (2011) Electrocatalysis of puerarin on a nano-CeO<sub>2</sub>/MWCNTs composite modified electrode and its determination in pharmaceutical preparations. *Chinese J Chem* 29:1017–1023
264. Lu TL, Tsai YC (2011) Sensitive electrochemical determination of acetaminophen in pharmaceutical formulations at multiwalled carbon nanotube-alumina-coated silica nanocomposite modified electrode. *Sensor Actuat B-Chem* 153:439–444
265. Kul D, Brett CMA (2011) Electroanalytical characterisation of dopa decarboxylase inhibitors carbidopa and benserazide on multiwalled carbon nanotube and poly(Nile blue A) modified glassy carbon electrodes. *Inter J Electrochem ID185684:1–7*
266. Pacios M, del Valle M, Bartroli J, Esplandiú MJ (2008) Electrochemical behavior of rigid carbon nanotube composite electrodes. *J Electroanal Chem* 619–620:117–124
267. Heli H, Majdi S, Jabbari A, Sattarahmady N, Moosavi-Movahedi AA (2010) Electrooxidation of dextromethorphan on a carbon nanotube–carbon microparticle–ionic liquid composite: applied to determination in pharmaceutical forms. *J Solid State Electrochem* 14:1515–1523
268. Goyal RN, Bachheti N, Tyagi A, Pandey AK (2007) Differential pulse voltammetric determination of methylprednisolone in pharmaceuticals and human biological fluids. *Anal Chim Acta* 605: 34–40
269. Jain R, Rather JA, Dwivedi A, Vikas DA (2010) Highly sensitive and selective voltammetric sensor fullerene modified glassy carbon electrode for determination of cefitizoxime in solubilized system. *Electroanalysis* 22:2600–2606
270. Goyal RN, Gupta VK, Chatterjee S (2009) Fullerene-C-60-modified edge plane pyrolytic graphite electrode for the determination of dexamethasone in pharmaceutical formulations and human biological fluids. *Biosens Bioelectron* 24:1649–1654
271. Goyal RN, Gupta VK, Chatterjee S (2009) A sensitive voltammetric sensor for determination of synthetic corticosteroid triamcinolone, abused for doping. *Biosens Bioelectron* 24:3562–3568
272. Goyal RN, Oyama M, Bachheti N, Singh SP (2009) Fullerene C-60 modified gold electrode and nanogold modified indium tin oxide electrode for prednisolone determination. *Bioelectrochemistry* 74:272–277
273. Goyal RN, Gupta VK, Bachheti N, Sharma R (2008) Electrochemical sensor for the determination of dopamine in presence of high concentration of ascorbic acid using a fullerene-C-60 coated gold electrode. *Electroanalysis* 20:757–764
274. Salem AEA, Barsoum BN, Saad GR, Izake EL (2002) Potentiometric determination of some 1,4-benzodiazepines in pharmaceutical preparations and biological samples. *J Electroanal Chem* 536:1–9
275. Gupta VK, Singh AK, Gupta B (2007) Development of membrane electrodes for selective determination of some antiepileptic drugs in pharmaceuticals, plasma and urine. *Anal Bioanal Chem* 389:2019–2028
276. Gamal AE, Mostafa GAE, Al-Majed A (2008) Characteristics of new composite- and classical potentiometric sensors for the determination of pioglitazone in some pharmaceutical formulations. *J Pharm Biomed Anal* 48:57–61
277. Mohamed GG, Ali TA, El-Shahat MF, Al-Sabagh AM, Migahed MA, Khaled E (2010) Potentiometric determination of cetylpyridinium chloride using a new type of screen-printed ion selective electrodes. *Anal Chim Acta* 673:79–87
278. Mohamed GG, El-Shahat MF, Al-Sabagh AM, Migahed MA, Ali TA (2011) Septonex-tetraphenylborate screen-printed ion selective electrode for the potentiometric determination of Septonex in pharmaceutical preparations. *Analyst* 136:1488–1495
279. Ensafi AA, Allafchian AR (2008) Novel and selective potentiometric membrane sensor for amiloride determination in pharmaceutical compounds and urine. *J Pharm Biomed Anal* 47:802–806
280. El-Naby EH (2008) Polymeric membrane sensors for the selective determination of dextromethorphan in pharmaceutical preparations. *Anal Sci* 24:1409–1414
281. Heba M, Ramadan N, El-Laithy M (2008) Polymeric matrix membrane sensors for stability-indicating potentiometric determination of oxybutynin hydrochloride and flavoxate hydrochloride urogenital system drugs. *J AOAC Inter* 91:1318–1330
282. Badawy WA, El-Ries MA, Mahdi IM (2009) Carbon paste and PVC membrane electrodes as sensitive sensors for the determination of antidiabetic drugs for type 2 diabetic patients. *Anal Sci* 25:1431–1436
283. Stefan-van Staden RI, Nhlapo NS, van Staden JF, Aboul-Enein HY (2009) Enantioanalysis of S-ketoprofen using enantioselective, potentiometric membrane electrodes. *Anal Lett* 42: 764–774
284. Staden RLSV, Lal B, Holo L (2007) Enantioselective potentiometric membrane electrodes based on C-60 fullerene and its derivatives for the assay of (L)-histidine. *Talanta* 71:1434–1437
285. Stefan-van Staden RI (2010) Enantioanalysis of S-ibuprofen using [5–6] fullerene-C-70 and diethyl (1,2-methanofullerene C-70)-71-71-dicarboxylate. *Anal Meth* 2:37–40
286. Stefan-van Staden RI (2010) Enantioanalysis of S-deprenyl using enantioselective, potentiometric membrane electrodes based on C-60 derivatives. *Electrochim Acta* 55:1772–1777
287. Saber AL (2010) Novel potentiometric sensors for determination of melatonin and oxomemazine in biological samples and in pharmaceutical formulations. *Electroanalysis* 22:2997–3002
288. Moreira FTP, Freitas VAP, Sales MGF (2011) Biomimetic norfloxacin sensors made of molecularly-imprinted materials for potentiometric transduction. *Microchim Acta* 172:15–23
289. Alonso-Lomillo MA, Yardimci C, Dominguez-Renedo O, Arcos-Martinez MJ (2009) CYP450 2B4 covalently attached to carbon and gold screen printed electrodes by diazonium salt and thiols monolayers. *Anal Chim Acta* 633:51–56
290. Alonso-Lomillo MA, Gonzalo-Ruiz J, Dominguez-Renedo O, Munoz F, Arcos-Martinez MJ (2008) CYP450 biosensors based on gold chips for antiepileptic drugs determination. *Biosens Bioelectron* 23:1733–1737
291. Alonso-Lomillo MA, Dominguez-Renedo O, Matos P, Arcos-Martinez MJ (2009) Electrochemical determination of levetiracetam by screen-printed based biosensors. *Bioelectrochemistry* 74:306–309
292. Alonso-Lomillo MA, Dominguez-Renedo O, Hernandez-Martin A, Arcos-Martinez MJ (2009) Horseradish peroxidase covalent grafting onto screen-printed carbon electrodes for levetiracetam chronoamperometric determination. *Anal Biochem* 395:86–90
293. Sima V, Cristea C, Bodoki E, Dutu G, Sandulescu R (2010) Screen-printed electrodes modified with HRP-zirconium alc oxide film for the development of a biosensor for acetaminophen detection. *Cent Eur J Chem* 8:1034–1040
294. Stefan-van Staden RI, Ozoemena KI (2009) Amperometric immunosensor for the determination of 20,30-dideoxyinosine. *Anal Lett* 42:758–763