Review Article

Electrochemical Analysis Techniques: A Review on Recent Pharmaceutical Applications

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Accepted on: 24-01-2014; **Finalized on:** 31-03-2014.

ABSTRACT

Electro analysis of high advantages due to high sensitivity, reduction in solvent and sample consumption, high-speed analysis, low operating cost and high scan rate in all cases. Electrochemical analysis is a powerful analytical technique that is utility in Pharmaceutical applications. A review of the modern electro analytical techniques, namely, cyclic, linear sweep, square wave and stripping voltametric techniques, are reported. This review gives Pharmaceutical applications used for each mode of electro analysis techniques.

Keywords: Electro analytical, Voltammetry, Stripping techniques, Pulse techniques, Pharmaceutical applications.

INTRODUCTION

Electrochemical analytical techniques can easily solve many problems of pharmaceutical interest with a high degree of accuracy, precision, sensitivity, and selectivity employing this approach. Some of the most useful electro analytical techniques are based on the concept of continuously changing the applied potentials to the electrode-solution interface and the resulting measured current (Kissinger and Heineman 1996; J. Wang 2006; Smyth and Vos 1992; Ozkan, Uslu, and Aboul-Enein 2003; Bard and Faulkner 2001; Kellner et al. 2004; Hart 1990;Bengi Uslu and Sibel A. Ozkan 2010). Most of the chemical compounds were found to be as electrochemically active [1].

Electrochemical techniques are powerful and versatile analytical techniques that offer high sensitivity, accuracy, and precision as well as large linear dynamic range, with relatively low-cost instrumentation. After developing more sensitive pulse methods, the electroanalytical studies are more regularly used on many applications like drug analysis in their dosage forms and especially in biological samples. During the past years, there has been extraordinary acceleration of progress in the discovery, synthesis, sensitive electrochemical analysis [1-13].

The aim of the present review is to give the basic information about electroanalytical analysis methods, working electrodes, techniques, and their pharmaceutical, applications. An attempt was made to choose some readily available publications describing some advances in methodology and applications. The important pharmaceutical applications highlighted in this review are:

1. Gastro-intestinal drugs
2. Antibiotics and antibacterial drugs
3. Antineoplastic drugs
4. Cardiovascular drugs
5. Anesthetic drugs
6. Flavonoids
7. Vitamins
8. Antifungal agents
9. Antidepressant drugs

ANALYTICAL APPLICATION OF SOME SELECTED MODERN ELECTROCHEMICAL TECHNIQUES

Elelctroanalytical techniques (specially stripping analysis) are well known as excellent procedures for the determination of trace chemical species. These techniques have been developed for various cations, anions and organic molecules. Several articles that reviewed the application and the use of such voltammetric techniques in the determination of pharmaceuticals in different samples have been reported. A review about the methodology and application of different electroanalytical techniques has been presented[13].

Electroanalytical application for the determination of pharmaceutical compounds

The electrochemical techniques, especially voltammetry, have gained steadily an importance during recent years. Such electrochemical techniques have been applied for the determination of pharmaceutical compounds in dosage forms (tablets, capsules, injections and suspension) and biological samples (real and spiked urine

samples, blood and serum). Table 1 shows some electroactive functional groups and their reactions.

Various types of pharmaceutical compounds analyzed by voltammetric techniques and these types like:

1. Gastro-intestinal drugs

Electrochemical oxidation of metoclopramide hydrochloride has been reported[14], where the metoclopramide hydrochloride was determined by second-derivative adsorptive anodic stripping voltammetry with a nafion-modified glassy carbon electrode. The stripping peak current was proportional to the concentration of metoclopramide hydrochloride over the range 0.4–154.7 ng mL^{-1} and the detection limit was 0.027 ng mL^{-1} with 4–min. accumulation time. The method has been successfully applied to the determination of MCP in human serum.

Our group have been introduced a simple, reliable and selective square wave anodic stripping voltammetric method at carbon paste electrode for the determination of metoclopramide hydrochloride in pharmaceutical dosage forms (tablet) and in biological fluids (spiked and real urine samples) [15]. A linear concentration ranges from 0.067 to 0.336, 0.067 to 0.269 and 0.067 to 0.269 ng mL^{-1} of metoclopramide hydrochloride, at accumulation times 60, 120 and 180 s, respectively, can be determined successfully.

The polarographic determination of cisapride by nitration with KNO_3 in H_2SO_4 was suggested [16]. The method is based on using Britton–Robinson buffer of pH 6.5 in presence of KNO_3/H_2SO_4 mixture as nitrating agent. The drug showed two reduction peaks in differential pulse polarography at –0.2 and –0.8 V.

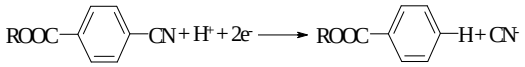
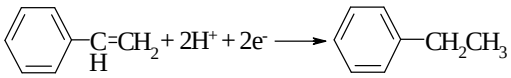
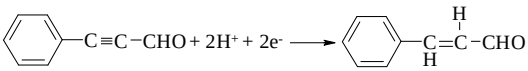
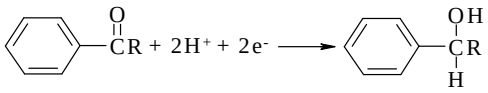
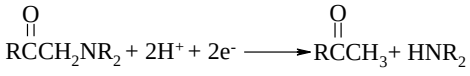
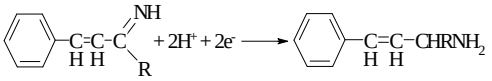
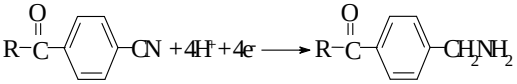
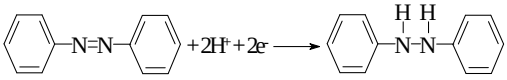
Differential pulse polarographic and anodic stripping voltammetric (ASV) techniques were utilized for the determination of cinitapride [16]. The two procedures are based on using acetate buffer or KNO_3 as supporting electrolyte. At accumulation time 30 s, scan rate 4 mV s^{-1} and accumulation potential of 0.0 V, cinitapride show peak potential at –0.3 V.

The electrochemical behavior of sulpiride at a HMDE was investigated. Linear sweep cathodic stripping voltammetry was used to determine sulpiride in the presence of acetate buffer of pH 10.5[17]. The linear concentration range is from 0.68 to 17.1 ng mL^{-1} sulpiride. Furthermore, a theoretical detection limit of 0.068 ng mL^{-1} sulpiride was calculated.

Differential pulse stripping voltammetric method was developed for the determination of paracetamol and phenobarbital in pharmaceuticals assisted by chemometrics [18]. Both of these analytes gave well-defined oxidation peaks in the Britton–Robinson buffer (pH 5.72) at a glassy carbon electrode. A linear relationship between current and concentration of paracetamol ranges: {0.09-0.93 mg L^{-1} (r^2 = 0.999) and 0.9-11.7 mg L^{-1} (r^2 = 0.999)}, and phenobarbital {1.0-22.0 mg L^{-1} (r^2 = 0.999)}. The proposed method was applied for the determination of paracetamol and phenobarbital in several commercial tablets with satisfactory results.

Direct electrochemical method based on the electrochemical oxidation of paracetamol was described for the determination of paracetamol in plasma [19]. A nanogold modified indium tin oxide (ITO) electrode was used for the determination of paracetamol at pH 7.2 [20]. Linear calibration curve is obtained over the range $2x10^{-7}$-$1.5x10^{-3}$ M with a correlation coefficient of 0.997. The detection limit (3σ) was estimated to be $1.8x10^{-7}$ M. The practical analytical utility of the method is illustrated by determination of paracetamol in pharmaceutical preparations.

Table 1: Some electroactive functional groups and their behavior:

Group	Reaction
C−C	
C=C	
C≡C	
C−X	$RCH_2Br + H^+ + e^- \longrightarrow RCH_3 + Br^-$
C=O	
C−N	
C=N	
C≡N	
N=N	
N=O	$RNO + 2H^+ + 2e^- \longrightarrow RNHOH$
NO_2	$RNO_2 + 4H^+ + 4e^- \longrightarrow RNHOH + H_2O$
O−O	$ROOR + 2H^+ + 2e^- \longrightarrow 2ROH$
S−S	$RSSR + 2H^+ + 2e^- \longrightarrow 2RSH$
S=O	$R_2S{=}O + 2H^+ + 2e^- \longrightarrow R_2S + H_2O$

Square-wave adsorptive cathodic stripping voltammetric procedure was described for the trace determination of chlordiazepoxide in bulk form, pharmaceutical formulation and human serum at a mercury electrode [21].

This procedure show lower limits of detection (LOD) ($4.4x10^{-10}$ M and $6.6x10^{-10}$ M) and limits of quantitation (LOQ) ($1.5x10^{-9}$ M and $2.2x10^{-9}$ M), respectively in pharmaceutical formulation and spiked human serum.

2. Antibiotics and antibacterial drugs

A highly sensitive adsorptive stripping voltammetric method was described for the determination of rufloxacin in tablets spiked plasma and urine [22].

Carbon paste electrode modified with poly(N-vinylimidazole) and poly(4-vinylpyridine) was used for the determination of amoxycillin in solid dosage forms without any separation step [23-25].

The electrochemical response of azithromycin has been attributed to oxidation of tertiary amino groups [26]. A simple and selective square-wave voltammetric method has been developed for the determination of azithromycin in pure form, in pharmaceutical preparation and in biological samples [27]. This method was accomplished with hand-make carbon paste electrode. The limits of detection and quantification of the pure drug are 0.463 and 1.544 ppb (with the correlation coefficient, *r*=0.9785and the standard deviation, S.D.=0.1 (*n*=5), for the accumulation time of 60 s), respectively. The method was successfully applied to the determination of the drug in urine and two forms of pharmaceutical formulations.

Adriamycin was determined using carbon paste electrode in presence of cetyltrimethyl ammonium bromide (CTAB) [28]. The suggested method show linearity range of $2.5x10^{-8}$-$5x10^{-6}$ mol L^{-1} with detection limit $4x10^{-10}$ mol L^{-1} at accumulation time 3 min.

Voltammetric study of the interaction of lomefloxacin (LMF)-Mg (II) complex with DNA and its analytical application at a mercury electrode is reported [29]. In NH_3-NH_4Cl buffer (pH~9.1), the adsorption phenomena of the LMF-Mg (II) complex were observed by linear sweep voltammetry. In the presence of calf thymus DNA (ctDNA), the peak current of LMF-Mg(II) complex decreased considerably, and a new well-defined adsorptive reduction peak appeared at -1.63 V. The new peak currents of LMF-Mg(II)-DNA system increased linearly correlated to the concentration of DNA in the $4x10^{-7}$-$2.6x10^{-6}$ g mL^{-1} range when the concentrations of LMF-Mg(II) complex was fixed at $5x10^{-6}$ mol L^{-1}, with the detection limits of $2.3x10^{-7}$ g mL^{-1}.

The adsorptive and electrochemical behavior of norfloxacin on a glassy carbon electrode was investigated by cyclic and square-wave voltammetry[30]. In acetate buffer of pH 5.0, norfloxacin gave a sensitive adsorptive oxidative peak at 0.9 V. Applicability to measurement of norfloxacin at submicromolar levels in urine samples was illustrated. The peak current was linear with the norfloxacin concentration in the range 5-50 µg mL^{-1} urine. The detection limit was 1.1µg mL^{-1} urine.

Square-wave adsorptive anodic stripping voltammetric procedure was described to assay of both the rifampicin (RIF) and isoniazid (INH) drugs separately or combined in pharmaceutical formulations and human serum has been investigated at a carbon paste electrode [31]. The proposed procedure was also successfully applied to simultaneous assay of rifampicin and isoniazid drugs combined in pharmaceutical formulations. Moreover, the proposed procedure was successfully applied to simultaneous assay of both drugs in human serum samples with limits of detection and quantitation of $5x10^{-8}$ and $1.7x10^{-7}$ M for RIF and $6.1x10^{-8}$ and $2x10^{-7}$ M for INH.

A systematic study of the adsorption and association of the cancerostatic drug actinomycin-C_1 (ACT) at a hanging mercury drop electrode has been conducted using phase-sensitive a.c. voltammetry and cyclic voltammetry [32]. Also, Adsorptive accumulation in stripping voltammetry has been applied for trace measurements of the ACT [33]. Accumulation is achieved by controlled adsorption of ACT film on the hanging mercury drop electrode (HMDE). The limit of detection after 5 minutes preconcentration is $8x10^{-10}$ M.

Cephalosporins (such as rocephin and cefobid), were determined by several voltammetric techniques [34-42]. Sulfadiazine was determined in artificial gastric and intestinal juices using differential pulse voltammetry [43]. Indirect differential pulse voltammetry was used for the determination of sulfonamide [44]. This procedure depend diazotization and coupling occurs between 1-naphthol and sulfonamide in alkaline medium.

Different antibacterial drugs were determined in dosage forms, plasma and urine by several voltammetric and polarographic methods using hanging mercury drop electrode (HMDE) and membrane selective electrode (MSE) [45-51].

Voltammetric behavior of chloroquine was investigated using cyclic voltammetry and differential pulse voltammetry [52]. DNA-modified carbon paste electrode was used in this study. Voltammogram obtained show linearity range of $1x10^{-7}$-$1x10^{-5}$ mol $L^{-1}$with detection limit $3x10^{-8}$ mol L^{-1}.

Dc-polarography, cyclic voltammetry, controlled-potential colormetry and square-wave adsorptive stripping voltammetry techniques were used to study the electrochemical behavior of cefazolin sodium (CFZ) in Britton-Robinson buffer (pH 2-11) at the mercury electrode[53]. Square-wave adsorptive cathodic stripping voltammetric procedure was described for the trace determination of CFZ in bulk form up to limits of detection and quantitation of $2.6x10^{-10}$ M and $8.6x10^{-10}$ M, respectively. The method was successfully applied for determination of CFZ in pharmaceutical preparation.

Different types of electrodes namely: dropping mercury electrode (DME), static mercury drop electrode (SMDE), glassy carbon electrode (GCE), carbon paste electrode (CPE), and modified carbon paste electrode (MCPE) were used to investigate the electrochemical behavior of the

monobactam antibiotic aztreonam at different electrodes and in biological fluids[54]. Differential pulse stripping voltammetry (DPSV) and Osteryoung square-wave stripping voltammetry (OSWSV) were utilized for the drug determination in either aqueous medium or in urine samples. Detection limits of $2x10^{-8}$ M and $8x10^{-8}$ M aztreonam were achieved in aqueous and urine samples, respectively.

3. Antineoplastic drugs

Modified carbon paste electrode was used for electrochemical studying of interaction between mitoxantrone and double-standard DNA (dsDNA) and single-standard DNA (ssDNA)[55]. This study was carried out using DNA-modified carbon paste electrode in combination with cyclic voltammetry and differential pulse voltammetry.

5-Fluorouracil was determined using cathodic stripping voltammetry in presence of trace concentrations of Cu(II)[56]. Linearity range of $5x10^{-9}$-$6x10^{-8}$ mol dm^{-3} of 5-fluorouracil with detection limit $4.6x10^{-10}$ mol dm^{-3} was obtained. Another method for the determination of 5-fluorouracil was suggested utilizing flow injection system with voltammetric detection[57].

Carboplatin was determined by differential pulse voltammetry using DNA-modified glassy carbon electrode[58]. This method was applied for determination in serum. Also, it was applied to pharmacokinetic studies on patients receiving carboplatin treatment.

The electrochemical oxidation and reduction behavior of adsorbed species of tarabine PFS at an in situ-mercury film electrode is studied using cyclic voltammetry and Osteryoung square-wave stripping voltammetry (OSWSV)[59]. The drug is easily detected as 0.134 ng mL^{-1}.

A sensitive procedure for trace measurement of tamoxifen is described [60]. The method is based on controlled adsorptive accumulation of the drug at an electrochemically treated glassy carbon electrode, followed by chronopotentio-metric measurement of the surface species.

A carbon paste electrode modified by hydrophobic molecules of hydroxypropyl β-cyclodextrin to form enantioselective membrane sensor was used for the enantioseparation of racemic methotrexate[61]. Also, determination of its enantiomeric purity in some pharmaceuticals in suggested.

Trace measurements of 2-thiouracil and 4-thiouridine in presence of Cu(II) is described[62]. In this method the adsorption and redox behavior occurs on hanging mercury drop electrode, and the reduction current of the accumulated complex is measured by cathodic stripping voltammetry.

4. Cardiovascular drugs

Indapamide was determined by an adsorptive stripping method using carbon paste electrode modified by castor oil [63]. Utilizing anodic stripping differential pulse voltammetry procedure, the calibration plot was linear in the range 18.3-36.5 ng mL^{-1} indapamide with detection limit of 1.8 ng mL^{-1}. The method was applied for the determination of indapamide in spiked serum.

Analytical method based on the adsorptive accumulation of Cu(II)-indapamide complex followed by the reduction of the complexed copper was developed for the indapamide determination [64]. Under the optimal experimental conditions, a linear calibration graph in the range 20-200 nmol L^{-1} and detection limit of 5 nmol L^{-1} were calculated.

1,4-Dihydropyridine derivatives such as nitrendipine, nifedipine, dehydro- nifedipine and other calcium antagonist members were determined by different voltammetric techniques[65-74].

Differential-pulse voltammetric method was developed for the determination of amlodipine based on the oxidation of the dihydropyridine group on the surface of glassy carbon electrode under stationary and rotating conditions[75]. The limit of detection (LOD) and the limit of quantitative (LOQ) for the rotating and stationary techniques were found to be 0.004 and 0.0072 mg mL^{-1} (for *S/N* = 3.3) and (LOQ) 0.012 and 0.022 mg mL^{-1} (for *S/N* = 10), respectively. The proposed method was applied to the tablets containing amlodipine and according to the statistical evaluations acceptable results were obtained at the 95 % probability level.

Captopril was subjected for different voltammetric techniques. The voltammetric behavior was studied [76, 77]. Carbon-paste electrode modified with cobalt-5-nitrolsalophen was used as a sensitive voltammetric sensor for detection of captopril[78]. Captopril was determined using adsorptive cathodic differential pulse stripping voltammetry with the HMDE [79]. Square-wave voltammetric determination of captopril also was suggested[80, 81]. Quite fast and inexpensive voltammetric method was suggested for the determination of captopril using differential pulse polarography in presence of oxygen[82]. Adsorptive cathodic stripping voltammetry is used for the determination of trace levels of captopril[83] in phosphoric acid (pH 2.3). The method was applied to determine the mentioned drug in pharmaceutical formulations, urine and blood-serum. The limit of detection was 0.019 ng/ml

Cyclic voltammetry, direct current polarography, differential pulse polarography and alternating current polarography were used to study the voltammetric behavior of ramipril[84]. Verapamil was determined by adsorptive stripping voltammetry[85]. The suggested procedure shows linearity range of $1x10^{-8}$-$1x10^{-6}$ M with detection limit $5x10^{-10}$ M. This procedure was successfully applied for the determination of verepamil in urine and in dosage forms

Diltiazem as an antihypertensive agent was determined in capsules and urine using adsorptive stripping

voltammetry[86]. The calculated detection limit of diltiazem in aqueous solution in 2.7 ng mL^{-1}.

The square-wave adsorptive cathodic stripping voltammogram of terazosin exhibited a single well-defined two-electron irreversible cathodic peak which may be attributed to the reduction of C=O double bond of the drug molecule[87]. The described procedure was suitable for the determination of terazosin in bulk form, tablets and human serum. Limits of detection (LOD) and quantitation (LOQ) of $1.5x10^{-11}$ and $5x10^{-11}$ M bulk terazosin were achieved, respectively. The proposed procedure was successfully applied to determination of the drug in tablets and human serum samples.

DC polarography and the determination of doxazosin employing different polarographic techniques are described in this study[88]. Since the sensitivity of suggested procedure was higher than the others, the determination of doxazosin was performed in filtered and unfiltered tablet solutions containing 4 mg active material.

Square wave voltammetry of antihipertensive doxazosin at nafion modified carbon paste electrode has been carried out[89]. The detection limit reached using square wave voltammetry was $2.33x10^{-11}$ M and the variation coefficient at $2.0x10^{-9}$ M level was 3.54%. The suggested procedure can be used to determine the drug at trace level in human urine samples with good recoveries.

A polarographic procedure of suffocate sensitivity for the determination of bulk amiloride drug in Britton–Robinson buffer at pH 2 using mercury electrodes is described [90]. The calibration graph was obtained over the concentration range $2.5x10^{-5}$-$2.5x10^{-4}$ M amiloride. The limits of detection (LOD) and quantitation (LOQ) of the procedure were $1x10^{-5}$ and $3.3x10^{-4}$ M bulk amiloride, respectively. Moreover, a differential-pulse adsorptive cathodic stripping voltammetric procedure has been described to assay of the drug at lower concentration levels. The calibration graph was obtained over the concentration range $2x10^{-8}$-$1x10^{-6}$ M for bulk amiloride. Both procedures were successfully applied to the determination of amiloride in tablets.

5. Anesthetic drugs

Anodic adsorptive stripping voltammetric determination of methohexital sodium was proposed [91]. This procedure is based on the formation of insoluble mercury salt on a hanging mercury drop electrode after preaccumulation by adsorption. The detection limit was found to be $2x10^{-7}$ M with 180-s accumulation time. The application of this method was tested in the determination of methohexital in spiked urine samples.

Cathodic stripping voltammetric method is described for the determination of thiopentone-sodium[92]. The method is based generally on the formation of a slightly soluble mercury salt of thiopentone-sodium with Hg onto HMDE surface. The proposed method was applied for the determination of the drug in pure pharmaceutical dosage form, urine, and human serum samples.

Ghandour *et al*[93] have been proposed a sensitive and simple voltammetric method for the trace determination of muscle relaxant gallamine triethiode (flaxedil).

6. Flavonoids

Characterization of voltammetric behavior and antioxidative activity for selected four flavonoids (quercetin, rutin, catechin and epigallocatechin gallate) was suggested using carbon paste electrode modified with dsDNA[94].

Square wave anodic stripping voltammetry was used for the determination of quercetin is investigated [95]. Under the optimal experimental conditions, the linear concentration ranged from 67.66 to 338.3 ppb quercetin. The detection limit of 6.77 ppb quercetin at 15 s accumulation time.

Electrochemical behavior of quercetin was studied in detail by field emission scanning electron microscope (FE-SEM), UV-spectroelectrochemical and various electrochemical methods[96]. A highly sensitive adsorptive stripping voltammetric measurement (AdSV) for quercetin was also shown at multi-wall carbon nanotubes-modified paraffin-impregnated graphite electrode, the adsorptive stripping response of the peak was proportional to the concentration in a range of $9x10^{-9}$ to $4x10^{-5}$ M with a detection limit of $4.8x10^{-9}$ M.

7. Vitamins

Water soluble vitamins (thiamine, riboflavin, pyridoxine and ascorbic acid) were determined by linear sweep voltammetry at carbon paste electrode[97]. Thiamine (vitamin B_1) was determined by different voltammetric methods[98-100]. Also, riboflavin was determined by square wave adsorptive stripping voltammetry at mercury film electrode[101-103].

Ascorbic acid was determined using different voltammetric techniques. Using modified carbon paste electrode to study the electrocatalytic determination of ascorbic acid in aqueous solution [104]. Also, ascorbic acid was determined in fruits and vegetables[105, 106]. Differential pulse voltammetric determination of ascorbic acid has been realized on the carbon paste electrode (CPE) [107]. The developed method has been applied to the direct determination of vitamin C in pharmaceutical tablets and in different types of fruit juices. Limits of determination are $1.5x10^{-7}$ M, $8x10^{-7}$ M and $1x10^{-5}$ M for tablets, dehydrated and liquid juices, respectively.

Ascorbic acid is simultaneously determined by voltammetric techniques; with uric acid[108, 109], with epinephrine [110] and with dopamine [111, 112]. Simultaneous determination of dopamine, ascorbic acid and uric acid at modified glassy carbon electrode is suggested [113]. Also, ascorbic acid, epinephrine and uric acid were determined at glassy carbon electrode modified with caffeic acid [114].

8. Antifungal agents

The electrochemical behavior of tinidazole was studied by normal and reverse pulse polarography [115]. According to electrochemical reduction peak obtained from tinidazole[116, 117], it could be determined easily in pharmaceutical preparations.

Clotrimazole as an example of weak bases with α-tocopherol, was determined by linear sweep voltammetry[118]. This method depends on the oxidation prepeak resulting from the oxidation of α-tocopherol. Clotrimazole can be determined by cathodic stripping voltammetry at 50 ng mL^{-1} level when pre-accumulated for 3 min at an accumulation potential of -0.20 V[119]. The proposed method is applied successfully for the determination of clotrimazole in a commercial formulation.

Two procedures, based on differential pulse polarography (DPP) and adsorptive differential pulse voltammetry (AdS-DPV) in aqueous medium were developed for the determination of ketoconazole in a gel formulation and spiked urine samples, respectively [120].

9. Antidepressant drugs

Imipramine-HCl, trimipramine and thioridazine were determined using carbon paste electrode modified with β-cyclodextrin[121]. Amitriptyline-HCl and imipramine-HCl were determined by voltammetry using polymer modified carbon paste electrode[122], fatty acid carbon paste electrode [123], platinum and activated glassy carbon electrode [124]. At lipid-coated glassy carbon electrode and lipid-coated carbon paste electrode, the desipramine, imipramine and trimipramine were determined by voltammetry[125].

Electrochemical behavior of trazodone-HCl was investigated using carbon paste electrode[126] and platinum electrode[127]. Also, direct current (DC_t), differential pulse (DPP) and alternating current (AC_t) polarography were used to study the voltammetric behavior of trazodone-HCl [128].

The electrochemical oxidation of tryptophan at graphite electrodes has been studied in aqueous solutions[129]. A simple, fast and sensitive method is proposed for tryptophan determination in pharmaceutical formulations containing other non-electroative amino acids, vitamins and hydroxycobalamines was suggested using carbon paste electrode[130].

CONCLUSION

The previous survey shows that the number of publications dealing with the application of some selected modern electrochemical techniques (voltammetric techniques) to determine pharmaceuticals. The importance of such applications increased steadily, and this due to the following advantages:

1. Only small volumes of samples are necessary.
2. Electroanalytical techniques (specially stripping analysis) are well known as excellent procedures for the determination of trace chemical species.
3. The sensitivity is sufficiently high and can be increased more by modifications of classical voltammetric techniques (modified microelectrodes and ultra-microelectrodes) that enhance significantly sensitivity and selectivity of the method.
4. Voltammetry coupled with different separation methods such as (HPLC, Flow Injection (FI) and Capillary Electrophoresis (CE)) enhancing the analytical properties for complex mixtures in different compounds.
5. Turbid and colored solutions, which are a problem with other methods, can be easily analyzed. The separation of the excipients, in pharmaceutical analysis, is in many cases not necessary and this simplified the preparation of samples.
6. Electroanalytical stripping procedures have been developed for the measuring down to sub-µg/L level.
7. Also, these techniques combine low maintenance costs with high sensitivity and selectivity that allows the determination of low levels of analytes without prior treatments of the samples.
8. Electroanalytical methods especially square wave voltammetry is a very sensitive and rapid analytical method due to it is high scan rate in all cases where the reacting species is accumulated by adsorption on the electrode surface.
9. The short analysis time in these methods makes it very attractive for routine determination of the analytes in different samples.

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Source of Support: Nil, **Conflict of Interest:** None.