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Voltammetric Determination of Pharmaceutical Compounds at Bare and Modified Solid Electrodes: A Review

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ABSTRACT

Electroanalysis is a powerful analytical technique that is increasing in utility in the pharmaceutical industry. Solid electrodes play a crucial role in the voltammetric determination of pharmaceuticals. The potential of solid electrodes has emerged in recent years thanks to their non–toxicity, broad spectrum of analytes, extremely broad concentration range and broad potential window in both anodic and cathodic directions. This review summarizes the application of solid electrodes (either bare or modified electrodes) in pharmaceutical analysis using different electroanalytical techniques, namely, cyclic, linear sweep, differential pulse, square wave and stripping voltammetric techniques. Only four types of solid electrodes will be taken into account, a regular home made solid electrode; carbon paste electrode (CPE) and a three new alternative electrodes; screen printed electrodes (SPE), boron–doped diamond electrode (BDDE) and pencil graphite electrode (PGE).

Keywords: Carbon paste electrode; Screen printed electrodes; Boron–doped diamond electrode; Pencil graphite electrode; Pharmaceutical analysis

Abbreviation: CPE: Carbon paste electrode; SPE: Screen printed electrodes; BDDE: Boron–doped diamond electrode; PGE: Pencil graphite electrode; DME: Dropping mercury electrode; HDME: Hanging dropping mercury electrode; SMDE: Static mercury drop electrode; MWCNT: Multi–walled carbon nanotubes; Ura/CPE: Uracil modified CPE; TCPE: Tyrosine modified CPE; CuHCF: Copper hexacyanoferrate; FMCPE: Ferrocene modified CPE; MMT−Ca−CPE: Montmorillonite−Ca modified CPE; Na–MMT–CPE: Sodiummontmorillonite modified CPE; ERGO: Electroreduced graphene oxide; PVP: Poly(vinyl pyrrolidone);MIP–CPE: Molecularly imprinted polymer modified CPE; NIP–CPE: Non–imprinted polymer modified CPE; CTAB: Cetyltrimethyl ammonium bromide; CDMCPE: β–Cyclodextrin modified CPE;PYCPE: Pyrogallol modified CPE; CNTs: Carbon nanotubes; DHB: 2,2′–[1,7–heptanediylbis(nitrile methylidene)]–bis(4–hydroxy phenol); 1M3BIB: 1–methyl–3–butylimidazolium bromide; GNS: Graphene nanosheet; Au NP: Gold nanoparticle; MWCPE: Multi–walled carbon nanotubes modified CPE; Fe2TiO5–MCPE: Iron titanate nanopowder–modified CPE; BNP–CPE: Boehmite nanoparticles modified CPE; TiO2NP–MCPE: Titanium dioxide modified CPE; Ru–TiO2/CPE: Ruthenium doped titanium dioxide nanoparticles modified CPE; ZnO/MWCNTs/CPE: ZnO nanoparticles and multi–walled carbon nanotubes modified CPE; DyNW/CPE: Dysprosium nanowire modified CPE;SPCE/PGA:L–glutamic acid modified SPE; SPGrE: Graphene modified SPE; MWCNT–PGE: Multi–walled carbon nanotubes modified PGE.

INTRODUCTION

Electrochemistry is an advantageous analytical tool which is cost relatively low–cost, portable and exhibits high sensitivity, selectivity, accuracy and precision as well as large linear dynamic range towards different target analytes either organic [1-5] and inorganic [6-10] analytes. The success in electro analytical techniques is largely due to the continued design and development of newer materials that meet the needs of the modern technology [11-14].

The pharmaceutical and biomedical analysis is among the most important branches of applied analytical chemistry. Regarding electrochemical techniques, the electrochemical detection of pharmaceuticals play a critical role for pharmaceutical quality assurance, quality control laboratories and forensic analysis research. The most widespread electro analytical techniques in pharmaceutical and biomedical analysis are voltammetry and polarography. The first examples of the pharmaceutical analysis using by polarographic methods were described in the 1930s and 1940s. It was found that the most of the pharmaceutical active compounds were found to be as an electrochemically active [15,16].

Different voltammetric techniques, such as cyclic voltammetry, linear sweep voltammetry, differential pulse voltammetry and square–wave voltammetry were applied successfully with high sensitivity for the determination of organic molecules including drugs and related molecules in pharmaceutical dosage forms (tablets, capsules, injections and suspension) and biological fluids (real and spiked urine, samples, blood and serum)[13,14,16-18].

Since the first invitation of polarography in 1922, the most famous working electrode was mercury electrodes (as dropping mercury electrode (DME), hanging dropping mercury electrode (HDME) and static mercury drop electrode (SME))[19]. This can be attributed to easy renewal surface, high sensitivity, high speed, broad spectrum of analytes, extremely broad concentration range and broad potential window in cathodic region. The latter advantages may be considered as main disadvantage of mercury electrodes, since they cannot be applied easily in anodic direction. Also, it's well–known about the high toxicity of mercury which required careful training of laboratory personnel [20,21].

So, scientists directed a large part of their effort to discover new platforms which used as an alternative working electrode for electroanalytical research. These alternative electrodes are solid electrodes thanks to their non–toxicity, which mean it can be used with minimum safety precaution. Also, solid electrodes characterized as good or at least reasonable, negative and positive potential ranges compared with the limited, almost non–existent, and mercury electrode positive potential range. The performance of an electro analytical method depends on the geometry and material composition of the solid electrode [22-24].

Surface of solid electrode is naturally much rougher than mercury electrodes, which mean that the electro active surface area is higher than the geometric area. The electrochemically pretreatment of solid electrodes can enhance its voltammetric response [25-27].

The most important characteristic of solid electrodes than mercury electrodes is its applicability for modification [28]. It is well–known that modification of the conventional working electrode surface imparts high sensitivity and selectivity to the analyte response.

The most usual used modifiers are perm selective membranes, organic ligands, micro and nano–particles, organometallic or inorganic catalysts, ion exchangers, biological materials, zeolites, clays and silica–based materials [29-31].

Advent of chemically modified electrodes has further enhanced the scope and analytical applicability of the technique in the field of drug analysis. As a result of chemical modification process, there is an improvement of analytical performance either by increasing their sensitivity or protecting the surface from undesired reactions.

Herein in this review, we aimed to highlight some noteworthy articles which used a regular home made solid electrode; carbon paste electrode (CPE) and a three new alternative electrodes; screen printed electrodes (SPE), boron–doped diamond electrode (BDDE) and pencil graphite electrode (PGE). We will focus in this review in applications of these electrodes in pharmaceutical analysis.

CARBON PASTE ELECTRODE (CPE)

Thanks to its non–toxic materials, low cost, low residual current, favorable signal to noise ratio, the long range of working potential and renewal of its surface is quite simple, carbon paste electrode have demonstrated their potential for use as electrochemical sensors from the appearance of the first carbon paste electrode, described by Adams [32]. In addition to these advantages, the sensitivity of the prepared carbon paste electrodes can be increased relatively easily with a variety of modifiers [33-36].

Below, we will review several articles in which carbon paste electrode (bare or modified) was applied for the pharmaceuticals determinations

Bare CPE

The individual voltammetric determination of prednisolone, dexamethasone and hydrocortisone was carried out using differential pulse voltammetry at bareCPE [37]. In Britton–Robinson (pH=3.0), prednisolone, dexamethasone and hydrocortisone were determined over the concentration range of 4×10^{-6}-3×10^{-5} M, 4×10^{-6}-2×10^{-5} M and 4×10^{-6}-2×10^{-5} M, respectively. Also, the calculated lower limit of detection and quantification was found to be1×10^{-6} and0.333×10^{-5} (prednisolone), 1.5×10^{-6} and 0.5×10^{-5} (dexamethasone) and 0.7×10^{-6} and0.233×10^{-5}

(hydrocortisone). Differential pulse voltammetry technique was used for the determination of prednisolone, dexamethasone and hydrocortisone in pharmaceuticals and biological fluid samples.

Using CPE, the electrochemical behavior of vardenafil hydrochloride and its trace determination was occurred using cyclic voltammetry and square wave adsorption anodic stripping voltammetry, respectively [38]. Linear variation of the recorded peak currents with vardenafil hydrochloride concentrations was obtained over the concentration range of 1×10^{-9} to 1×10^{-7} $molL^{-1}$. The described stripping voltammetric method is highly sensitive (detection limit $=3 \times 10^{-10} molL^{-1}$ and quantitation limit$=1 \times 10^{-9} molL^{-1}$).The described method showed excellent performance for determination of vardenafil hydrochloride in its formulation "tablets" without interference from excipients.

CPE made of multi-walled carbon nanotubes (MWCNTsP) was used for the simultaneous voltammetric determination of binary mixture containing enalapril and hydrochlorothiazide [39].In Britton-Robinson buffer (pH=5.0), and applying square–wave voltammetry, thebinary mixture of enalapril and hydrochlorothiazide was analyzed over a concentration range of 5.0×10^{-6}-8.3×10^{-5} $molL^{-1}$ and 4.9×10^{-7}-$4.5 \times 10^{-5} molL^{-1}$, respectively. The detection limits were found to be1.4×10^{-8}mol $L^{-1}$and 4.1×10^{-8}mol $L^{-1}$for the determination of enalapril and hydrochlorothiazide, respectively. Using the prepared CPE, the simultaneous determination of enalapril and hydrochlorothiazide in combined dosage forms was achieved.

Cyclic voltammetry was used to study the electrochemical behavior of tinidazole at CPE [40]. Tinidazole showed an irreversible reduction peak at about -440 mV. The differential pulse voltammetric peak current of tinidazole showed linear dependence on concentration in the range 5.0-200 μM with lower limits of detection and quantification of 5.1×10^{-7} and 1.7×10^{-6}μM, respectively. The developed method was applied for the determination of tinidazole in pharmaceutical tablets.

The interaction of D-penicillamine with copper (as cupric ions; Cu^{+2}) at CPE was used for the determination of D-penicillamine without applying of any modifier [41]. In acetate buffer (pH=6.0) and in presence of 1.0 mM Cu^{+2},D-penicillamine was determined over the linearity rangeof1.0×10^{-6} to 1.0×10^{-4}M with an experimental detection limit of 1.0×10^{-7}M. Regarding sensitivity and selectivity of the proposed method, D-penicillamine was successfully determined in real urine sample.

In presence of Triton X-100, CPE was applied for the determination of antiviral drug fosamprenavir [42]. A developed electro analytical procedure was suggested using CPE as working electrode in Britton-Robinson buffer (pH=2.0) and square wave voltammetry. Linearity range was obtained in concentration range of $1 \times 10^{-6}$to 5×10^{-5} M fosamprenavir with detection limit of 4.8×10^{-7}M. The proposed method was used for the determination of fosamprenavir in pharmaceutical dosage form.

The enhancement effect of Triton X^{-100}, was exploited in the determination of entacapone at CPE in Britton–Robinson buffer containing Triton X^{-100} [43]. A good linear relationship was obtained within the concentration range from 1.0×10^{-6} to 3.8×10^{-5} mol L^{-1}. The limits of detection and quantification were found to be 1.13×10^{-7} and 3.76×10^{-7} mol L^{-1}, respectively. The proposed method was suitable for routine analysis of entacapone in pharmaceutical dosage forms and human plasma.

Another effort showed the enhancement effect of surfactant of electrochemical signal (in this case: sodium dodecyl sulfate) was presented in the determination of antihypertensive drug moexipril hydrochloride at CPE [44]. Moexipril hydrochloride exhibits a well–defined irreversible oxidation peak in Britton-Robinson buffer. The peak current varied linearly over the range from 4.0×10^{-7} to 5.2×10^{-6} mol L^{-1}. The limits of detection and quantification were 6.87×10^{-8} mol L^{-1} and 2.29×10^{-7} mol L^{-1}, respectively. The proposed method was successfully used to determine moexipril hydrochloride in tablets.

CPE was applied for the determination of silymarin which have ability to protect and rebuild the liver cells damaged by alcohol and other toxic substances [45]. In acetate buffer (pH=4.0) and using bare CPE, silymarin was determined over concentration range 1×10^{-7}-4×10^{-6} mol $L^{-1}$with detection and quantification limits of 3×10^{-8} and 1×10^{-7} mol L^{-1}, respectively. The proposed procedure was applied for the determination of silymarin in commercial formulations (capsules) and human serum.

Ropinirole hydrochloride was determined in bulk, dosage forms and biological samples on CPE and square wave voltammetry [46]. In a voltammetric cell containing 10 mL of 0.1 mole L^{-1} H2SO4as supporting electrolyte, a good linearity was obtained over a range of 4.96×10^{-6} to 3.90×10^{-5} mol L^{-1}, with lower detection and quantification limits of $1.48 \times 10^{-6}$and 4.96×10^{-6} mol L^{-1}, respectively.

Bare CPE was applied for the determination of metoclopramide hydrochloride using square wave anodic stripping voltammetry [47]. In HCl-sodium acetate buffer (pH=6.2) containing 0.2 M KCl, metoclopramide hydrochloride was determined over a three concentration ranges; from 0.067 to 0.336, 0.067 to 0.269 and 0.067 to 0.269 $ngmL^{-1}$. The presented procedure was successfully applied for the determination of metoclopramide hydrochloride in pharmaceutical formulations and in biological fluids (spiked and real urine samples).

Square wave anodic stripping voltammetric procedure was presented for the determination of mebeverin hydrochloride at CPE [48]. In phosphate buffer (pH=8.0) containing 0.1 M KCl, a calibration curve was constructed over the concentration range of 0.233-42.406 μg mL^{-1} of mebeverin hydrochloride. Using standard addition method, the proposed procedure was applied for the determination of mebeverin hydrochloride in dosage forms, spiked and real urine samples.

The electrochemical behavior of pramipexole dihydrochloride was studied at CPE in Britton-Robinson buffer (pH=6.08), using cyclic and differential pulse voltammetric techniques [49]. A differential pulse anodicvoltammetric procedure has been developed for determination of the drug over the concentration range of 1.20-8.23 μgmL^{-1}, with detection and quantification limitsof 0.21 and 0.68 μg mL^{-1}, respectively. The proposed method was successfully applied for the determination of pramipexole dihydrochloride in its commercial tablets.

The electrochemical behavior of anticancer drug 5-fluorouracil was studied at CPE using cyclic voltammetry and its determination was accomplished using differential pulse voltammetry [50]. In phosphate buffer solution (pH=7.0), the differential pulse voltammograms was recorded with increasing amounts of 5-fluorouracil in the range of 1.0×10^{-7}-4×10^{-5} M with calculated limit of detection and quantification of 12.25 and 40.8 nM, respectively. The constructed calibration plot was used for quantitative analysis of 5–fluorouracil in pharmaceutical and human urine sample.

Differential pulse voltammetry was used to determine doxycycline hyclate at CPE [51]. Doxycycline hyclate exhibits a well–defined irreversible oxidation peak in Britton–Robinson (pH=3.0). The peak current increased linearly in concentration range of 2.0×10^{-7}-3.0×10^{-6} $molL^{-1}$ with calculated limits of detection and quantification of 6.56×10^{-8} and 2.19×10^{-7} $molL^{-1}$, respectively. Using proposed procedure, doxycycline hyclate was successfully determined in pharmaceutical form.

Normal and differential pulse voltammetry were used to determine nisoldipine in bulk and tablets [52]. At CPE, nisoldipine showed well–defined irreversible oxidation peak in Britton–Robinson. The peak current increased linearly in the concentration ranges of 1.6 × 10–6–5.2×10^{-6}mol $L^{-1}$and 8.0×10^{-7}–5.6×10^{-6}mol L^{-1} for normal and differential pulse voltammetry, respectively. In case of normal pulse voltammetry the limits of detection and quantification were 2.73×10^{-7} and 9.11×10^{-7} mol L^{-1}, respectively. For differential pulse voltammetry, detection and quantification limits were $9.37 \times 10^{-8}$and 3.12×10^{-7}mol L^{-1}, respectively. The proposed method was successfully applied to determine nisoldipine in dosage form.

Using square wave anodic stripping voltammetry and CPE, electrochemical determination of quercetin was achieved [53]. In phosphate buffer (pH=4) containing 0.1 M KCl, and under the optimal experimental conditions, the adsorbed form of quercetin is oxidized irreversibly. The linear concentration ranged from 67.66 to 338.3 ppb quercetin with detection limit of 6.77 ppb at 15s accumulation time. The method was applied to the analysis of quercetin in spiked urine samples.

Determination of azithromycin (which is the first member of a class of macrolide azalides antibiotics called azolides) was accomplished with hand–made CPE [54]. The best results were obtained in acetonitrile/aq. 1 M sodium acetate–acetic acid buffer (pH=4.6) containing 0.1 M KCl. A well–defined peak was observed over the concentration range 0.471–7.065 ppb after 30 and 60 s, and over the range 1.57–392.5 ppb at 5 and 10s.The limits of detection and quantification of the pure drug are 0.463 and 1.544 ppb. The method was successfully applied to the determination of azithromycin in urine and two forms of pharmaceutical formulations.

Modified CPE

Uracil covalently grafted CPE was prepared by electro–deposition of uracil on CPE (Ura/CPE) [55]. Uracil modified CPE was applied for the quantitative determination of nevirapine (which is used as anti–HIV drug). The results indicated that the electrochemical reaction of nevirapine on modified CPE is an adsorption–controlled process. Under optimized conditions, the linearity between the oxidation peak current and nevirapine concentration was obtained in the range of 0.1-70.0 μM with detection limit of 0.05 μM. Uracil modified CPE was successfully applied to detect the concentration of nevirapine in human serum samples.

As a modifier, nevirapine was used to modify CPE in order to simultaneous determination of paracetamol and folic acid [56]. The CPE modified with nevirapine showed a strong resolving capacity for overlapping voltammetric response of paracetamol and folic acid into two well resolved peaks, as compared to the bare CPE. The obtained results confirmed that the peak current of paracetamol was proportional to its concentration, which is increased from 2 to 12 μM while keeping the concentration of folic acid constant. Also, the obtained data showed that in presence of constant paracetamol concentration, the anodic peak current of folic acid increases linearly with increasing its concentration from 5 to 45 μM. At nevirapine modified CPE, the detection limit of paracetamol and folic acid were found to be 0.77 μM and 2.53 μM, respectively. The practical utility of the proposed electrode was evaluated by analyzing paracetamol in pharmaceutical sample.

The electrochemical oxidation of 5-fluorouracil has been investigated at methylene blue modified CPE.Modification procedure based on electrochemical deposition of methylene blue on surface of CPE[57]. The peak currents obtained from differential pulse voltammetry was linear with concentration of 5–fluorouracil in the range 4×10^{-5}-1×10^{-7} M and detection limit and quantification limit were calculated to be 2.04 nM and 6.18 nM, respectively. Further, the sensor was successfully applied in pharmaceutical and biological fluid sample analysis

The oxidative behavior of diclofenac sodium has been investigated by cyclic voltammetric and differential pulse voltammetric techniques, using a tyrosine modified CPE (TCPE) [58]. In phosphate buffer (pH=7.0) diclofenac sodium exhibited a sensitive diffusion controlled oxidative peak at 0.67 V. The peak current of diclofenac sodium varied linearly with its concentration in the range between10μM and 140μM with a detection limit of 3.28μM. The proposed methodology was applied for the determination of diclofenac sodium in pharmaceutical samples and human urine samples.

Square wave voltammetric method was used to study the electrochemical properties of pyridoxine (Vitamin B6) and determine it in pharmaceutical preparations using cobal thexa cyano ferrate modified CPE [59]. The peak current depends linearly on the concentration of pyridoxine from 5.0 × 10−6 to 2.6 × 10−5 M with detection limit of 1.72×10^{-7} M. The developed voltammetric method was applied for the determination of pyridoxine in Vitamin B6 tablets.

Copper hexa cyano ferrate (CuHCF) modified CPE was applied for the determination of dipyrone and acetaminophen by cyclic voltammetry in acetate buffer (pH=7.4) [60]. The analytical curve was linear in the dipyrone and acetaminophen concentration ranges of 1.25×10^{-5}-1.23×10^{-3}mol L^{-1} and 2.84×10^{-4}-2.59×10^{-3} $molL^{-1}$, respectively. The detection and quantification limits were calculated to be 5.08×10^{-6} and $1.01 \times 10^{-5}$$molL^{-1}$(dipyrone), 6.39×10^{-6} and $2.56 \times 10^{-5}$$molL^{-1}$ (acetaminophen), respectively. CPE modified with CuHCF was successfully applied for the determination of dipyrone and acetaminophen in pharmaceutical preparations.

The kinetics of the electrocatalytic reaction of captopril was studied using CPE modified with copper–cobalt hexacyanoferrate [61]. Modification procedure consist of successive potential cycles were applied to bare CPE in KNO3 solution at scan rate of 50 mV s^{-1}. Then, in a solution containing $Cu(NO_3)_2$, $CoCl_2$, $K_3Fe(CN)_6$ (each of them 6.25×10^{-4} M) and KNO_3, repeated potential cycling from 0 to 1.0 V (30 cycles) were applied at a scan rate of 50 mV s–1.Using modified CPE, a linear relationship was observed between anodic current and the concentration of captopril in the range of 5.0×10^{-6}-3.1×10^{-5} μM with a detection limit of 4.2 μM. The modified electrode was used in the analysis of captopril tablets successfully.

Ferrocene modified CPE (FMCPE) and polyethylene glycol modified CPE were utilized for the determination of flavoxate HCl and tolterodine tartrate, respectively [62]. The electrochemical behavior of flavoxate HCl and tolterodine tartrate showed irreversible diffusion–controlled oxidation processes in Britton–Robinson buffer.The linear ranges were 7.8×10^{-6}-1.2×10^{-4} $molL^{-1}$and 7.6×10^{-7}-2.2×10^{-4} $molL^{-1}$for flavoxate HCl and tolterodine tartrate, respectively. The limits of detection and quantification were 5.9×10^{-7} and 2×10^{-6} for flavoxate HCl and 8.6×10^{-8} $molL^{-1}$ and 2.9×10^{-7} $molL^{-1}$for tolterodine tartrate. The modified electrode was used in the analysis of flavoxate HCl and tolterodine tartrate in pharmaceutical dosage forms

CPE modified with carbon nanotube and benzoyl ferrocene was fabricated. The modified electrode was employed to study the electrocatalytic oxidation of captopril, using cyclic voltammetry, chronoamperometry and square wave voltammetry [63]. Square wave voltammetry exhibits a linear dynamic range from 1.0×10^{-7} to 3.5×10^{-4} M and a detection limit of 3.0×10^{-8} M for captopril. Finally the modified CPE was used for determination of captopril in pharmaceutical formulations (tablet) and urine sample.

An electrochemical study of diazepam, temazepam and oxazepam using CPE modified with bentonite was presented [64].Cyclic and differential pulse voltammetry were used to electrochemical study and analytical determination of studied drugs. At studied optimum conditions, diazepam, temazepam and oxazepam were determined over the concentration ranges of 0.025-3.0, 0.025-0.8 and 0.025-1.0 μg mL^{-1}, respectively. The proposed methodology was applied for the voltammetric measurements of diazepamin plasma and oxazepam in urine.

Montmorillonite−Ca natural clay was applied as a modifier for CPE (MMT-Ca-CPE) [45]. When MMT−Ca modified CPEcoupled with square−wave adsorptive anodic stripping voltammetry, it's applied successfully for the determination of silymarin. In acetate buffer (pH=4.0)and over linear dynamic range of 7×10^{-9}-1.5×10^{-6} $molL^{-1}$, silymarin was determined successfully with detection and quantification limits of 2.1×10^{-9}and7×10^{-9} $molL^{-1}$, respectively. The proposed methodology was successfully applied for the determination of silymarin in five different pharmaceutical samples (capsules).

CPE was bulk modified with sodium montmorillonite clay (Na–MMT–CPE) and the modified electrode was successfully used in studying the electrochemical behavior and voltammetric determination of pipazethate hydrochloride [65]. Linear dynamic ranges of 8.0×10^{-7}-6.0×10^{-6} $molL^{-1}$ and 1.0×10^{-7}-6.0×10^{-6} $molL^{-1}$ of pipazethate hydrochloride were obtained using linear−sweep and square−wave adsorptive anodic stripping voltammetric methods, respectively. The limits of detection (2.4×10^{-7} and 3.0×10^{-8} $molL^{-1}$) and quantitation (8.0

$\times 10^{-7}$ and 1.0×10^{-7} mol L^{-1}) were achieved by the optimized linear−sweep and square−wave adsorptive anodic stripping voltammetric methods, respectively, respectively. The modified electrode was successfully applied for determination of pipazethate hydrochloride in pharmaceutical formulation and in spiked human serum.

Composite of sodium montmorillonite nanoclay (NaMM)/electroreduced graphene oxide (ERGO) was used as CPE modifier [66]. The developed modified CPE (NaMM/ERGO/CPE) was applied for the electrochemical determination of cefotaxime. The electrooxidation of cefotaxime was studied on NaMM/ERGO/CPEusing cyclic and differential pulse voltammetry as diagnostic techniques. Under optimized conditions, the modified electrode exhibited a linear response over two linear concentration ranges from 0.5 to 40 nM and 40 to 2400 nM cefotaxime, with a detection limit of 0.1 nM. The proposed sensor was successfully applied for monitoring of cefotaxime in serum and urine samples.

At nano claymodified CPE, the voltammetric determination of acyclovir was achieved by employing cyclic and square wave voltammetry techniques in phosphate buffer (pH=5.0) [67]. The electro−oxidation current of acyclovir was enhanced two times greater by the modification CPE. The effect of acyclovir concentration variation was studied using square wave voltammetry technique over the concentration range of 5.0 × 10−8–1.0 × 10^{-6}Mwithcalculated detection limit of 0.2 nM. The modified CPE was employed for the determination of acyclovir in pharmaceutical and human urine samples.

Acyclovir was also determined using CPE modified with poly (vinyl pyrrolidone) (PVP), which is a macromolecule surfactant [68]. In acetate buffer (pH=5.0), the electrochemical behavior of acyclovir was studied, and a sensitive oxidation peak at 1.03 V was observed. A calibration plot of acyclovir determination was constructed starting from 1 $\times 10^{-8}$ to 7.5×10^{-7} M acyclovir with detection limit of 2.5×10^{-9} M. The proposed method was demonstrated using acyclovir injection and tablets.

In phosphate buffer (pH=7.5), CPE modified electrode was applied for the determination of nifedipine in tablet samples [69]. Using differential pulse voltammetry technique, CPE modified with poly (vinyl pyrrolidone) (PVP) and the modified electrode was applied for the determination of nifedipine over the concentration range of 75 nM to 50 µM, and the detection limit was 20 nM.

A CPE modified with poly (vinyl pyrrolidone) (PVP) was evaluated through electrochemical studies and the electro analytical determination of quercetin [70]. Using the modified CPE, cyclic voltammograms of quercetin showed three oxidation peaks at 0.32, 0.78 and 1.04 V. Using square–wave voltammetry; the calibration curve was linear in the concentration range of 0.5 to 5.5 µmolL^{-1}. The limits of detection and quantification obtained were 0.17 and 0.52 µmolL^{-1}, respectively. CPE modified with PVP was successfully used for the determination of quercetin in a pharmaceutical sample.

CPE modified with molecularly imprinted polymer (MIP–CPE) and a non–imprinted polymer (NIP–CPE) was applied for the determination of lamotrigine [71]. A lamotrigine selective MIP and a NIP were synthesized and then incorporated in the CPE. The proposed electrochemical sensor was applied for lamotrigine determination using differential pulse voltammetric method. From obtained results the calibration curve was plotted and two dynamic linear ranges of 0.8–25 and 25–400 nM were obtained with calculated detection limit as 0.21 nM. This sensor was used successfully for lamotrigine determination in pharmaceutical preparations.

Another application of MIP–CPEand NIP–CPE was the determination of rivastigmine [72]. The electrochemical behavior of the sensor toward rivastigmine was investigated by cyclic voltammetry and differential pulse voltammetry. The MIP–CPE showed very high recognition ability in comparison to NIP–CPE. A linear range of 2.0–1000 µmol L−1 was obtained with calculated detection limit of 0.44 µmolL^{-1}. This sensor was used successfully for rivastigmine determination in capsule and spiked serum and urine samples.

Trace amount of sulfasalazine was determined using MIP–CPE and NIP–CPE. The MIP–CPE showed high recognition ability of sulfasalazine in comparison with the NIP–CPE [73]. Under optimal conditions, the MIP based sensor exhibited good performance for sulfasalazine over the concentration range of 1.0×10^{-8} to 1.0×10^{-6} molL^{-1} with a detection limit of 4.6×10^{-9} molL^{-1} and sensitivity 1.11×10^{7} µALmol^{-1}. The MIP based sensor was successfully applied to the determination of sulfasalazine in a commercial pharmaceutical formulation and human serum.

Sadeghi et al. [74] presented another application of MIP–CPE and NIP–CPE for the determination of sulfadiazine in milk and human serum samples. Cyclic voltammetry and differential pulse voltammetry methods were performed to study the binding event and electrochemical behavior of sulfadiazine at MIP–CPE and NIP–CPE. Under the optimized operational conditions, the peak current obtained at the MIP–CPE was proportional to the sulfadiazine concentration within the range of 2.0×10^{-7}-1.0×10^{-4} molL^{-1} with a detection limit of 1.4×10^{-7} molL^{-1}.

When molecularly imprinted polymers (MIP) were grafted on the surface of functionalized multi–walledcarbon nanotubes (MWCNTs), the produced composite used for modification of CPE [75]. The modified CPE was used for the determination of diazepam. The diazepam binding experiments indicated that the sensor modified by MWCNTs–

MIP has much higher adsorption ability than the MWCNTs based non–imprinted polymer (MWCNTs–NIP).The CPE modified by MWCNTs–MIPwas successfully used for the determination of diazepam in range of 8.0×10^{-9} to 1.0×10^{-6} $molL^{-1}$and detection limit of 3.7×10^{-9} $molL^{-1}$. The modified CPE was applied for determination of diazepam in tablets andhuman serum samples

The electrochemical behavior of mesalazine was investigated at cetyltrimethyl ammonium bromide (CTAB) immobilized CPE in phosphate buffer (pH=7.4) by cyclic voltammetry [76]. CTAB modified CPE was exhibited a good electrochemical activity towards the oxidation of mesalazine. Under optimal experimental conditions, the electrochemical response to mesalazine was linear in the concentration range from 60μM to 140μM with a detection limit of 1.9 nM. The proposed method was successfully applied to determine mesalazine in pharmaceutical samples.

β–Cyclodextrin was used for the modification of CPE (CDMCPE). The produced modified CPE was used for the determination of prednisolone, dexamethasone and hydrocortisone [37]. Using cyclic voltammetry, these drugs exhibit a well–defined single peak in Britton–Robinson (pH=3.0) which is attributed to the reduction of keto–group in irreversible and adsorption controlled process. The reduction peak currents at CDMCPE for prednisolone, dexamethasone and hydrocortisone changes linearly over the concentration range of 5.6×10^{-7}-2×10^{-5} M, 4.1×10^{-7}-2×10^{-5}M and 4.2×10^{-7}-2.5×10^{-5}M, respectively. The calculated values of detection and quantification limits were found to be 4.8×10^{-7} and 1.599×10^{-6} (prednisolone), 3.6×10^{-7} and 1.199×10^{-6} (dexamethasone) and 3.7×10^{-7} and 1.233×10^{-6} (hydrocortisone). CDMCPE was applied for the determination of prednisolone, dexamethasone and hydrocortisone in dosage forms and spiked human serum samples.

Another application of β–cyclodextrin modified CPE was illustrated in the individual determination of gemifloxacin and nadifloxacin [77]. Cyclic voltammetric studies in Britton–Robinson buffer indicatethat the electrochemical behavior of gemifloxacin and nadifloxacin was irreversible and diffusion controlled with some adsorption character. Differential pulse voltammetry was used to determine gemifloxacin and nadifloxacin.The peak current increased linearly for both drugs in the concentration range of 5.0×10^{-8}-2.0×10^{-7} $molL^{-1}$. For gemifloxacin and nadifloxacin, the detection limits were calculated as 1.2×10^{-8} and 1.0×10^{-8} $molL^{-1}$, respectively. The calculated limits of quantification were 4.3×10^{-8} and 3.3×10^{-8} mol L^{-1} for gemifloxacin and nadifloxacin, respectively. The developed procedure was applied for the determination of gemifloxacin commercial dosage form (tablets).

The electrooxidative behavior and determination of metformin hydrochloride, anti–hyperglycemic drug, on pyrogallolmodified CPE(PYCPE) was investigated using cyclic voltammetry and differential pulse voltammetry[78]. In Britton–Robinson buffer, metformin hydrochloride showed an irreversible oxidation behavior at PYCPE. The peak current increased linearly in the range comprised between 8.0 × 10–7and 6.0 × 10–6molL–1 with detection and quantification limits of 6.63 × 10–8 and 2.21×10^{-7} $molL^{-1}$. The method was proposed for the determination of metformin hydrochloride in dosage forms and urine.

A CPE modified with 2,2′–[1,7–heptanediylbis(nitrilomethylidene)]–bis(4–hydroxy phenol) (DHB) and carbon nanotubes (CNTs) was prepared[79]. The modified CPE (DHB/CNTs/CPE) was used as an electrochemical sensor for the determination of captopril. Differential pulse voltammetry of captopril at DHB/CNTs/CPE exhibited two linear dynamic ranges (7.0–100.0 and 100.0–2,500.0 μM) with a detection limit of 2.43 μM. DHB/CNTs/CPE was used for the determination of captopril in the presence of acetaminophen and tryptophan, captopril in the presence of folic acid, and captopril in the presence of L–cysteine (L–Cys).DHB/CNTs/CPE was successfully applied for the accurate determination of these substrates in human serum samples.

Ananostructure sensor based on NiO/graphene oxide nanocomposite–ionic liquids (1–methyl–3–butylimidazolium bromide; 1M3BIB) was used to modify CPE (NiO/GO/1M3BIB/CPE) for the electrochemical analysis of sulfamethoxazole [80]. The electrochemical response was found to be linearly proportional to sulfamethoxazole concentration in the range of 0.08–550 μM with a detection limit of 0.04 μM. NiO/GO/1M3BIB/CPE has been successfully applied for the assay of sulfamethoxazole in pharmaceutical and biological samples.

Acomposite consist of the same ionic liquid (1–methyl–3–butylimidazolium bromide) and ZnO nanoparticles was used as modifier for CPE (ZnO/NPs/ILs/CPE) [81]. The modified electrode was applied for the determination of promazine which showed an oxidation peak at 685 mV.The linear response range and detection limit were found to be 0.08–450 and 0.04 mmol L^{-1}, respectively. ZnO/NPs/ILs/CPE wassuccessfullyusedforthe determinationof promazine in commercial dosage forms and biological fluids.

Another CPE modifier consist of ionic liquid (1,3–dipropylimidazolium bromide) and NiO nanoparticle (NiO/NPs) was presented [82]. The modified CPE (IL/NiO/NPs/CPE) was applied to study the electrochemical behavior of isuprel followed by its determination. The linear response range and detection limit were found to be 0.4–500 $\mu molL^{-1}$and 0.1$\mu molL^{-1}$, respectively. IL/NiO/NPs/CPE was successfully applied for the determination of isuprel in biological fluids (urine and serum samples).

Ionic liquid–MgO NPs modified CPE (MgO NPs/IL/CPE) was used for the investigation of the electrochemical oxidation of methyldopa using voltammetric methods [83]. Under optimal conditions in phosphate buffer (pH=7.0),

the anodic peak currents increased linearly with methyldopa concentration in the range of 0.08–380 μmolL^{-1} with a detection limit of 0.03 μmolL^{-1}. The proposed sensor was applied successfully for the determination of methyldopa in real samples such as drug and patient human urine samples.

Graphene modified CPE was applied for studying the electrochemical oxidation and the determination of eugenol which showed a well–defined irreversible oxidation peak at about 0.7 V in Britton–Robinson buffer (pH=2.0) [84]. The differential pulse voltammetric peak currents were found to be linear in the concentration range of 1.0×10^{-7} to 1.7×10^{-5} M. The limit of detection and the limit of quantification were obtained to be 7.0×10^{-9} and 2.3×10^{-8} M, respectively. The validated voltammetric method was applied for quantitative analysis of eugenol in a pharmaceutical formulation.

Rivastigmine was also determined using CPE modified with graphene nanosheet (GNS)–gold nanoparticle (AuNP) composite [85]. The oxidation of rivastigmine was studied at GNS–AuNP–CPE using adsorptive stripping differential pulse voltammetry. Under the optimized conditions, the peak current is found to be proportional to the rivastigmine concentration in the range of 2.0×10^{-7}-6.0×10^{-4} M with a detection limit of 5.3×10^{-8} M. GNS–AuNP–CPE was used for the determination of rivastigmine in pharmaceuticals formulations, blood serum, and urine samples

Gold nanoparticles electrodeposited on a multi–walled modified carbon paste electrode (GNPs/MWCPE) presented asan efficient electrochemical sensor for the determination of cefixime in urine and pharmaceutical [86]. The voltammetric behavior of cefixime on GNPs/MWCPE was studied using cyclic voltammetric techniques. At the optimum conditions, the concentration of cefixime was determined using square wave voltammetry in a linear range from0.01 to 200 μmol L^{-1} with a detection limit of 3.0×10^{-9} molL^{-1}.GNPs/MWCPE was applied for the determination of cefixime in dosage forms and human urine samples.

Zhang et al. presented an electrochemical sensor based on Au nanoparticles/poly (L–arginine) modified CPE (AuNPs/Parg/CPE) which utilized for the determination of cefotaxime [87]. The electrooxidation of cefotaxime at AuNPs/Parg/CPE surface was performed by cyclic and linear sweep voltammetry. The calibration curve was linear over the cefotaxime concentration range of 0.01–100.0 μM with a detectionlimitof 2.3 nM. AuNPs/Parg/CPE had been applied for the determination of cefotaxime in pharmaceutical formulations and human serum samples.

The colloidal gold nanoparticles modified CPE (GN–CPE) was used for the determination of atenolol in drug formulations by cyclic and differential pulse voltammetry [88]. In Britton–Robinson buffer (pH=10.0), a linear analytical curve was observed in the range of 1.96×10^{-6} to 9.09×10^{-4} mol L^{-1}. The detection limit for this method is 7.3×10^{-8}mol L^{-1}. The modified electrode had been successfully applied to the determination of atenolol in tablets and human urine.

In presence of tween 80, gold nanoparticles modified CPE (GNCPE) had been developed for the determination of gemifloxacin mesylate using differential pulse voltammetry [89]. The electrochemical behavior of gemifloxacin mesylate has been investigated by using cyclic voltammetry and differential pulse voltammetry techniques. The anodic peak current varied linearly over the range from 8.0×10^{-7} to 2.8×10^{-5} M. The limits of detection and quantification were 7.32×10^{-8} M and 2.44×10^{-7} M, respectively. Standard addition method was successfully applied to the direct determination of gemifloxacin mesylate in dosage forms and human urine samples using GNCPE.

Attia et al. [90] continued their effort in studying enhancement effect of different surfactants on peak current. This was occurred in study the electrochemical behavior of sparfloxacin HCl and besifloxacin HCl at gold nanoparticles modified CPE (AuCPE) using cyclic and differential pulse voltammetry modes in the presence of sodium dodecyl sulphate. AuCPE shows highly sensitive sensing giving an excellent response for SPAR and BESI. The peak current varied linearly over the concentration ranges of1.1×10^{-7}–3.3×10^{-6} and 2.2×10^{-6}–5.5×10^{-5} molL^{-1} forsparfloxacin HCl and besifloxacin HCl, respectively. The detections limits were 2.87×10^{-8} and 3.76×10^{-7} molL^{-1} for sparfloxacin HCl and besifloxacin HCl, respectively. The proposed method has been successfully applied to determine sparfloxacin HCl and besifloxacin HCl in human urine and plasma samples.

Two modified CPE was suggested for the determination of methadone. The first electrode is multi–walled carbon nanotubes modified CPE (MWCPE) while the second one is gold nanoparticles which electrodeposited on a multi–walled carbon nanotube modified CPE (GNPs/MWCPE) [91]. The oxidation of methadone was irreversible and exhibited an adsorption controlled process at the GNPs/MWCPE and a diffusion controlled process at the MWCPE. At the optimum conditions, the concentration of methadone was determined using square wave voltammetry in a linear range of 0.1 to 500.0 μmolL^{-1} at GNPs/MWCPE, and 0.5 to 300.0 μmolL^{-1} at MWCPE and the detection limits were found to be 0.005 and 0.3 μmolL^{-1}, respectively. The two modified CPE were successfully applied to the determination of methadone in a pharmaceutical dosage form, urine and saliva samples.

Multi–walled carbon nanotubes (MWCNTs) modified CPEwas prepared for the voltammetric determination of anti–inflammatory drug nimesulide [92]. In phosphate buffer solution (pH=5.0) using differential pulse voltammetry, a

linearresponse between nimesulide oxidation peak current and its concentration was obtained in the range of the concentration from 6×10^{-8}–1×10^{-5}M with detection and quantification limit of1.07×10^{-9} and 3.24×10^{-9}M, respectively. Using modified electrode was successfully applied to the determination of nimesulide indosage forms and human serum samples.

Multiwall carbon nanotubes (MWCNTs) chemically modified with N–(3,4–dihydroxyphenethyl)–3,5–dinitrobenzamide was used as modifier to enhance CPE sensitivity for use in the determination of trace amounts of isoprenaline [93]. Under the optimum conditions, measurements using square wave voltammetry had a linear range in the range of 0.3 to 125.0 $\mu molL^{-1}$ of isoprenaline and a detection limit of 0.1 $\mu molL^{-1}$. This electrochemical sensor was successfully applied for the determination of isoprenaline in human urine and injection solution samples.

Modified CPE was applied for the determination of haloperidol by differential pulse and square wave voltammetry [94]. Modified CPE was prepared by mix certain amount of graphite powder with multi–walled carbon nanotubes functionalized with magnetic Fe3O4nanoparticle (Fe3O4NPs/MWCNTs).In Britton–Robinson buffer (pH=7.5), the recorded peak currents of haloperidol increased linearly with its concentration in the ranges of 1.2 × 10−3–5.2 × 10^{-1} and 6.5×10^{-4}–5.2×10^{-1} $\mu molL^{-1}$, with detection limits of $7.02 \times 10^{-4}$and 1.33×10^{-4} μmolL−1for differential pulse and square wave voltammetry, respectively. CPE modified withFe3O4NPs/MWCNTs was successfully applied to determine haloperidol in pharmaceutical samples and biological fluids.

CPE modified in–situ with ZnFe2O4 magnetic nanoparticles (ZnFe2O4/MNPs) and 1,3–dipropylimidazolium bromide ionic liquid (ZnFe2O4/MNPs/IL/CPE)was developed for the determination of 5–fluorouracile[95]. After the experimental conditions were optimized,and using ZnFe2O4/MNPs/IL/CPE, the oxidation peak currents for 5–fluorouracile was found to vary linearly with its concentrations in the range of 0.1–1400 μM using square wave voltammety. The ZnFe2O4/MNPs/IL/CPE was successfully applied for the analysis of 5–fluorouracile in pharmaceutical and urine samples.

An electrochemical sensor based on CPE modified with graphene–zinc oxide nanocomposite (GNS–ZnO–CPE) was introduced for the voltammetric determination of pyrazinamide which is a widely used drug for the treatment of tuberculosis [96]. The electro catalytic response of pyrazinamide at GNS–ZnO–CPE was measured using cyclic voltammetry and differential pulse voltammetry. Under the optimized conditions, the recorded peak current was proportional to pyrazinamide concentration in the range of 1.5×10^{-7} to 4.0×10^{-4} M with a detection limit of 4.31×10^{-8} M. GNS–ZnO–CPE was used successively for analysis of pyrazinamide in dosage forms, urine and blood serum samples.

Differential pulse adsorptive stripping voltammetric technique was applied for the determination of salbutamol using an iron titanate nanopowder–modified CPE (Fe2TiO5–MCPE) [97]. The produced modified electrode exhibited a linear response in the range of 0.2–25 nM of salbutamol with a detection limit of 90 pM. Fe2TiO5–MCPE was successfully applied to determine salbutamol in pharmaceutical formulations and human blood plasma.

CPE made of glassy carbon spherical microparticles (GCPE) was modified with In2O3 nanoparticles (In2O3 NPs/GCPE) and the produced modified GCPE was applied for the determination of luteolin [98]. In Britton–Robinson buffer (pH=5.0) and under the optimized experimental conditions, the proposed sensor exhibited a rapid response to luteolin in a linear range from 9.98×10^{-9} to 8.84×10^{-8} M luteolin and a lower detection limit was found tobe 1.99×10^{-10}M. The analytical performance of In2O3 NPs/GCPE was evaluated for the detection of luteolin inspiked human biological fluids (serum and urine).

The voltammetric oxidation of piroxicam was studied at boehmite nanoparticles modified CPE (BNP–CPE) by cyclic voltammetry and its determination were carried out by anodic stripping differential pulse voltammetry [99].Under the optimal conditions at BNP–CPE, a linear relationship was realized between the anodic peak currents and piroxicam concentrations in the range of 0.5 to 100.0 nM, with the detection limit of 0.11 nM. The proposed method was applied to the determination of piroxicam in serum and pharmaceutical samples.

Titanium dioxide (TiO_2) nanoparticles modified CPE was fabricated and applied to get very well–defined oxidation peak current of amlodipine under the optimized conditions [100]. The developed voltammetric method for the determination of amlodipine offers a linear relationship between the peak current and concentration in the range of 1.0×10^{-8}–1.0×10^{-6} M with detection limit of 2.97×10^{-9}M. The produced modified CPE was successfully applied for the quantitative analysis of amlodipine in commercial tablets.

Another application of CPE modified with TiO2nanoparticles (TiO_2NP–MCPE) was the electrochemical determination of clozapine [101]. The electrochemical behavior of the modified electrode and the mechanism of the oxidation of clozapine were investigated using cyclic voltammetry. Using adsorptive differential pulse voltammetry at optimum parameters a linear dynamic range of 0.5–45 μM clozapine was observed with detection limit of 61.0 nM. This method was used for determination of clozapine in clozapine tablets with satisfactory results.

CPE modified with ruthenium doped titanium dioxide nanoparticles (Ru–TiO2/CPE) was successfully applied for the determination of clozapine [102]. The suggested modification of CPE increases the electro–oxidation of

clozapine with increased current intensity. The effect of clozapine concentration variation was studied using square wave voltammetric technique in the range of 9.0×10^{-7} M to 4.0×10^{-5} M with the detection limit of 0.43 nM. Ru–TiO_2/CPE electrochemical sensor was used for the determination of clozapine in pharmaceutical formulations and human urine.

ZnO nanoparticles and multi–walled carbon nanotubes were used as CPE modifiers and the produced modified electrode (ZnO/MWCNTs/CPE) was employed for the investigation of electrochemical oxidation of naproxen [103]. In phosphate buffer (pH=7.0), naproxenwas determined over a linear concentration range of 1.0×10^{-6} to 2.0×10^{-4}M by square wave voltammetry with detection limits of 2.3×10^{-7}M. The electrochemical oxidation of naproxen at ZnO/MWCNTs/CPE was employed for the voltammetric determination of naproxen in pharmaceutical formulations.

Dysprosium nanowire modified CPE (DyNW/CPE) was introduced for the determination of diphenhydramin by continuous square wave voltammetry in flow injection system [104].At modified CPE, diphenhydramin presented one irreversible oxidation peak at 1080 mV vs. Ag/AgCl reference electrode. The calibration curve constructed for diphenhydramin was linear over the concentration range of 0.1–0.0001 µM. Also, the calculated values of lower limit of detection and quantification were found to be $4.0 \times 10^{-11}$and 8.0×10^{-11} M, respectively. A good recovery was obtained for assay spiked urine samples and a good quantification of diphenhydramine was achieved in a commercial formulation.

The same modified electrode; (DyNW/CPE), was successfully applied for the simultaneous determination of naproxen and paracetamol by square wave voltammetry [105]. DyNW/CPE exhibited a potent and persistent electron−mediating behavior followed by well−separated oxidation peaks toward naproxen and paracetamol at a scanrate of 100 mVs−1with a potential difference of about 300 mV, which was large enough to determine naproxen and paracetamol individually and simultaneously. Linear calibration curves are obtained in the range 1.0 × 10−9–5.0 × 10^{-4} mol L^{-1} and 1.0×10^{-8}–2.5×10^{-4} mol L^{-1} with a detection limit of 0.5 and 0.3 nmol L−1 for naproxen and paracetamol, respectively. DyNW/CPE was successfully applied for the determination of naproxen and paracetamol in pharmaceutical and urine samples.

SCREENPRINTED ELECTRODE (SPE)

Screen printed electrode (SPE) composed of working, reference and auxiliary electrodes are developed by printing different conductive inks on various types of plastics or ceramic materials [106-108].In the field of electrochemical sensors, screen–printed electrodes have attracted great interest due to they provide a low cost, highly reproducible and reliable electrochemical measurement of the target samples from different origins.

Screen printed electrodes are inexpensive to manufacture which allows them to be disposable. This aspect is clearly important when testing biological samples and thus avoids surface fouling complications (like what happened in carbon paste electrode) [109]. Moreover, it must be highlighted that unlike glassy carbon electrodes, SPEs do not require any polishing procedure prior to use.

Bare SPE

A SPE surface was pretreated by applying a fixed potential of 1.6 V for 3min. vs. Agpseudo reference electrode [110]. The peak current of ibuprofen oxidation was recorded at 1.1 V in acetate buffer (pH=4.7).Linear dependency of the recorded current was observed vs. ibuprofen concentration in the range of 2.0–10.0 µg cm–3.Pretreated PGE was applied for the determination of ibuprofen in waste water and river water samples.

The electro analytical sensing of Rohypnol® (flunitrazepam); which used as a potent sedative for the treatment of insomnia, is reported utilizing SPE without any additional pretreatment or modification [111]. Cyclic voltammetric responses obtained in phosphate buffer solution (pH=2.0) shows a linear response between the recorded current and rohypnol over the concentration range of 1.0–95.24 µgmL^{-1} with lower limits of detection equal 0.47 µg mL–1. The proposed methodology was useful for determination rohypnolat low levels (µgmL^{-1}) in two internationally favored drinks: Coca Cola™and the alcopop WKD™ without any sample pre–treatment.

The oxidation of esomeprazole (which used in treatment of acid–related diseases) was shown to be irreversible and diffusion–adsorption controlled driven process at SPE in phosphate buffer (pH=7.0) [112]. Under optimized conditions, the differential pulse voltammetric peak currents were in a linear relationship to esomeprazole concentrations in the range of 1.0 × 10–6–1.0 × 10^{-4}mol $L^{-1}$with a detection limit of 3.5×10^{-8} mol L^{-1}. The proposed methodology was employed successfully for the determination of esomeprazole in capsules.

The electrochemical oxidation behavior of gemifloxacin and its voltammetric assay were investigated using cyclic and differential–pulse voltammetry on a SPE [113]. Voltammograms of gemifloxacin in Tris–HCl buffer (pH=7.0) exhibited a well–defined single oxidation peak at 0.75 V vs. Ag/AgCl reference electrode. The obtained studies showed the gemifloxacin oxidation at the electrode surface is an adsorption–controlled process. The calibration was

linear from 0.5 to 10.0 mM, and the limits of detection and quantification were 0.15 and 5.0 mM. The method was successfully applied to the determination of gemifloxacin in pharmaceutical tablets without any pre–treatment.

Modified SPE

SPE modified with L–glutamic acid was developed via two different approaches, electro polymerization (SPCE/PGA) and aryl diazonium electrochemical grafting (SPCE/EGA) [114]. The produced two modified SPE were applied for the determination of hydrochlorothiazide by differential pulse voltammetry. The linearity range and detection limits were found to be 28.5–300.0 and 8.55 μmol L^{-1} (for SPCE/PGA) and 3.78–200.0 and 1.13 μmol L^{-1} (for SPCE/EGA), respectively. The L–glutamic acid modified SPE (SPCE/EGA) was successfully applied for the determination of hydrochlorothiazide in an anti–hypertensive drug dosage forms as capsules and tablets.

Graphene modified screen printed electrodes (SPGrE) were used for the determination of aspirin [115].Cyclic voltammetry technique was employed to investigate aspirin electrochemical behavior and for the determination of aspirin. In a concentration range from 0.1 to 100 μM, aspirin was determined in phosphate buffer (pH=4) using SPGrE. The proposed procedure was applied successfully in aspirin determination in drug preparations and human oral fluid over the concentration range of 10 to 150 μM.

The same electrode was used to investigate the electrochemical behavior and the determination of paracetamol using cyclic voltammetry technique [116]. In this work, results of SPGrE were compared to those obtained by bare SPE. It was shown that the response with graphene was greater than without. This is due to its unique characteristics physical and chemical, π–π interactions and a strong adsorptive capability. The proposed procedure was successfully applied for the determination of paracetamol in concentration range of 0.1–50 μM (carbonate buffer; pH=9) with detection limit of 20 nM. The proposed electrode was applied for the determination of paracetamol in human oral fluid sample solution over the concentration range 10–100 μM.

A sensitive electrochemical sensor for sildenafil citrate (the active component of viagra) was fabricated by electro deposition of gold nanoparticles onto SPE [117]. Cyclic and square wave voltammetry were used to characterize the redox behavior of sildenafil citrate in absence and presence of gold nanoparticles. In Britton–Robinson buffer (pH=7.3), the peak currents for sildenafil citrate at gold nanoparticles modified SPE shows a linear response in the concentration range from 1.8×10^{-6} to 3.3×10^{-5} mol L^{-1} with detection limit of 5.2×10^{-10} mol L^{-1}. The modified SPE was applied for the determination of sildenafil citrate in pharmaceutical formulations and spiked and real human urine samples.

The zirconium dioxide nanoparticles modified SPE was found to exhibit an electro–catalytic activity for the electrochemical oxidation of propranololin0.1Mphosphate buffer solution (pH=7.0) [118]. In this study, cyclic and differential pulse voltammetry were employed to study the electrochemical behavior and determination of propranolol using the modified SPE. The electrochemical oxidation of propranolol occurs at 0.95 V with a limit of detection found to be 1.5 μM and with linear range of 10.0 μM to 200.0 μM. The modified electrode was applied for the determination of propranololin pharmaceutical formulations and human urine samples.

At bare and mercury modified SPE, and using differential pulse adsorptive stripping voltammetry, lamotrigine was determined in Britton–Robinson (pH=5.0) [119]. The detection limit found was 5.0×10^{-6} and 2.0×10^{-6} M for bare and mercury modified SPE, respectively. The calibration curves was obtained by differential pulse adsorptive stripping voltammetry lamotrigine determination over the concentration range of 5.0 × 10–6–2.1 × 10^{-5} M (at bare SPE) and 2.0 × 10–6–5.0 × 10^{-6} M (for mercury modified SPE). The developed mercury modified SPE was successfully applied in the determination of lamotrigine in pharmaceutical preparations.

Electrochemical determination of ibuprofen has been employed by cyclic voltammetry and differential pulse voltammetry, using SPE modified with carbon nanofibers [120]. A well–defined anodic oxidation peak has been obtained at + 1.08 V vs. Ag/AgCl electrode in 0.2 M acetate buffer (pH=4.5). The quantitative determination of ibuprofen has been conducted in optimal experimental conditions by differential pulse voltammetry, in the linear range of 8 × 10–7–3 × 10^{-5} M and a detection limit of 3.5×10^{-7} M was established. The prepared nanofibers modified SPE was recommended for the analysis ibuprofen in pharmaceutical products.

Self–assembly monolayer of cysteine on the surface of gold nanoparticles modified SPE was utilized for rapid and simultaneous determination of tetracycline and cefixime antibiotics by square wave voltammetry [121].It is possible to simultaneously determine the tetracycline and cefixime concentrations in the ranges of 10^{-5} and 10^{-3} mol L^{-1}, under the optimum conditions. Moreover, the presented modified SPE when used together with chemometrics tools was successfully applied to the determination of tetracycline and cefixime in biological fluids.

Nafion modified–SPEs was sued for the study of the electro–oxidation process of isoniazid and its determination in pharmaceutical formulations and biological fluids [122]. The study of the electrochemical behavior of isoniazid was performed by cyclic voltammetry and its determination was achieved by square wave voltammetry. Under studied optimum conditions, isoniazid was determined over a concentration range of $2.5 \times 10^{-5}$to 2.0×10^{-4}M with a

detection limits of 1.4×10^{-5} M and quantification limits of 4.7×10^{-5} M. The proposed method was applied for the determination of isoniazid in complex matrixes, pharmaceutical formulations, human urine and serum samples.

BORON–DOPED DIAMOND ELECTRODE (BDDE)

Recently, boron–doped diamond electrode (BDDE)gained a great attention particularly in the field of electro analysis due to their unusual and extremely useful properties such as low and stable background current [123,124].The advantageous performance of BDDE over conventional electrode materials lies in its higher chemical stability, wider electrochemical potential window in aqueous solutions and non–aqueous solvent, lower capacitive current, excellent resistance to electrode fouling, good biocompatibility and stability of response are the most important ones [125-127].Furthermore, BDDE is non–toxic electrode material and shows high possibility of measurement at high anodic potentials and in extreme conditions such as strong acid media[128].

Cathodically Pretreated BDDE

Cathodically pretreated boron–doped diamond electrode (BDDE) was used for the individual determination of antihypertensive drug metoprolol and its association with hydrochlorothiazide using differential pulse voltammetry [129]. In lactate buffer solution (pH=4.0) and under the optimum analytical experimental conditions, the proposed procedure was used for individual determination of metoprolol in the concentration range 0.38–22 μmol L^{-1}, with detection limit of 0.034 μmol L^{-1}.In case of simultaneous determination study, both of hydrochlorothiazide and metoprolol were determined over the concentrations range of 0.51–18.7 and 1.23–22.8 μmol L^{-1}, with detection limit of 0.376 and 0.077 μmol L^{-1} for hydrochlorothiazide and metoprolol, respectively. The individual and simultaneous methods were successfully applied in the determination of hydrochlorothiazide and metoprolol content in several pharmaceutical formulations.

Also, cathodic pretreated BDDE was combined with square–wave voltammetry for the individual determination of two β–blocker agents, namely propranolol and atenolol in pharmaceutical formulations [130]. An excellent calibration curve was obtained for propranolol ranging from 0.2 to 0.9 μmol L^{-1} with detection limit of 0.18 μmol L^{-1} in 0.1 molL^{-1} H_2SO_4. A similar calibration curve was obtained for atenolol ranging from 2.0 to 41 μmol L^{-1} with detection limit of 0.93 μmol L^{-1}. The proposed method was successfully applied in the determination of both β-blocker agents in several pharmaceutical formulations.

For the voltammetric determination of antihistaminic hydroxyzine, square–wave voltammetry and a cathodically pretreated BDDE was successfully applied [131]. In 0.1 mol L^{-1} HCl solution, hydroxyzine was successfully determined in the concentration range 0.50–20.0 μmol L^{-1}, with a detection limit of 0.43 μmol L^{-1}. Addition and recovery studies in commercial tables and liquid formulations showed excellent recovery values ranging from 94.3 % to 104 %. Furthermore, the proposed method was successfully applied in the determination of hydroxyzine in several pharmaceutical formulations.

Codeine was determined individually in Britton–Robinson buffer (pH=7.0) using BDDE [132]. Codeine provided a single well–defined oxidation peak at 1.0 V vs. Ag/AgCl reference electrode. At studied optimum conditions, differential pulse voltammetric technique was used for the determination of codeine over the concentration range of 0.1–60 μM with detection limit of 0.08 μM. The method was successfully applied in the determination of codeine in real samples including pharmaceutical tablets and real human urine samples.

In acetate buffer (pH=4.0) solution, cathodically pretreated BDDE was used for the individual determination of codeine or simultaneous determination of codeine with paracetamol [133]. Using square wave and differential pulse voltammetry techniques, codeine was detected at 1.19 and 1.40 nmol L^{-1}, respectively. The obtained linear range for both techniques was of 8.99×10^{-8}–9.81×10^{-6} molL^{-1}. Only square wave voltammetry was used for the simultaneous determination of codeine and paracetamol. The obtained results showed linear relationship between recorded current and drug concentration over the concentration ranges of 0.20–95.8 μmolL^{-1}, for paracetamol, and 0.40–9.58 μmolL^{-1}, for codeine, with detection limits of 18 and 14 nmolL^{-1}, respectively. The proposed SWV method was successfully applied in the simultaneous determination of codeine and paracetamol in four samples of pharmaceutical tablets. Additionally, adequate results were obtained when concentrations of codeine and paracetamol were determined in human urine or serum samples.

At cathodically pretreated BDDE and using square–wave voltammetry in Britton–Robinson buffer (pH=2.0), bezafibrate (a derivative of fibric acid that is used for the treatment of hyperlipidemia) was successfully determined [134]. Bezafibrate shows one irreversible oxidation peak at 1.20 V (vs. Ag/AgCl). Under optimized square–wave voltammetry conditions, a linear analytical curve is obtained for the bezafibrate concentration range 0.10–9.1mmol L^{-1}, with a detection limit of 0.098mmol L^{-1}. The proposed method was successfully applied in the determination of the bezafibrate content in several pharmaceutical formulations.

The electrochemical oxidation of captopril was recorded at BDDE. Captopril oxidation on BDDE is characterized by the presence of two well–defined irreversible oxidation peaks at 1.0 and 1.8 V (vs. Ag/AgCl) [135]. The

determination of captopril was carried out in 0.04 mol L^{-1} Britton–Robinson buffer solution (pH=9) using square wave voltammetry technique. Regarding to captopril oxidation peak at 1.0 V, the analytical curve was obtained in the concentration range from 20 to 100 mg L^{-1} with a detection and quantification limits of 36.0 and 121.95 μg L^{-1}, respectively. Using standard addition method, square wave voltammetry technique was applied to determine captopril content in commercial pharmaceutical products.

Anodically Pretreated BDDE

Hydrochlorothiazide was simultaneously determined with losartan in dosage forms using anodically pretreated BDDE and differential–pulse voltammetry [136]. Two well–resolved and reproducible oxidation peaks of hydrochlorothiazide and losartan, with separation of 0.23 V, were obtained in Britton–Robinson buffer (pH=9.5). Under the optimum analytical experimental conditions, the voltammetric method exhibited linear responses for the simultaneous determination of hydrochlorothiazide and losartan in the concentration range from 3.0×10^{-6} to7.4×10^{-5} mol L^{-1} for both compounds, with detection limits of 1.2×10^{-6} and 9.5×10^{-7} mol L^{-1}, respectively. The proposed method was successfully applied in the simultaneous determination of hydrochlorothiazide and losartan content in pharmaceutical formulations.

A new generation of anticancer drug, imatinib, was determined using differential pulse voltammetry on anodically pretreated BDDE [137].The obtained results showed that imatinib provided well–shaped oxidation peak at positive potential of+1.0 V (vs.Ag/AgCl/KCl) in the Britton–Robinson buffer at pH=2.0. A simple, rapid, selective and sensitive DPV procedure for the determination of imatinib was performed in the concentration range of 3.0 × 10−8–2.5×10^{-7}mol $L^{-1}$with limit of detection and limit of quantificationof$6.3 \times 10^{-9}$and 2.1×10^{-8}mol L^{-1}, respectively. The proposed method was successfully applied in analysis of imatinib spiked human urine samples.

The simultaneous determination of nifedipine and atenolol using an anodically pretreated BDDE coupled to differential pulse voltammetry technique was developed [138]. It was found that in TRIS buffer solution (pH=8.0), nifedipine and atenolol provided two well–shaped and reproducible oxidation peaks at 0.97 V and 1.36 V (vs. Ag/AgCl), respectively. At optimized differential pulse voltammetric parameters, the current response of nifedipine and atenolol was proportionally linear in the concentration range of 3.98–10^{7} μmol L^{-1} and 1.99–47.2 μmol L^{-1}, with detection limit of 0.612 and 0.999 μmol L^{-1}, respectively. The proposed method was successfully applied in the determination of nifedipine and atenolol in several commercial combined dosage forms.

An electroanalytical procedure was proposed for the determination of tricyclic antidepressant imipramine in commercial pharmaceutical formulations using BDDE and square–wave voltammetry [139]. The voltammetric results showed two well–defined oxidation peaks at potentials of 0.04 and 0.82 V for peaks 1 and 2, respectively. Under the selected optimum conditions, the calibration curves were obtained in the concentration range of 1.73×10^{-7}–2.53×10^{-6} molL^{-1} (r=0.9984), with detection and quantitation limits 4.35×10^{-8} molL^{-1} and 1.45×10^{-7} molL^{-1}, respectively. The proposed method was applied with success in the determination of imipramine in commercial pharmaceutical formulations and validated by comparison with standard method for determination of imipramine.

Using square wave voltammetry and BDDE, the non–steroidal anti–inflammatory drug mesalazine shows well–developed oxidation peak –900 mV (vs. saturated Ag/AgCl reference electrode) in Britton–Robinson buffer (pH=7.0) [140]. Mesalazine was determined in linear dynamic range of 2.0×10^{-6}–3.0×10^{-4} molL^{-1}. The limit of detection and quantification were calculated to be 7.0×10^{-7} and 2.3×10^{-6} mol L^{-1}, respectively. Applicability of the proposed method was verified by an analysis of a pharmaceutical preparation and spiked human urine

A novel application of BDDE was introduced for the determination of ambroxol in in aqueous solutions with and without the addition of surfactant [141].Using square–wave stripping mode, ambroxol yielded a well–defined voltammetric response in phosphate buffer (pH=2.5) containing 4×10^{-4} M sodium dodecylsulfate (as anionic surfactant) at +1.02 V vs. Ag/AgCl reference electrode. Ambroxol was determined in the concentration range of 0.05–0.7 μM, with a detection limit of 0.01 μM. The suggested method was successfully applied to pharmaceuticals and spiked human urine samples.

Both of differential pulse and square–wave voltammetric techniques were used for the voltammetric determination of the 1,3–dimethylxanthine alkaloid theophylline on BDDE [142]. In 1.0 molL^{-1} H_2SO_4, the studied analyte shows well–shaped irreversible peak at very positive potentials (1.63 V) vs. Ag/AgCl reference electrode was observed. Under the optimum conditions, 1,3–dimethylxanthine alkaloid theophylline was determined over the concentration range of 2–380 μmol L^{-1} (in both cases differential pulse and square–wave voltammetric techniques). The proposed sensor may be employed for the determination of 1,3–dimethylxanthine alkaloid theophylline in pharmaceutical dosages and human urine samples.

Švorcet al. [143] used for the first time, BDDE as a perspective electrochemical sensor for the sensitive determination of amlodipine, calcium channel blocker drug of 1,4–dihydropyridine type. Cyclic voltammetric studies indicated that in Britton Robinson buffer (pH=5), the electrochemical oxidation of amlodipine is irreversible

with single and well–shaped peak at a potential of +0.75 V (vs. Ag/AgCl reference electrode). Under optimized conditions and using differential pulse voltammetry, the current response of amlodipine was proportional in a concentration range of 0.2–38 μM with a detection limit of 0.07 μM and a good repeatability. The practical applicability of the proposed method was demonstrated in the assessment of total content of amlodipine in pharmaceutical tablets with sufficient recoveries in the range of 101.3–104.1%. Additionally, a biological relevance of the developed procedure was demonstrated by analysis of model human urine samples with adequate recoveries (94.1% and 105.7%).

The electrochemical oxidation of antiviral drug valacyclovir was investigated in aqueous either in absence and presence of surfactant solutions by cyclic and linear sweep voltammetry using BDDE [144]. Using phosphate buffer (pH=3.0), valacyclovircould be determined in the concentration range 8×10^{-7}–6×10^{-5} M (absence of surfactant). While in presence of sodium dodecylsulfate (anionic surfactant) valacyclovir was determined in concentration range of 8 × 10–8–8 × 10^{-6} M. Either in absence and presence of sodium dodecylsulfate, valacyclovir can be detected at 1.0×10^{-7} M and 2.1×10^{-8} M, respectively. The newly developed approach was verified by the assays of pharmaceutical formulations (tablets), spiked human urine and simulated gastric fluid samples.

The electrooxidative behavior and determination of zolmitriptan at BDDE were investigated using cyclic, linear sweep, differential pulse and square wave voltammetric techniques [145]. In phosphate buffer (pH=3.03), DPV and SWV techniques were used for the determination of zolmitriptan over the two different concentration ranges (8 × 10–7–8 × 10^{-6} M and 1×10^{-5}–1×10^{-4} M). A linear response was obtained in phosphate buffer over two different concentration ranges (6 × 10–7– 8 × 10^{-6} M and 1×10^{-5}–1×10^{-4} M) for spiked serum samples and pharmaceutical dosage form in phosphate buffer (pH=3.03) for both techniques.

The electrooxidation of naproxen was studied, using BDDE by cyclic and differential pulse voltammetry in nonaqueous solvent supporting electrolyte system [146]. In 0.1 M LiClO4 containing CH3CN (as supporting electrolyte) and using cyclic voltammetry, naproxen shows only one well–defined anodic peak was noted at 1.44 V (vs. Ag/AgCl reference electrode). With a scan rate of 50 mV s–1, the differential pulse voltammetry technique was able to determine the naproxen concentrations in the range of 0.5 to 50 μM with a detection limit of 30 nM. The proposed procedure was used for the determination of naproxen in pharmaceutical formulations.

In connection with differential pulse voltammetry, BDDE was used for the voltammetric determination of methotrexate [147]. In acidic medium, methotrexate shows only one well–developed oxidation peak suitable for analytical purposes at about 1000 mV (vs. Ag/AgCl reference electrode). In 0.05 molL^{-1} H_2SO_4, the recorded current was linearly increased with increasing methotrexate concentration in the range of 5.0×10^{-8} to 2.0×10^{-5} with detection limit of 1.0×10^{-8} mol L^{-1}. The proposed procedure was successfully applied for analysis of methotrexate in real drug preparations and spiked human urine.

A flow injection system combined with BDDE was used for the electrochemical analysis of acetaminophen [148].Using BDDE and cyclic voltammetry, acetaminophen undergoes quasi–reversible reaction in phosphate buffer (pH=8). BDDE provided a linear dynamic range from 0.1 to 8 mM and a detection of 10 μM for voltammetric measurement. The flow injection analysis results at BDDE, acetaminophen can be determined over a linear dynamic range from 0.5 to 50 μM and a detection limit of 10 nM. Acetaminophen in syrup samples has also been investigated.

A new methodology for the simultaneous determination of paracetamol and ibuprofen in pharmaceutical formulations by differential pulse voltammetry using BDDE was introduced [149]. The oxidation processes observed for both analytes in 0.1 mol L^{-1} H2SO4 solution containing 10% (v/v) of ethanol where a well–defined oxidation peak was observed using BDDE for each analyte (0.85 V for paracetamol and 1.72 V for ibuprofen) vs. Ag/AgCl.Calibration curves for the simultaneous determination of paracetamol and ibuprofen showed a linear response for both drugs in a concentration range of 20 to 400 μmol L^{-1}, with a detection limit of 7.1 μmol $L^{-1}$for paracetamol and 3.8 μmol L^{-1} for ibuprofen. Both of paracetamol and ibuprofen were also investigated in dosage forms using the suggested procedure.

Oxidation behavior of piribedil was investigated using BDDE combined with cyclic and differential pulse voltammetric techniques [150]. The oxidation of piribedil gave irreversible peak at 1.2 V vs. Ag/AgCl reference electrode. In acetate buffer (pH=3.7), using differential pulse voltammetry, the linearity was obtained in the range of 1.34×10^{-7}–3.35×10^{-5} M with 1.95×10^{-8} M detection limit. The proposed procedure was used for the determination of piribedil in pharmaceutical dosage forms.

The electrooxidative behavior and determination of paroxetine on BDDE were investigated using cyclic, differential pulse, and square wave voltammetric methods [151]. The oxidation process was irreversible and exhibited mixed diffusion–adsorption controlled process depending on pH. The linear responses have been obtained in the range from 7.0 × 10−7 to 3.5×10^{-6} M with 6.95×10^{-9} M detection limit. The developed methods have been successfully applied for the determination of paroxetine in pharmaceutical dosage form.

The electrooxidative behavior and determination of lercanidipine were investigated in aqueous acetonitrile medium at a BDDE using cyclic and square wave voltammetric techniques [152]. Lercanidipine in selected supporting electrolyte presents a well–defined anodicresponse at 0.944 V, studied by the proposed method. The linear response was obtainedin the ranges of 4 × 10–6–2 × 10^{-4} mmol L^{-1}, with calculated values of detection and quantification limits of 1.47 × 10^{-7} and 4.47 × 10^{-7} mmol L^{-1}, respectively. With no interference from the excipients and endogenous substances, lercanidipine was successfully determined in pharmaceutical dosage form and in human urine.

PENCIL GRAPHITE ELECTRODE (PGE)

The pencil graphite leads are composite materials containing graphite (~65%), clay (~30%), and a binder (wax, resins, or high polymer) [153].

According to the European Letter Scale, graphite pencils are marked with letters H (hardness) and B(blackness) and numbers indicating the degree of hardnessor blackness from 9H (the hardest) to 8B (the softest). B type leads contain more graphite and are softer, and the harder Htype leads have more lead, whereas HB type pencil leads contain equal portions of graphite and clay [154-156].

Since graphite pencil lead used as electrochemical sensor, and due to different interactions may be exist between an analyte and the common components of a graphite pencil lead, it is possible that electroactive species exhibit different voltammetric behavior on graphite pencil leads of the same hardness but are produced by various manufacturers [157].

Like the other carbon–based electrodes, PGE have the same advantages, such as high electrochemical reactivity, commercial availability, good mechanical rigidity, disposability, low cost and ease of modification [158]. Moreover, it was reported that PGE offer an easier way to regenerate the surface with simpler and faster polishing procedures than that used with common with other solid electrodes, and the obtained result shows a good reproducibility for individual surfaces.

Bare PGE

PGE was used for the electrochemical investigation of acebutolol, a beta–blocker drug, using was carried out using cyclic and square wave voltammetry [159]. In Britton–Robinson buffer (pH=10), acebutolol displayed a reversible and adsorption–controlled oxidation peak at 0.78 V. By using square wave anodic stripping voltammetry, the recorded oxidation peak current showed a linear relationship with acebutolol concentration at 0.4^{-7} nM with a detection limit of 0.09 nM. The PGE was used for the determination of acebutolol in pharmaceutical formulations and urine.

Another procedure for studying electrochemical behavior and determination of acebutolol using PGE in phosphate buffer (pH=7.0) was introduced [160]. Cyclic, differential pulse and square–wave voltammetric techniques were used in this study. The electrochemical behavior of acebutolol at PGE was a diffusion–controlled process and it shows maximum peak current at potential of +0.855 V. Under the optimal conditions, the recorded anodic peak current was linearly proportional to the concentration of acebutolol in the range from 1.0 to 15.0 μM with a limit of detection 1.26 × 10^{-8} M and 1.28 × 10^{-8} M for differential pulse and square wave voltammetry techniques. This method was applied for quantitative determination of the acebutolol levels in urine as real samples.

An activated PGE was used for the voltammetric determination of levofloxacin in pharmaceutical samples and body fluids were searched [161].At pH value of 4.0, and over a concentration range of 0.01–2.5 μM, levofloxacin was determined with detection limit of 0.0075 μM. Using activated PGE, the determination of levofloxacin in blood serum, urine and pharmaceuticals were successfully achieved.

Voltammetric determination of zolpidem using PGE was achieved in Britton–Robinson buffer (pH=8.0) [162]. Cyclic voltammetry was used to study electrochemical behavior of zolpidem while square wave voltammetry was used for its determination. At 0.98 V, zolpidem shows a well–defined irreversible anodic peak and a linear relationship between recorded current response and zolpidem concentration was obtained over a concentration range of 10–30 μM, with detection and quantitation limits of 1 and 3 μM, respectively. PGE was successfully used to determine zolpidem in standard and tablet dosage forms.

PGE displayed a very good electrochemical behavior with significant enhancement of the peak current of antiviral drug; acyclovir [163]. In Britton–Robinson buffer solution (pH=4) containing 0.1 M KCl, and under studied experimental conditions, PGE had a linear response range from 1.0 to 100.0 μM acyclovir with a detection limit of 0.3 μM. The proposed voltammetric procedure was successfully applied to the direct determination of acyclovir in real pharmaceutical samples.

Simultaneous determination of acyclovir and methotrexate was achieved using activated PGE. The proposed sensor has a wide linear range of 2 × 10^{-7} to 1.4 × 10^{-6} M for methotrexate and 5 × 10^{-7} to 3 × 10^{-6} M for acyclovir [164].

The detection limits values were found to be 1.13×10^{-8}M and 6.07×10^{-8}M for methotrexate and acyclovir, respectively. Also, quantitation limits values were found to be 3.42×10^{-8} and 1.84×10^{-7} for methotrexate and acyclovir, respectively. The proposed method was applied for the simultaneous determination of acyclovir and methotrexate in their pharmaceutical formulations and human plasma.

A low–cost sensitive and selective procedure was developed for determination of niclosamide by recording differential pulse voltammo grams of niclosamide in Britton–Robinson buffer (pH=7.0) containing 0.1 M KCl and 30 % DMF at PGE [165]. Under experimental conditions, PGE had a linear response range from 0.05to10 μM niclosamide with a detection limit of 0.015 μM. The proposed voltammetric method was successfully applied to the direct determination of niclosamide in tablets with no interference from the usual tablet excipients.

Antiemetic drug, metoclopramide was analyzed electrochemically using pre–treated PGE combined with differential pulse and cyclic voltammetry. In phosphate buffer (pH=3.0), metoclopramide showing anodic peak at 1.19 V [166]. At this peak potential, a calibration curve was constructed for metoclopramide determination in the range from$1.0 \times 10^{-8}$to 1.3×10^{-6} M with detection limit of 1.29×10^{-11}M. The proposed method was successfully applied to metoclopramide determination in pharmaceutical formulations and urine samples.

The pre–treated PGE showed excellent electro–catalytic activity towards the oxidation of albandazole in phosphate buffer (pH=3.0) [167]. Under the optimum conditions the peak current was linear to the concentration of albandazole in the range 250 μM to 1450 μM for PGE and the detection limit was found to be 5.42 nM. The proposed method was successfully applied for the determination of albendazole in the spiked urine and pharmaceutical samples.

In phosphate buffer (pH=6.81), cyclic and differential pulse voltammetric techniques were used for quantitative determination of famotidine on PGE [168]. The anodic peak current of famotidine varies linearly with the analyte concentration in the range 4.72 × 10–7–4.95 × 10^{-4}M with detection and quantification limits of 1.51×10^{-7} M and 5.04 × 10–7M famotidine, respectively. The developed differential pulse voltammetric method using PGE was successfully applied to the simple and rapid determination of famotidine in pharmaceutical samples.

The electrochemical oxidation of nalbuphine hydrochloride was studied on PGE using cyclic voltammetry, differential pulse voltammetry, and square wave voltammetry techniques [169]. In Britton–Robinson buffer (pH=6.0), a linear relationships between the peak current and nalbuphine hydrochloride concentration were developed for its quantitative determination. The linear response was obtained in the range from1.6×10^{-5} to1.5×10^{-4} mol L^{-1}. In case of differential pulse voltammetry, the calculated values of detection and quantification limits were found to be 6.38×10^{-6} and 1.93×10^{-5} molL^{-1}, respectively. While in case of square wave voltammetry detection and quantification limits were found to be 3.91×10^{-5} and 1.18×10^{-4} molL^{-1}, respectively. The proposed procedure was applied for the determination of nalbuphine hydrochloride in pharmaceutical and human biological fluids.

Paclitaxel, an anticancer drug was electrochemically studied in phosphate buffer (pH=7.0) using PGE and cyclic voltammetry technique at 1.214 V [170]. For determination purpose, differential pulse voltammetry technique was applied for the paclitaxel determination in the concentration range of 4.0×10^{-7}–3.0×10^{-6}M with a detection and quantifications limit of 2.46×10^{-9} and 8.23×10^{-9} M, respectively. The proposed procedure was successfully applied for the determination of paclitaxel in dosage forms and biological fluids (urine samples and human serum).

Over a pH range of 1.81–11 (Britton–Robinson buffer), the voltammetric behavior of trepibutone was investigated at a PGE by cyclic and square–wave voltammetry [171]. Based on the recorded oxidation peak at 1.06 V in Britton–Robinson buffer (pH=1.81), a square–wave voltammetric method is proposed for the determination of trepibutone. A linear relationship is obtained from 0.24 to 10 μgmL^{-1} with a detection and quantification limits of 25 and 80 ng mL–1, respectively, the proposed method is applied to the determination of trepibutone in pharmaceutical formulations.

A sensitive electrochemical method based on square wave cathodic adsorptive stripping voltammetry using PGE wasdeveloped for the individual and simultaneous determination of the anticancer drugs flutamide and irinotecan[172]. For individual determination, the calibration curves present a good linear response in the concentration range of 3.98×10^{-7} M–6.36×10^{-6}Mand 7.94×10^{-8} M–4.03×10^{-7} M for flutamide and irinotecan, respectively. The calculated detection and quantification limits were 1.55×10^{-8}M and 5.16×10^{-8}M (for flutamide) and 1.68×10^{-9}M and 5.63×10^{-9} M (foririnotecan), respectively. For simultaneous determination, flutamide and irinotecan were determined over the concentration ranges of 1.99×10^{-6}–5.3×10^{-5}M and 1.99×10^{-7}–4.96×10^{-6} M, respectively. The calculated detection and quantification limits were 2.10×10^{-7}M and 6.89×10^{-7} M (for flutamide) and 2.17×10^{-8} M and 7.25×10^{-8} M (foririnotecan), respectively. The application of the illustrated procedure was shown in individual and simultaneous determination of both drugs in bulk form, human urine and serum samples.

Using PGE, the electrochemical behavior and possible oxidation mechanism of itraconazole (orally administered triazole antifungal agent) was studied using cyclic voltammetry [173]. Also, traces concentrations of itraconazole were determined by anodic stripping differential pulse and anodic stripping square wave voltammetric techniques at PGE. In Britton–Robinson buffer (pH=3.0), the recorded differential pulse voltammograms showed good linearity between the peak currentand itraconazole concentration over the concentration range of 32–169 ng mL^{-1} with detection and quantification limits of 9.1 and 30.2 ng mL^{-1}. The proposed method was applied to the quantitative analysis of itraconazole in pharmaceuticals and biological fluids.

Dantrolene sodium (skeletal muscle relaxant drug) shows one reversible cathodic anodic peak at –0.302, –0.249 V and another irreversible cathodic one at –0.748using PGE combined with cyclic voltammetry [174]. Differential pulse and square wave voltammetry techniques were applied to investigate the reversible cathodic peak of dantrolene sodium. Using PGE, a calibration curve was constructed over a concentration range of 0.395–2.955 and 0.395–1.9μgmL^{-1} for differential pulse and square wave voltammetry techniques, respectively. Also, the detection and quantification limits were calculated to be 0.09 and 0.273 μg mL^{-1} (for Differential pulse voltammetry) and 0.052 and 0.158 μg mL^{-1} (for square wave voltammetry). The proposed procedures were successfully applied to the determination of dantrolene sodium with good recovery in pharmaceutical dosage form, human mother milk and urine directly without any pretreatment at PGE.

Modified PGE

PGE was modified with poly [2,5–di(2–thiophenyl)–1–p–(tolyl)pyrrole] and the produced electrochemical sensor was successfully applied for the electrochemical determination of acetaminophen over the linear dynamic range from 0.025 to 5 μM with detection limit of 1.94 nM [175]. The voltammetric studies reveal that the polymer modified PGE have a remarkable electro catalytic activity towards acetaminophen compared with the unmodified pencil graphite electrode.

A new electrochemical sensor was prepared by the modification of PGE with aniline using cyclic voltammetry procedure and the reduction of silver nanoparticle on the polyaniline modified PGE [176]. The obtained electrode was used for the differential pulse stripping voltammetric quantification of acetaminophen in the pharmaceutical products, tablet and syrup. At the new sensor; acetaminophen shows a well–defined and higher peak current at the potential, 570 mV. The calibration curve was found linear in the range of 5 × 10−8–8 × 10^{-7}M for acetaminophen with calculated values of detection and quantification limits of 1.01 × 10^{-8} and 3.35 × 10^{-8} M, respectively. The validity and applicability of the proposed voltammetric method was tested by analyzing acetaminophen in real tablet and syrup samples.

PGE modified with cetyl trimethylammonium bromide (CTAB) was used for the voltammetric determination of aspirin in pharmaceutical samples [177]. In 0.1 M phosphate buffer (pH=7), aspirin shows an oxidation peak at 0.87 V vs. standard calomel electrode as reference electrode. Differential pulse voltammetry was used to construct calibration curve for aspirin determination in the concentration range of 50–300 μM. The proposed PGE modified with cetyl trimethylammonium bromide was successfully used for the determination of aspirin in dosage forms.

Adsorptive square wave stripping voltammetry was used for the indirect determination of antiviral compound valacyclovir on a novel sensor of copper micro particles–modified PGE [178]. The bare and porous Cu–modified PGE were characterized by cyclic voltammetry and scanning electron microscopy. The porous Cu–modified PGE displayed distinct electro catalytic activities in response to the electrochemical redox reaction of Cu+2ion in the Cu–valacyclovir complex. Under experimental conditions, the modified electrode had a linear response range from 2.0 × $10^{-9}$to 1.0 × 10^{-8}M valacyclovir with a detection limit of1.78 × 10^{-10}M. The procedure was applied to the assay of VAL in tablets.

A novel electrochemical sensor based on polymerization of β–cyclodextrin on electrochemically pretreated PGE was used for the adsorptive square wave voltammetric determination of acyclovir [179]. A synergistic effect of β–cyclodextrin was used to construct this sensor for quantification of acyclovir. In Teorell Stenhagen buffer (pH=3.0), square wave voltammetric technique exhibited two linear dynamic ranges of 5.0 × 10^{-8} to 6.0 × 10^{-7}M and 1.0 × 10^{-6} to 9.0 × 10^{-6} M acyclovir. The calculated detection and quantitation limits were 7.59 × 10^{-9} and 2.3 × 10^{-8} M acyclovir, respectively. The prepared electrochemical sensor was applied for the determination of acyclovir dosageforms and human urine as a real sample.

The interaction of taxol with salmon–sperm double–stranded DNA (ds–DNA) based on the decreasing of the oxidation signals of guanine and adenine bases was studied electrochemically with a PGE using a differential pulse voltammetric technique [180]. The decreases in the intensity of the guanine and adenine oxidation signals after interaction with taxol were used as indicator signals for the sensitive determination of taxol. Differential pulse voltammetric technique exhibits a linear dynamic range of 2.0 × $10^{-7}$to 1.0 × 10^{-5} M for taxol with a detection limit of 8.0 × 10^{-8} M. The prepared electrochemical biosensor was applied for the determination of taxol in pharmaceuticals, human blood serum and urine samples.

In situ mercury film modified PGE was prepared and applied for selective and sensitive electrochemical determination of anticancer drug lomustine [181]. The bare and modified PGE were characterized by cyclic voltammetry, square wave voltammetry and scanning electron microscopy. In Britton–Robinson buffer (pH=5.0) in presence of 0.5 M sulphate ions as indifferent supporting electrolyte, lomustine yields a well–defined and sensitive reduction peak at the mercury film modified PGE and the recorded current was linearly increased over the concentration range of 1.92×10^{-7}–1.36×10^{-5} M lomustine. The achieved detection and quantification limits were 8.13×10^{-8} and 2.71×10^{-7}M using square wave cathodic adsorptive stripping voltammetry, respectively. Mercury film modified PGE was used as a sensor for the detection of lomustine in human blood and urine samples with good accuracy and precision.

Bismuth modified pretreated PGE was employed for the determination of diazepam [182]. First, PGE was electrochemically pretreated and then bismuth film was prepared by ex–situ plating of bismuth on the pretreated PGE. The modified electrode displayed enhanced electro activity toward the reduction of diazepam compared to simple bare PGE. The electrochemical reduction of diazepam on the modified PGE was totally irreversible and controlled by diffusion. Under optimum conditions, differential pulse voltammetry was used for the determination of diazepam, which showed a linear calibration graph over diazepam concentration range of 1.4 to 16.7µM. The determined detection limit was 1.1µM. Finally, bismuth modified PGE was used for determination of diazepam in tablets and biological samples such as human urine using standard addition method.

The surface of PGE was modified with thiol–functionalized silica thin film that incorporates with sodium dodecyl sulfate (SDS), as an extracting phase [183]. Flutamide (which is prescribed for prostate cancer patients) is extracted from a sample solution into the silica thin film, and then, it was accumulated, as a reduced form (by applying a suitable potential), at the PGE surface. The differential pulse voltammetric responses of different concentrations of flutamide were linear in the range of 0.10–100.0 nmol $L^{-1}$and 0.10–100.0 µmol $L^{-1}$with a detection limit of 34 pmol L^{-1}. The modified PGE was successfully applied for the determination of flutamide in human urine and plasma samples.

Ensafi et al. [184] continue their efforts with modified PGE. They present a new electrochemical sensor based on PGE modified with multi–walled carbon nanotubes (MWCNTs). The modified PGE was applied for the determination of buprenorphine which is a strong semi–synthetic opiate pain killer. Differential pulse voltammetry exhibited two linear dynamic ranges of 1.0-109.0 pmolL^{-1} and 0.109 nmolL^{-1} -0.11µmol$L^{-1}$of buprenorphine and the detection limit was found to be as low as 0.6 pmolL^{-1} of buprenorphine. The obtained results indicate that MWCNT–PGE was successfully used for buprenorphine detection in biological samples such as human urine and plasma of both drug–addict and non–addict human subjects.

Another modification procedure for PGE was presented by Rezaei et al.[185]. This procedure based on use highly amino–functionalized fluorescent carbon quantum dots (CD), multiwall carbon nanotubes and poly (diallyl–dimethyl ammonium chloride) (PDDA) as PGE modifier (PDDA/MWCNT/CD/PGE). The produced modified electrode was successfully used for the determination of dextromethorphan. Both of cyclic and differential pulse voltammetry were used studying electrochemical behavior and voltammetric determination of dextromethorphan. Under the optimal experimental conditions, a calibration curve of 2.0–600 µM dextromethorphan was constructed with the detection limit of 0.2 µM. This sensor was successfully applied to determine dextromethorphan in the cough syrups, human urine and plasma samples.

PGE modified multi–walled carbon nanotubes (MCPGE) had been developed for the electrochemical investigation of aceclofenac[186]. Phosphate buffer (pH=7.0) was used as a suitable electrolytic medium, in which aceclofenac exhibited a sensitive adsorption controlled oxidation peaks at +0.12, +0.32 and +0.51 V and a reduction peak at -0.26 V (vs. Ag/AgCl). The oxidative peak currents were varied linearly with aceclofenac concentration in the range between 1×10^{-6} and 60×10^{-6} M with a detection limit of 2.6×10^{-9} M. The applicability of the MCPGE was illustrated by the determination of aceclofenac present in pharmaceutical and human urine samples.

CONCLUSION

Electrochemistry is a well-established and rapidly growing area with a number of possible applications in the pharmaceutical field. Modern electrochemical methods are sensitive, selective, rapid, and provide easy techniques applicable to analyses in the pharmaceutical field and, indeed, in most areas of analytical chemistry.

Applications of solid electrodes in voltammetric determination of pharmaceuticals gain a great attention. This can be attributed to its easy modification procedure, and highest electrochemical active surface area. Different types of modifiers were used to enhance the recorded current intensity and electrode sensitivity to trace determination of pharmaceuticals. Also, the solid electrode can be used with minimum safety precaution since it is non-toxic.

The term of disposable electrodes make electrochemical determination of pharmaceuticals easier than the beginning of pharmaceuticals in 1940s. This term is accompanied with solid electrodes which the focus of this review. In current review we concerning the most home–made traditional solid electrode carbon paste electrode, screen printed electrode, boron doped–diamond electrode and pencil graphite electrode. Both of screen printed and pencil graphite electrode can be described as disposable electrodes.

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