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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 pretreatment 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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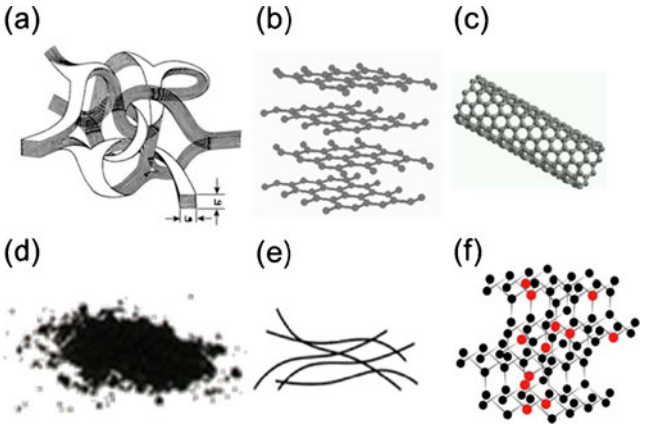

Fig. 1 Structures of **a** glassy carbon, **b** graphite, **c** carbon nanotubes, **d** graphite powder, **e** carbon fibres, and **f** boron-doped diamond

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 μm) 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	2.2×10^{-7} M	[6]
Acetaminophen	CV/FIA	pH 5.5 acetate buffer	0.27	1.7×10^{-6} M	[7]
Adriamycin	CV DPV SWV	pH 4.5 acetate buffer	0.45	7.9×10^{-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_2SO_4	1.05	9.410^{-7} M	[12]
Amisulpride	DPV SWV	pH 7.0 BRb, pH 3.0 BRb	0.80–1.25	2.2×10^{-8} M	[13]
Amlodipine besylate	AdSSWV	pH 11.0 BRb	0.51	1.4×10^{-8} M	[14]
Amlodipine besylate	CV DPV SWV	pH 5.0 BRb	0.85	8.0×10^{-7} M	[15]
Apomorphine	DPV	pH 9 borate buffer	0.8	5.0×10^{-7} M	[16, 17]
Ascorbic acid	CV DPV SWV	–	0.40	7.0×10^{-7} M	[18]
Atenolol	DPV	–	1.04	1.6×10^{-4} M	[19]
Atomoxetine	CV DPV	pH 5.0 BRb	1.46	6.9×10^{-5} M	[20]
Atorvastatin	DPV SWV	0.1 M H_2SO_4, pH 3.0 BRb	1.02	2.1×10^{-7} M	[21]
Atorvastatin	CV DPV SWV	pH 5.0 BRb	0.92	6.0×10^{-7} M	[15]
Azithromycin	DPV	pH 7.0 phosphate buffer	0.700	9.2×10^{-7} M	[22, 23]
Benperidol	CV	0.1 M H_2SO_4	1.45	8.0×10^{-4} M	[24]
Benznidazole	CV DPV	pH 7.5 phosphate buffer	−0.46	1.0×10^{-5} M	[25]
Berberine	CV DPV SWV	pH 3.3 acetate buffer	1.17	1.0×10^{-5} M	[26]
Bromhexine	CV DPV	pH 2.5 BRb (methanol)	1.01	1.4×10^{-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	2.0×10^{-7} M	[29]
Candesartan cilexetil	AdSDPV AdSSWV	pH 5.0 phosphate buffer	1.60	9.2×10^{-7} M	[30]
Carvedilol	DPV SWV	0.2 M H_2SO_4	1.22	2.1×10^{-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	6.4×10^{-7} M	[34]
Cefoperazone	DPV SWV	pH 2.0 phosphate buffer	0.87	2.9×10^{-7} M	[35]
Cefotaxime	DPV SWV	pH 2.0 phosphate buffer	0.87	2.8×10^{-7} M	[36]
Ceftazidime	DPSV OSWSV	pH 2.7 phosphate buffer	−1.0	2.0×10^{-10} M	[37]
Ciprofloxacin	Amperometric biosensor	pH 7.0 phosphate buffer	−0.20	4.0×10^{-8} M	[38]
Cinnarizine	Cv CAdSV	pH 3.7 acetate buffer	0.44	9.0×10^{-9} M	[39]
Cisapride	DPV SWV	pH 3.5 acetate buffer	1.02	1.9×10^{-7} M	[40]
Citalopram	CV DPV SWV	pH 8.2 phosphate buffer	0.85	9.5×10^{-6} M	[41]
Codeine	DPV SWV	pH 3.0 acetate buffer	1.2	3.0×10^{-6} M	[42]
Dihydrocodeine	SWV	pH 3.0 acetate buffer	1.2	1.4×10^{-5} M	[43]
Dopamine	FIA/amperometry		0.1	1.5×10^{-4} M	[44]
Disopyramide	CV DPV SWV	pH 7.0 phosphate buffer	0.7	1.3×10^{-6} M	[45]
Dopamine	CV DPV SWV	–	0.40	7.0×10^{-7} M	[18]
Doxycycline	Potentiometry		–	4.0×10^{-5} M	[46]
Droperidol	CV	0.1 M H_2SO_4	1.45	8.0×10^{-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	6.8×10^{-7} M	[48]
β-Estradiol	DPV	0.05 M H_2SO_4	1.00	4.0×10^{-5} M	[49]
Fexofenadine HCl	DPV SWV	pH 7.0 BRb	0.86	6.6×10^{-9} M	[50]
Flunarizine	CV	0.5 M H_2SO_4 (20% methanol)	1.27	6.0×10^{-6} M	[51]
Flupentixol	DPV SWV	pH 7.0 BRb	0.75	1.2×10^{-7} M	[52]
Fluphenazine	CV	0.1 M H_2SO_4	1.35	–	[53]
Fluvastatin sodium	DPV SWV	pH 10.0 BRb	0.80	1.1×10^{-6} M	[54]
Formoterol fumarate	LSV, DPV, SWV	–	–	8.0×10^{-6} M	[55]

Table 1 (continued)

Analyte	Technique	Medium	Potential/V	LOD	Ref.
Ganciclovir	DPV SWV	pH 2.0 BRb	1.15	8.1×10^{-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_2SO_4	1.15	–	[62]
Indinavir	DPV SWV	pH 10.0 BRb	0.75	1.3×10^{-7} M	[63]
Indole-3-propionamide	CV DPV	pH 2.0 BRb	0.78	1.0×10^{-5} M	[64]
5-(3′-Indolyl)-2-thiohydantoin derivatives	CV DPV	pH 1.0–pH 4.71	0.46–0.90	1.0×10^{-6} M	[65]
Isoniazid	CV	pH 9.0 NH_3/NH_4Cl buffer	0.1	3.2×10^{-6} M	[66–68]
Lacidipine	DPV SWV	0.1 M H_2SO_4	0.85	1.4×10^{-7} M	[68]
Lamivudine	DPV SWV	pH 4.5 acetate buffer	−1.26	6.3×10^{-8} M	[69]
Levofloxacin	CV	pH 5.0 acetate buffer	0.80	1.0×10^{-7} M	[70, 71]
Levodopa Carbidopa	DPV	0.1 M $HClO_4$	0.58–1.02	4.2×10^{-8} M	[72]
α-Lipoic acid	CV DPV SWV	pH 6.9 phosphate buffer	0.76	1.8×10^{-6} M	[73]
Loracarbef	DPV SWV	0.1 M H_2SO_4	1.28	2.4×10^{-7} M	[74]
Mefloquine	DPV SWV	pH 11.1 BRb	−1.21	4.5×10^{-7} M	[75]
Melatonin and pyridoxine	DPV	0.5 M H_2SO_4	0.72–1.29	5.9×10^{-6} M	[76]
Metolazone	CV DPV SWV	pH 7.0 phosphate buffer	0.82	–	[77]
Metronidazole	DPV	pH 9.0 BRb	−0.71	2.0×10^{-8} M	[78–83]
Mitoxantrone	CV DPV SWV	pH 2.1 BRb	0.65	1.9×10^{-7} M	[84, 85]
Navelbine	CV DPV	pH 9.3 borax buffer	0.60	1.0×10^{-5} M	[86]
Nefazodone	DPV SWV	0.1 M H_2SO_4	1.00	2.1×10^{-7} M	[88]
Niclosamide	CV DPV SWV	pH 4.5 acetate buffer	−0.06	1.0×10^{-5} M	[89]
Nifedipine	CV	0.2 M H_2SO_4 (20% methanol)	1.0	1.1×10^{-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	5.8×10^{-7} M	[92]
Omeprazole	CV DPV SWV	pH 7.0 phosphate buffer	0.8	1.0×10^{-6} M	[93]
Opipramol	DPV	pH 3.70 acetate buffer	0.82	2.7×10^{-7} M	[94]
Ornidazole	CV	pH 4.7 acetate buffer	−0.350.65	6.0×10^{-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	1.0×10^{-6} M	[97]
Pentoxifylline	CV DPV	pH 3.0 phosphate buffer	1.35	4.4×10^{-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	$6.0–7.5\times10^{-7}$ M	[99]
2-Phenylindole	CV	–	–	–	[100]
Pimozide	DPV	pH 2.1 BRb	1.10	6.0×10^{-7} M	[101]
Piribedil	DPV SWV	0.1 M H_2SO_4, pH 5.7 acetate buffer	1.27–1.29	5.6×10^{-7} M	[102]
Prednisolone	SWV	0.5 M H_2SO_4	0.59	3.4×10^{-7} M	[103]
Promethazine	CV	pH 4.7 acetate buffer	0.8	2.0×10^{-5} M	[104]
Repaglinide	CV DPV	pH 7.0 BRb	0.75	1.1×10^{-7} M	[105]
Quetiapine	DPV SWV	pH 3.5 acetate buffer	1.00	4.0×10^{-8} M	[106]
S-Adenosyl-methionine	DPV SWV	pH 2.0 phosphate buffer	1.50	2.6×10^{-6} M	[107]
Salbutamol	BIA/amperometry	–	0.9	2.5×10^{-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	1.0×10^{-5} M	[110]
Sertindole	CV DPV SWV	pH 3.5 acetate buffer	1.08	1.9×10^{-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	5.7×10^{-6} M	[112]
Simvastatin	DPV SWV	0.1 M H_2SO_4	1.10	2.7×10^{-7} M	[113]
Sparfloxacin	DPV	–	–	–	[114]
Tamsulosin	DPV SWV	pH 4.5 acetate buffer	1.15	3.3×10^{-7} M	[115]
Tegaserod	DPV	pH 9.0 BRb	0.16	3.0×10^{-10} M	[116]
Terbutaline	CV	pH 6.0 phosphate buffer	0.80	8.0×10^{-6} M	[117]
Thalidomide	CV DPV SWV	pH 7.0 phosphate buffer	0.74–1.10	–	[118, 119]
Tinidazole	CV	–	−1.0	2.0 10^{-6} M	[120]
Tramadol	CV DPV	pH 9.3	–	2.2×10^{-6} M	[121]
Trimebutine	DPV	Acetonitrile/0.1 M $LiClO_4$	1.32	0.3 mg/L	[122]
Trimetazidine	AdSSWV	pH 5.0 acetate buffer	0.75	2.0×10^{-8} M	[123]
Tropolone	CV	–	−0.014	1.0×10^{-7} M	[124]
Valacyclovir	DPV SWV	pH 10.0 BRb	0.90	1.0×10^{-7} M	[125]
Verapamil	DPV SWV	pH 3.7 acetate buffer	0.94	1.6×10^{-7} M	[126]
Vardenafil	DPV SWV	pH 2.0 phosphate buffer	1.35	2.3×10^{-8} M	[127]
Vincristine, vindesine, vinblastine	CV DPV	pH 9.3 borax buffer	0.6	1.0×10^{-5} M	[87]
Vitamin C	Amperometry	–	–	–	[128]
Zolpidem	DPV	pH 8.0 BRb	0.889	2.0×10^{-7} M	[129]
Zuclopenthixol	DPV	pH 5.2 phosphate buffer	0.82	2.2×10^{-7} M	[130]
Ziprasidone	CV	0.1 M H_2SO_4	1.0	1.0×10^{-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,

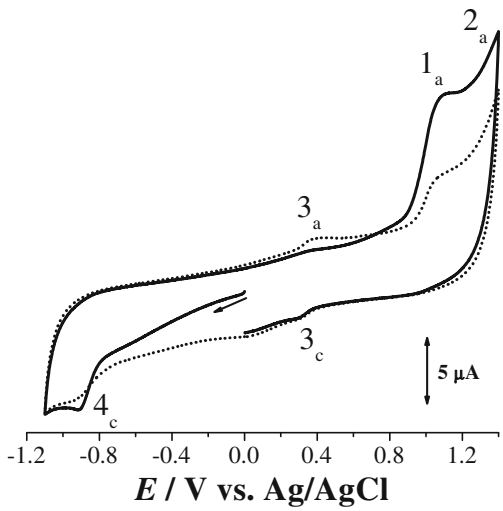

Fig. 2 Redox processes of glivec. CV obtained with a GCE in a solution of 50 µM glivec in pH 4.5 0.1 M acetate buffer saturated with N_2; (*solid line*) first and (*dotted line*) second scan at ν=500 mV s^{-1}. Reproduced with permission from [57]

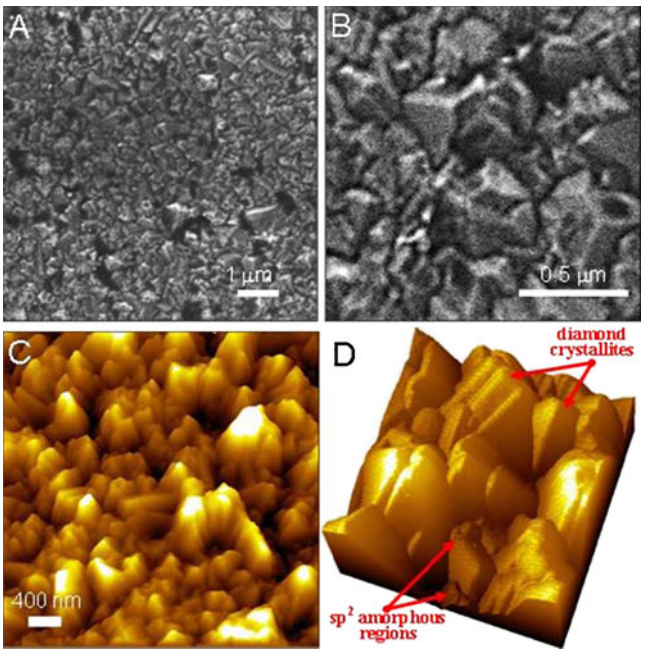

Fig. 3 BDD electrode surface. SEM images: **a** 10,000 and **b** 50,000 times. AFM images: **c** 4,000×4,000×150 nm^3 and **d** 1,000×1,000×150 nm^3. Reproduced with permission from [149]

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].

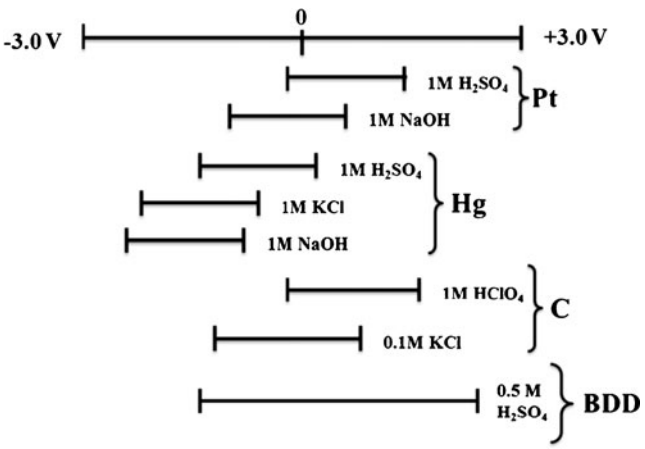

Fig. 4 Supporting electrolyte approximate potential ranges for platinum, mercury, carbon and boron-doped diamond electrodes

A comparison of the effect of anodic and cathodic electrochemical pre-treatments [applying ±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 2.50×10^{-6}–1.05×10^{-4} M, with a LOD of 2.0 μM. 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 1.9×10^{-5} to 2.1×10^{-4} M for AA and from 9.7×10^{-6} to 1.1×10^{-4} M for CAF, with detection limits of 19 μM and 7.0 μM, 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)

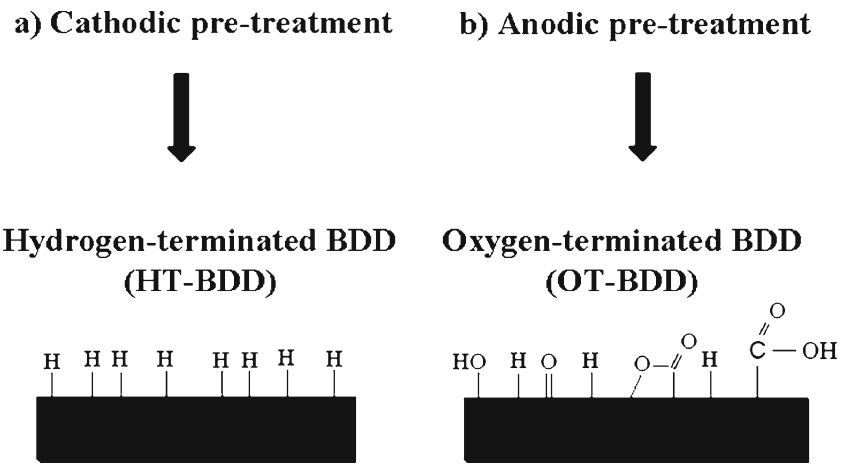

Fig. 5 Surface termination after boron-doped diamond electrode **a** cathodic and **b** anodic pre-treatments

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 μM for both compounds. The LOD values for the simultaneous determination of paracetamol and caffeine were 0.49 and 0.035 μM, 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 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-3,16α,17β-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 2.0×10^{-7} to 2.0×10^{-5} M (r=0.9994), with a detection limit of 1.7×10^{-7} M and a quantification limit of 8.5×10^{-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 $HClO_4$ 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 2.42×10^{-5} to 1.14×10^{-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-naphthyloxy)-2-propranolol) and atenolol (ATN) (4-(2-hydroxy-3-isopropylaminopropoxy) phenylacetamide) are cardioselective β-adrenergic receptor blocking agents. These β-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 β-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 H_2SO_4 or 0.5 M $NaNO_3$ (pH 1.0, adjusted with concentrated HNO_3), respectively. The analytical curves obtained ranging from 0.20 to 9.0 μM for PROP and from 2.0 to 41 μM for ATN, with detection limits of 0.18 and 0.93 μM, 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 β-blockers in several pharmaceutical formulations.

Sildenafil citrate (1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1-H-pyrazolo[4,3-d]pirydin-5-yl)-4-ethoxyphenyl] sulphonyl]-4-methylpiperazine citrate), commonly known under trade name Viagra®, 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 A cm^{-2} for 240 s in 0.5 M H_2SO_4) pre-treated BDD electrode for the determination of Viagra® 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®. Cyclic voltammetric studies show that sidenafil presents two irreversible oxidation peaks, at ~1.5 and ~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 sidenafil concentration interval from 7.3×10^{-7} to 7.3×10^{-6} M with a limit of detection of 6.4×10^{-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−) or an anodically (OT−) 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 A cm^{-2}, respectively, during 60 s, in a 0.5 M H_2SO_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 mg L^{-1} for SMX and TMP, respectively. The calculated values for the LOD and the limit of quantification were 3.65 μg L^{-1} (14.4 nM) and 12.2 μg L^{-1} (48.2 nM) for SMX and 3.92 μg L^{-1} (13.5 nM) and 13.1 μg L^{-1} (45.1 nM) for TMP. Besides this, repeatability tests carried out by successive measurements (n=10) in the same solution (10 mg L^{-1} SMX and 2.0 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 H_2SO_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 8.01×10^{-6} to 1.19×10^{-4} M (r=0.9995) for sulphadiazine and from 6.10×10^{-6} to 6.01×10^{-5} M (r=0.9995) with limits of detection of 2.19 and 1.15 μM 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 pyrolitic 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 coworkers [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.

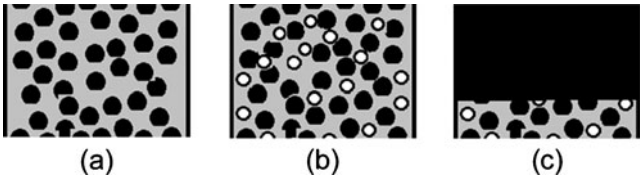

Fig. 6 Representation of composite electrodes: **a** unmodified, **b** body modified and **c** modified composite deposited on a substrate electrode surface. In these representations, the *grey phase* represents the agglutinant, the *black circles* the graphite and the *hollow circles* represent the 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 μm. 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
GPUE					
Atenolol	DPV	Universal buffer pH 10	4×10^{-6}–100×10^{-6}	3.16×10^{-6}	[206]
Atenolol	FIA	Universal buffer pH 10	0.2×10^{-3}–3×10^{-3}	18.1×10^{-6}	[207]
Dopamine	SWV	BR buffer pH 7.4	6.6×10^{-6}–24.1×10^{-6}	6.4×10^{-8}	[203]
Furosemide	DPV SWV	Acetate, phosphate or borax buffer solutions pH 1.2 to 13	0.75×10^{-6}–6.5×10^{-6} 3×10^{-6}–9×10^{-6}	0.15×10^{-6} 0.96×10^{-6}	[211]
Imipramine	SWV	BR buffer pH 7.0	3.04×10^{-7}–30.4×10^{-7}	4.6×10^{-9}	[208]
Nortriptyline	CV	BR buffer pH 7.4	1.66×10^{-5}–17.3610^{-5}	–	[211]
Paracetamol	SWV	Universal buffer pH 8	1.0×10^{-7}–1.0×10^{-5}	6.7×10^{-8}	[210]
Rutin	SWV	BR buffer pH 5.0	1.1×10^{-6} to 3.1×10^{-6}	7.1×10^{-9}	[205]
Verapamil	DPV SWV	Acetate buffer pH 5.3 Acetate buffer pH 5.3	2×10^{-6}–30×10^{-6} 2×10^{-6}–14×10^{-6}	0.7×10^{-6} 0.7×10^{-6}	[209]
GEE					
2-Aminonaphtalene	DPV	BR buffer pH 8	2×10^{-6}–10×10^{-6}	0.92×10^{-6}	[215]
Adenine, guanine	DPV	Phosphate buffer pH 7	1×10^{-4}–2.5×10^{-4}	–	[215]
Ascorbic acid	Amperometry	Phosphate buffer pH 5	9.93×10^{-7}–2.85×10^{-4}	0.65 ng mL^{-1}	[214]
Ascorbic acid	CV	0.1 M phosphate buffer/0.1 M KCl pH 7 and 2 0.1 M H_2SO_4	– –	– –	[216]
GSRE					
Propranolol	DPV	BR buffer pH 7.4	5–80.6×10^{-6}	1.1×10^{-6}	[224]
Rutin	DPV	BR buffer pH 4	5–50×10^{-8}	1.8×10^{-8}	[223]
Other composites					
Ascorbate	Amperometric	0.1 M Sodium phosphate buffer pH 7	–	7.7×10^{-6}	[227]
Ascorbic acid	FIA	0.1 M KBr	5×10^{-5}–1×10^{-3}	1.51×10^{-5}	[227]
Benzhexol	CV	0.1 M phosphate buffer pH 8	3.5×10^{-5}–2×10^{-6}	3×10^{-7}	[233]
Procyclidine		0.1 M phosphate buffer pH 8.5	2.5×10^{-4}–3×10^{-6}	4×10^{-7}	
Diclofenac	DPV SWV	0.1 M $HClO_4$	6×10^{-8}–10^{-6} 5×10^{-9}–6×10^{-7}	5×10^{-8} 5×10^{-9}	[228]
Folic acid	DPASV	0.1 M phosphate buffer pH 7.8	9.1×10^{-12}–3.4×10^{-8}	0.034–0.038 ng mL^{-1}	[234]
L-Tryptophan	DPASV	0.1 M phosphate buffer pH 2	4.4×10^{-9}–9.1×10^{-8}	0.24 ng mL^{-1}	[235]
Acetylsalicylic acid	FIA	Phosphate buffer pH 7	1×10^{-3}–5×10^{-3}	1.1×10^{-5}	[225]
Kaempferol	DPV	Methanol–$NaClO_4$	2.4×10^{-7}–3.4×10^{-6}	6 ng mL^{-1}	[229]
Oxalic acid	DPV, LSV, CA	Na_2SO_4	0.5–3×10^{-3}	0.05×10^{-3}	[230]
Quercetin	DPV	Methanol–$NaClO_4$	3.2×10^{-7}–9.9×10^{-7}	6 ng mL^{-1}	[229]
Rutin	LSV	0.1 M KNO_3/10^{-6} M HNO_3 pH 6	9.9×10^{-7}–8.07×10^{-6}	2.65×10^{-8}	[226]
Rutin	DPV	0.1 M phosphate buffer pH 7	2×10^{-8}–1.0×10^{-6}	1.5×10^{-8}	[232]
Salicylic acid	FIA	Phosphate buffer pH 7	1×10^{-5}–5×10^{-5}	3.5×10^{-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 μM 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 $[Fe(CN)_6]^{3-}$ 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-aminonaphtalene, 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±0.06 μA (n=10).

The GSRE was also used in the determination of the antihypertensive 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±0.1 μA (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 $[Fe(CN)_6]^{4-}$ 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 KNO_3/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®, 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® 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–$NaClO_4$ (0.1 M) (30:30:40, *v/v/v*) and (b) non-polar medium composed of dioxane–hexane–[LiCl/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 Na_2SO_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 $KMnO_4$.

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

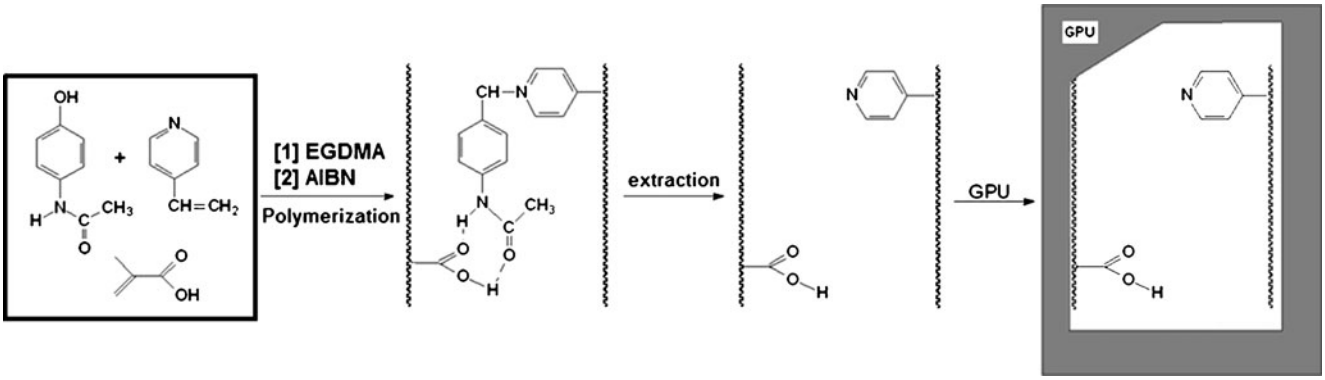

Fig. 7 Steps of the GPUE paracetamol MIP-modified composite electrode preparation: **a** a mixture of methacrylic acid, 4-vinylpyridine and paracetamol is polymerized in the presence of azobis-isobutyronitrile (*AIBN*) and ethylene glycol dimethacrylate (*EGDMA*) in acetonitrile at 65 °C for 24 h; **b** 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 a 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^{-1} [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^{-1} [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 tetrapyridinoporphyrazine 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 methyldopa,

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

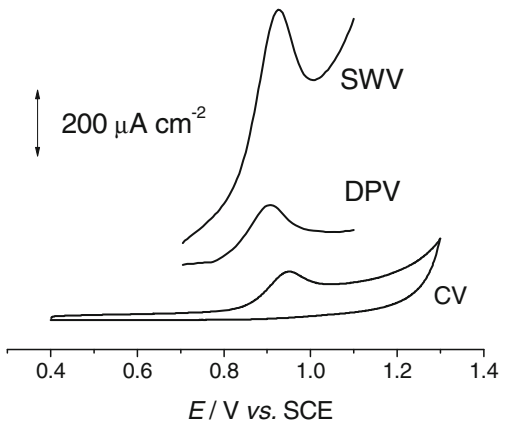

Fig. 8 Voltammograms of 50 μmol L^{-1} propranolol in B-R buffer pH 7.0 at MWCNT/silicone rubber composite electrode using the techniques SWV, DPV and CV. Conditions—SWV: pulse amplitude= 50 mV, frequency=25 Hz and step potential l=5 mV. DPV: scan rate= 25 mV s^{-1} and pulse amplitude=50 mV. CV: scan rate=50 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 antihypertensive 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 P4502B4 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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