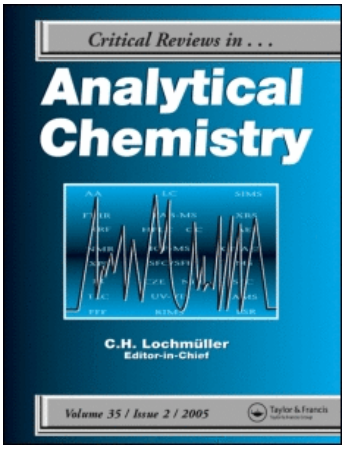

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Analysis of Pharmaceuticals and Biological Fluids Using Modern Electroanalytical Techniques

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ABSTRACT: A review of the principles and application of modern electroanalytical techniques, namely, cyclic voltammetry, linear sweep voltammetry, differential pulse voltammetry, differential pulse polarography, square wave voltammetry, square wave polarography, stripping voltammetric, and stripping polarographic techniques, is presented. The use and advantages of these techniques at different electrodes are discussed. The analytical applications of these techniques to pharmaceutical compounds in dosage forms and biological media are also discussed. Various selected studies on these subjects since 1995 are reviewed.

KEY WORDS: cyclic voltammetry, linear sweep voltammetry, differential pulse voltammetry (polarography), square wave voltammetry (polarography), stripping voltammetry (polarography), pharmaceuticals, biological media.

ABBREVIATIONS: HMDE, Hanging Mercury Drop Electrode; **SMDE**, Static Mercury Drop Electrode; **CP**, Carbon paste; **Pt**, Platinum; **GC**, Glassy Carbon; **Au**, Gold; **DME**, Dropping Mercury Electrode; **AdS**, Adsorptive Stripping.

I. INTRODUCTION

Some of the most useful electroanalytical techniques are based on the concept of continuously varying the potential that is applied across the electrode-solution interface and measuring the resulting current.

Electrochemical techniques are a powerful and versatile analytical technique that offers high sensitivity, accuracy, and precision as well as a large linear dynamic range, with relatively low-cost instrumentation. Voltammetry and polarography, as the name suggest, are a current-voltage technique; the recording of current vs. potential is termed a voltammogram and polarogram. Electrochemical measurements are two-dimensional, with the potential being related to qualitative properties (with thermodynamic or kinetic control) and the current related to quantitative properties (controlled either by mass transport process or reaction rates). Thus, compounds can be selectively detected by electrochemical methods. This selectivity depends on the accessible potential range, the number of compounds that are active in

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this range, and on the half-width of the single signals.

Voltammetry represents a type of electroanalytical techniques in which the current at the working electrode is measured as a function of the potential applied to that electrode. The potential at the electrode serves as the driving force for the electrochemical reaction. Solid electrode voltammetry, which is typically employed for oxidations (anodic process), can use a platinum electrode (disc or wire), a gold electrode (disc or wire), a ruthenium electrode, a wax-impregnated graphite electrode, a carbon paste electrode, or a glassy carbon electrode.[1–4] This technique is also used for cathodic processes (for reduction). For this technique, dropping mercury, hanging mercury drop, static mercury drop, carbon paste, and glassy carbon electrodes can be used as a working electrode.

The commonly used voltammetric methods are linear sweep, cyclic, hydrodynamic, differential pulse, square wave, and stripping voltammetry, which involves a preconcentration step followed by voltammetric and polarographic measurements (d.c., fast-scan and differential pulse).

Although voltammetry represents a rather specialized area of instrumental analysis. Voltammetric measurements and mechanistic probing of redox system of various electroactive samples of biological significance (drugs, metals, hormones, and vitamins) have been reported. The voltammetric and polarographic techniques are the more sensitive, reproducible, and easily used electroanalytical methods can be an alternative to more frequently used separation and spectrometric methods. Furthermore, in some cases there is a relationship between voltammetry and pharmaceutical samples, and the knowledge of the mechanism of their electrode reactions can give a useful clue in elucidation of the mechanism of their interaction with living cells. The voltammetric and polarographic analysis of drugs in pharmaceutical preparations by far the most common use of electrochemistry for analytical-pharmaceutical problems. As a rule, many of the active compounds of the formulations can be readily oxidized or reduced. As has been pointed out, electrochemical techniques are well suited for the determination of drugs in various samples, that is, raw material, pharmaceutical dosage forms even those involving a complex matrix such as syrups, tablets, creams, suppositories, or ointments or else in biological fluids. The principal advantage of the modern electrochemical methods is that the excipients do not interfere, and generally the separation and extraction procedure is not necessary. Thus, sample preparation usually consists of dissolving out the active ingredient from the pharmaceutical dosage form with a suitable solvent and performing direct analysis on an aliquot portion of this solution.[1,2,5] In addition to the analytical aspect, electrochemistry allows the establishment of the electrochemical behaviour of a given drug through mechanistic studies. This is of particular interest with respect to the pharmacological knowledge of the drug. Electrochemical techniques are most suitable to investigate the redox properties of a new drug; this can give insights into its metabolic fate. Electrochemical data are often correlated to the molecular structure and the pharmacological activity. Interactions of drugs with metal ions or with proteins as well as degradation processes occurring on photo- or pH-sensitive drugs may be studied using modern electrochemical techniques.[5]

The aim of this review is to show that modern electrochemical techniques can be used successfully for the determination of various pharmaceutical samples in biological media or in dosage forms. The extent of this review makes it impossible to quote all papers dealing with various polarographic and especially the voltammetric determination of drugs. Thus, only selected examples demonstrating the applicability in biological

media or in dosage forms of these methods for various classes of drugs are presented.

II. CYCLIC AND LINEAR SWEEP VOLTAMMETRY

A simple potential wave form that is used often in electrochemical experiments is the linear wave form, that is, the potential is continuously changed as a linear function of time. The rate of change of potential with time is referred to as the scan rate. Cyclic voltammetry (CV) is a potential controlled electrochemical experiment. A more commonly used variation of the technique is CV, in which the direction of the potential is reversed at the end of the first scan. Thus, the waveform is usually of the form of an isosceles triangle. The repetitive triangular potential excitation signal for CV causes the potential of the working electrode to sweep back and forth between two designated values (the switching potentials). CV is the most widely used technique for acquiring qualitative information about electrochemical reactions.[6–9] It is a powerful tool for the determination of formal redox potentials, detection of chemical reactions that precede or follow the electrochemical reaction, and evaluation of electron transfer kinetics. CV is often the first experiment performed in an electrochemical study of a compound, a biological material, or an electrode surface.

Accordingly, the technique has been used widely in studying the redox mechanism of many biologically significant molecules. The result of such investigations into the redox mechanism of drugs may have profound effects on understanding of their *in vivo* redox processes of pharmaceutical activity.[4,5]

A potentiostat system sets the control parameters of the experiment. Its aim is to impose on a working electrode, a cyclic linear potential sweep and to output the resulting current-potential curve. This sweep is described in general by its initial, high, final potentials and scan rate. More complicated sweeps are possible. Repetitive cycles are sometimes used, but in many instances these are not more informative than a single cycle.[7–9]

The simplest technique that uses this wave form is linear sweep voltammetry (LSV). The term LSV is used for a half-cycle CV. The potential range is scanned in one direction, starting at the initial potential and finishing at the final potential.

LSV and CV involve the application of a rapid linear potential sweep, usually 10 to 1000 mVs^{-1}. It is a very useful technique at most solid electrodes because rapid analysis times can be achieved.[2]

The important parameters of a CV scan are the magnitude of the peak current and the peak potential. The peak current can be described by Randles-Sevcik equation:

$$I = 2.69\ n^{3/2}AD^{1/2}C\nu^{1/2}$$

where I: peak current (Amperes), n: electron stoichiometry (equivalent/mol), A: electrode area (cm^2), D: diffusion coefficient (cm^2/sec), C: concentration (mole/cm^3) and ν : scan rate (V/sec).

A redox couple in which both species are stable and rapidly exchange electrons with the working electrode is termed an electrochemically reversible couple. The number of electrons transferred during the electrode reaction for a reversible couple can be determined from the separation between the anodic and cathodic peak potentials at about 0.059 V/n.[2,3,9]

CV and LSV are well suited for analytical studies devoted to the rapid, simple, and accurate determination of drugs in raw materials, pharmaceuticals, or in biological samples. Most publications are related to this analytical aspect by the numerous review articles published in the field.[8–13] CV and LSV with inherent detection limits of about 10^{-6} *M*, are generally not sensitive enough to determine drugs in body fluids

after therapeutic doses. However, LSV remains of great interest, together with CV for the elucidation of electrode process and redox mechanisms. CV and LSV are most suitable to investigate the redox properties of a new drug, and this can give insights into its metabolic fate. Some metabolites can be differentiated from the parent drug because metabolism often proceeds through the addition or the modification of a substituent, and this gives rise to additional waves or to a shift of the main wave.

The CV tracing of the sample (plasma or other body fluids, tissue homogenate, or in pharmaceutical preparations) is constituted of anodic wave(s). The oxidation potential of an anodic wave is characterized by $E_{1/2}$, the potential at half-height of the anodic wave. $E_{1/2}$ is a compound-specific value that correlates with the ability of the specific compound to donate electron(s). The anodic wave is also characterized by its current height (intensity), Ia, which correlates with the concentration of the component.

Examples of CV and LSV determination of organic compounds in pharmaceuticals include many classes of drugs: antibiotics, diuretics, antineoplastics, muscle relaxants, neuroleptics, analgesics, vitamins, hormones, and others. Some analytical data on the CV and LSV determination of organic compounds in pharmaceutical preparations and biological media are listed in Table 1; these are complied from some selected literature sources since 1995. The measurements were carried out using different electrodes.

III. DIFFERENTIAL PULSE VOLTAMMETRY /POLAROGRAPHY

This technique was proposed by Barker and Gardner[98] in order to improve the polarographic performance and to lower the detection limits for electroactive species.

Pulse voltammetry/polarography has been developed from the desire to suppress the charging background current and hence lower the detection limits of the measurements. The basis of all pulse techniques is the difference in the rate of the decay of the charging and the faradaic currents following a potential step or pulse. The charging current decays exponentially, whereas the faradaic current (for a diffusion-controlled current) decays as a function of $1/(\text{time})^{1/2}$ that is, the rate of decay of the charging current is considerably faster than the decay of the faradaic current.

The important parameters for pulse techniques are as follows:

1. Pulse amplitude (this is the height of the potential pulse)
2. Pulse width (this is the duration of the potential pulse)
3. Sample period (this is the time at the end of the pulse during which the current is measured)
4. Pulse period or drop time (It must also be specified for some pulse techniques)

Differential pulse voltammetry/polarography (DPV/DPP) has been extremely useful for low amount determination of electroactive compound in pharmaceuticals, tissues, and biological fluids. In DPV or DPP, fixed-magnitude pulses-superimposed on a linear potential ramp are applied to the working electrode at a time just before the end of the drop. The current shortly before the pulse is applied, and that at the end of the pulse is measured, and the difference between these values as a function of the potential is recorded. The application of these pulses allows for discrimination of the unwanted capacity current from the required faradaic current. Differential pulse curves are peak shaped and thus are well suited to analytical purposes. The limit of detection is about 10^{-8} *M*.[1–5]

Because of these advantages, easily applicability, and the availability of low-coast instruments. DPV/DPP is often the method

TABLE 1
Some Selected Pharmaceutical Compounds Determined by CV and LSV in Pharmaceutical Preparations and Biological Media with References

Compounds	Working electrode	Detection or determination limit	Technique	References
Loprazolam,Flunitrazepam	HMDE	----	CV	14
Loprazolam	CP	$1.5x10^{-7}$ M	CV	15
Imipramine HCl, Amitriptyline HCl	Modified CP	$6x10^{-5}$ M,$1x10^{-5}$ M	CV	16
Imipramine HCl	Pt, GC	$4x10^{-4}$ M, $4x10^{-5}$ M	CV	17
Olanzapine	GC	3 μg/ml	LSV	18
Haloperidol	GC	$8x10^{-5}$ M	CV	19
Clozapine	GC	$2x10^{-6}$ M	CV	20
Fluphenazine HCl	GC,Pt	$2x10^{-5}$ M, $2x10^{-4}$ M	CV	21
Droperidol, Benperidol	GC	$8x10^{-5}$ M, $6x10^{-5}$ M	CV	22
Phenothiazines	GC,Au	0.5 μM	CV	23,24
Zuclopenthixol HCl	GC	----	CV,LSV	25
Inosine	GC	$5x10^{-4}$ M	CV,LSV	26
Cefotaxime	Mercury,GC	$2x10^{-5}$ M	CV	27,28
Enoxacin	HMDE,DME	$4x10^{-9}$ M,$6.25x10^{-9}$ M	LSV	29,30
Ofloxacin	HMDE	$4x10^{-6}$ M	CV	31
Ceftazidime	GC,CP,SMDE	$2x10^{-10}$ M	CV	32
Ceftriaxone	Pt,GC	$2x10^{-5}$ M	CV	33
Cefepime	SMDE	$9x10^{-7}$ M	CV	34
Erythromycin, Oleandomycin Spiramycin	Mercury film	$3x10^{-7}$ M,$3x10^{-7}$ M, $7.5x10^{-8}$ M	CV	35
Salazosulfapyridine	HMDE	0.2 ng/ml	CV	36
Cefadroxil monohydrate	GC	----	CV	37

TABLE 1 (continued)

Nitrofurazone	HMDE	---	LSV	38
Sulfa drugs	GC,Diamond	50 nM	CV	39
Amoxicillin	Modified CP	$8x10^{-6}$ M, $1x10^{-6}$ M	CV	40,41
Lapachol	CP	---	CV	42
Furazolidone	GC	$4x10^{-6}$M	CV	43
Tinidazole	GC	$2x10^{-6}$M	CV	44
Ornidazole	GC	$4x10^{-6}$M	CV	45
Metronidazole	GC	$3x10^{-6}$M	CV	46
Secnidazole	GC	$1x10^{-5}$M	CV	47
Ketoconazole	Pt, Au, GC	$1x10^{-6}$M	CV	48
Nifuroxazide	CP, Modified CP	$5x10^{-6}$M	CV	49
Anthtamycin	DME	70 nM	CV	50
Platinum compounds	modified wax-impregnated graphite	----	CV	51
Adriamycin	Modified GC	$2.7x10^{-7}$M, $5x10^{-8}$M	CV	52-54
Mitoxantrone	Modified CP, GC, Mercury	$4.2x10^{-8}$M, $3.5x10^{-7}$M, $1x10^{-7}$M	LSV,CV	55-57
Nogalamycin	GC	0.993 $\mu g.ml^{-1}$	CV	58
Pharmorubicin	GC	1.2 $\mu g.ml^{-1}$	CV	59
Imidazoacridinone derivatives	GC,Pt,Au	----	CV	60
Tenoxicam	CP	0.14 ppm	CV	61
Diazepam	GC	---	CV	62
Nimesulide	HMDE	---	CV	63
Tetracaine	GC	$5x10^{-4}$ M	CV	64
CBS-113A	GC	---	CV	65
Buprenorphine	CP	$2x10^{-7}$ M	CV	66

TABLE 1 (continued)

Acetaminophen	CP	$3x10^{-6}$ M	LSV	67
Aceclofenac	Modified CP	---	CV	68
Ketorolac	HMDE	$4x10^{-6}$ M	CV	69
Etodolac	GC	---	CV,LSV	70
Naltroxene	CP	$7x10^{-6}$ M	CV,LSV	71
Riboflavin	GC	0.1 μM	CV	72
Ascorbic acid	GC, rotating GC	$5x10^{-5}$ M	CV	73
Loratadine	HMDE	---	CV	74
Flunarizine	GC	$6x10^{-6}$ M	CV	75
Clenbuterol	modified CP	---	CV	76
Salbutamol	Pt,GC	$2x10^{-5}$ M	CV	77
Terbutaline	GC	$8x10^{-6}$ M	CV	78
Triamterene	DME	---	CV	79
Epinephrine	Carbon fiber, Gold ultramicro	7.8 ng/ml	CV	80,81
Adenosine	Carbon fiber ultra micro	---	CV	82
Isradipine	Optically transparent thin layer electrode of carbon cloth	0.5 ng/ml	CV	83
Nisoldipine	GC,CP,Pt,HMDE	$2.5x10^{-6}$ M	CV	84
Nifedipine	GC	$2x10^{-5}$ M	CV	85
L-Dopa	GC	$2x10^{-4}$ M	CV	86
Dopamine	Modified GC	$5x10^{-6}$ M	CV	87

TABLE 1 (continued)

Tyrptophan	Graphite-methacrylate composite electrode	---	CV	88
Serotonin	Nafion coated GC	2 nM	CV	89
Tyrosine, tryptophan	Graphite-methacrylate composite electrode	---	CV	90
5-hydroxydole-3-acetic acid	GC	80 nM	CV	91
Estradiol valerate	SMDE	$1.1x10^{-8}$ M	CV,LSV	92
Melatonin	CP	$2.3x10^{-6}$ M	CV	93,94
Dipyridamole	Pt,Pd,Au,carbon fiber	---	CV	95
Irganox 1076	GC	---	CV	96
Tocopherol	Pt	---	LSV	97

of choice for analysis of pharmaceutical formulation and body fluids. Numerous applications on pharmaceuticals and biological samples are shown in Table 2.

IV. SQUARE WAVE VOLTAMMETRY/ POLAROGRAPHY

Square wave voltammetry/polarography (SWV/SWP) is a large amplitude differential technique in which a waveform composed of a symmetrical square wave, superimposed on a staircase, is applied to the working electrode. The waveform is a direct analog to sinusoidal ac voltammetry with a symmetric square wave of frequency and amplitude riding on either a ramp or slow staircase waveform. Multiple cycles of the square wave are applied for each drop of the DME or step of the staircase. The current is sampled twice during each square-wave cycle, once at the end of the forward pulse, and once at the end of the reverse pulse. The difference between the two measurements is plotted vs. the staircase potential. The resulting peak-shaped voltammogram displays excellent sensitivity and effective discrimination against background contributions. This signal possesses good faradaic to double-layer signal characteristics for reasons analogous to those discussed for DPV or DPP. In addition, SWV/SWP is also more sensitive even than DPV/DPP; this is because both forward and reverse currents are measured in the former, but only the forward currents are measured in the latter.

The major advantage of SWV/SWP is its speed. Frequencies of 1 to 100 square wave cycles per second permit the use of extremely fast potential scan rates. The analysis time is reduced; a complete voltammogram (or polarogram) can be recorded within a few seconds, when compared with about 3 min in DPV/DPP.

TABLE 2
Some Selected Pharmaceutical Compounds Determined by DPV/DPP in Pharmaceutical Formulations and Biological Fluids

Compounds	Working electrode	Detection or determination limit	References
Diazepam	SMDE	15 $\mu g.L^{-1}$	99
Trazodone	Rotating Pt	$1.7x10^{-6}$ M	100
Mefexamide	GC	0.8 $\mu g.ml^{-1}$	101
Imipramine,		$2x10^{-8}$ M,	
Trimipramine,	Modified CP	$2x10^{-8}$ M,	102
Thioridazine		$7x10^{-9}$ M	
Zuclopenthixol HCl	GC	$2.2x10^{-7}$ M	25
Roxarsone	Modified CP	0.1 $\mu mol .L^{-1}$	103
Ofloxacin	DME	$3x10^{-7}$ M	104,105
Ceftazidime,			
Ceftizoxime,	DME	$2.4x10^{-8}$ M	106
Ceftriaxone			
Ceftazidime	HMDE,DME	1$\mu g.ml^{-1}$	107
Cefadroxil monohydrate	GC	$8x10^{-6}$ M	37
Teicoplanin	DME	$7.1x10^{-7}$ M	108
Ceftamet-Na	DME,SMDE	$8x10^{-7}$ M	109
Enrofloxacin,		$1x10^{-7}$ M,	
Sparfloxacin,	DME	$1x10^{-7}$ M,	110
Fleroxacin		$2x10^{-7}$ M	
Secnidazol	DME	---	111
Tinidazol	HMDE	0.03 $\mu g.ml^{-1}$	112
Benznidazole	DME	$4x10^{-7}$ M	113

TABLE 2 (continued)

N,N'-dinitrosopiperazine	DME	$5x10^{-7}$ M	114
Azaribine	HMDE,DME	0.2 μM	115
Mitoxantrone	GC	$1x10^{-7}$ M	56
Etodolac	GC	$6.8x10^{-7}$ M	70
Tenoxicam	SMDE	25 $ng.ml^{-1}$	116, 117
Clonixin	GC,DME	$2.8x10^{-6}$ M	118
Diflunisal	SMDE	50 $\mu g.ml^{-1}$	119
Ketorolac	HMDE,DME,GC	$4.04 x10^{-6}$ M	69, 120
Meloxicam	DME	$1x10^{-5}$ M	121
Fenoterol	DME	$2.6x10^{-8}$ M	122
Isoxsuprine		$6x10^{-8}$ M	
Formoterol	GC	$3.54x10^{-7}$ M	123
Clenbuterol	Modified CP	$1.02x10^{-9}$ M	124
Amiloride, Hydrochlorothiazide	DME	---	125
Doxazosin	DME	$2x10^{-5}$ M, 8 $\mu g.ml^{-1}$	126, 127, 128
Prazosin	Modified CP, DME	$3.1x10^{-11}$ M	129,130
Nicardipine	DME	$1.01x10^{-4}$ M	131
Nisoldipine	DME	$2x10^{-5}$ M	132
Atenolol, Propranolol	DME	$5x10^{-8}$ M, $3x10^{-8}$ M	133
Ramipril	DME, Pt	$4.8x10^{-8}$ M	134
Nicergolide	CP	$5x10^{-8}$ M	135
Furosemide, Piretanide	GC	$1.38x10^{-7}$ M, $1.51x10^{-7}$ M	136
Indapamide	CP,GC	$9.87x10^{-8}$ M	137
Omeprazole	DME	----	138
Lansoprazole	SMDE	0.03 $\mu g.ml^{-1}$	139
Olsalazine-Na	GC	$5.75x10^{-7}$ M	140
Nizatidine	DME	$2x10^{-7}$ M	141

TABLE 2 (continued)

Tacrine	DME,HMDE,GC	$4.8x10^{-6}$ M	142
Tacrine, 1-Hydroxytacrine	CP	0.06 $\mu g.ml^{-1}$, 0.08 $\mu g.ml^{-1}$	143
Pravastatin-Na	DME	$8x10^{-5}$ M	144
Ethamivan	GC,Pt	4 $\mu g.ml^{-1}$	145
Cisatracurium	CP	0.38 $\mu g.ml^{-1}$	146
Loratadine	HMDE	$1x10^{-7}$ M	74
Clenbuterol	Modified CP	$5x10^{-9}$ M	76
Tocopherols	Pt	$2x10^{-8}$ M	97

SWV/SWP is a complex but powerful technique that requires the power and flexibility of the mini-computer for its development and modern microprocessors for its commercial implementation.[1–5,9,147] Microprocessors have been used to compensate for the practical problem of solution resistance, and recently menu-selectable software has been incorporated in a stand-alone instrument that allows background substraction and signal differentiation. Simplex optimization to maximize peak current by varying the waveform parameters has been examined and SWV has also been used in thin layers.

Various applications on pharmaceuticals and biological samples are illustrated in Table 3.

V. STRIPPING VOLTAMMETRY/ POLAROGRAPHY

The quantitation of trace and ultra-trace compounds in sample of environmental, clinical, or pharmaceutical formulations represents an important task of modern analytical chemistry. In the analysis of such dilute samples, it is often necessary to employ some type of preconcentration step prior to the actual quantitation. This happens when the analyte concentration is below the detection limit of the instrumental technique applied. Stripping voltammetry/polarography (SV/SP) is the best known analytical method that incorporates an electrolytic preconcentration step.[1,2,4,5]

The stripping techniques can boast the following advantages:

- Low detection limit
- Low determination limit
- High sensitivity
- Wide spectrum of the test material and analytes
- Relative simplicity, rapidity and low cost of equipment
- Insignificant effect of the matrix (in certain instances)

SV/SP involves two separate steps. Initially there is a preconcentration step to accumulate the analyte into, or onto, the working electrode, which is then electrochemically stripped back into solution in the current measurement step. During the preconcentration step, at a deposition potential, the solution is usually stirred, and this is discontinued before scanning. This is followed by the stripping step (the measurement step) that involves the stripping (dissolution) of the deposit.[1,2,4,5,160–164]

TABLE 3
Some Selected Pharmaceuticals Determined by SWV/SWP in Pharmaceutical Formulations and Biological Fluids

Compounds	Working electrode	Detection or determination limit	References
Fluvoxamine	HMDE	$2x10^{-8}$ M	148
Venlafaxine	HMDE	0.124 $mg.ml^{-1}$	149
Caffeine, Acetaminophen	GC, Modified GC	2.2μM, 1.2 μM	150
Etodolac	GC	$1.1x10^{-6}$ M	70
Sulphamethoxypyridazine Trimethoprim	HMDE	---	151
5-Fluorouracil	SMDE	---	152
Carbovir	Pt micro electrode	$6x10^{-5}$ M	153
Sildenafil citrate	HMDE	$1x10^{-8}$ M	154
Ascorbic acid	rotating GC	$3x10^{-6}$ M	155
Ephedrine	Modified CP	---	156
Doxazosine	Modified CP	$0.5x10^{-6}$ M	157
Timolol	HMDE	$2.5x10^{-8}$M	158
Arbutin	clay-coated screen-printed electrode	0.18 μM	159
Formoterol	GC	$4.04x10^{-7}$ M	123

In the stripping step, the accumulated material is oxidized or reduced back into the solution. The response, recorded during this step, is proportional to the concentration of the analyte in or on the electrode, and thus in the sample solution. There are different type of SV/SP analysis, each dependent on the nature of its preconcentration and stripping steps.

When the potential is held at a negative potential followed by scanning in a positive direction, the technique is known as anodic stripping voltammetry/polarography (ASV/ASP). ASV/ASP is the most widely used form of stripping voltammtery. Following the preselected time of the deposition step, the potential is scanned anodically, linearly, or in a more sensitive potential-time wave form (differential pulse, square wave, linear sweep, staircase, alterning current). The resulting peak current depends on various parameters of the deposition and stripping steps as well as on the characteristics of the metal ion (diffusion coefficient, number of electrons) and the electrode geometry.

When the potential is held at a positive value followed by scanning in a negative direction, this technique is cathodic stripping voltammetry/polarography (CSV/CSP); CSV/CSP involves anodic deposition of an insoluble film of material on the electrode; subsequently, it is stripped off during a negative-going potential sweep CSV/CSP is the mirror image of ASV/ASP.[1,4]

When the preconcentration step is adsorption, the technique is adsorptive stripping voltammetry/polarography (AdSV/AdSP). In electrochemistry adsorption means the attachment of molecules or ions to the surface of the electrode. The voltammetric response is directly related to the amount of the adsorbate on the electrode surface; hence, for quantitative purposes it is important to relate the surface and bulk concentration of the analyte. The working electrodes used are fundamentally of two types: mercury (HMDE, SMDE, DME) or inert solid electrodes (CP, GC, Au, Pt, etc.). The solid electrodes are especially suitable for studying adsorbable substances that can be oxidized at the electrode, because they can be polarized to much more positive potential than a mercury electrode that, on the other hand, can be used in a wider negative potential range. Thus, this is preferable for studying reducible substances.

To achieve maximum sensitivity with the AdSV/AdSP method, optimum conditions for maximum adsorption should be utilized during the accumulation step. So, the measured peak height depends on many variables, such as type of electrode material, accumulation time, accumulation potential, solvent, surface properties of the compound, electrode area, ionic strength, pH, temperature, waveform of the scan (linear scan, differential pulse, square wave, etc.). AdSV/AdSP is a well-established and fast-growing area with a number of possible applications in clinical chemistry and laboratory medicine.

The other attractive version of stripping analysis is potentiometric stripping voltammetry/polarography (PSV/PSP). The preconcentration step in PSV/PSP is the same as for ASV/ASP, that is, the metal is electrolytically deposited (via reduction) onto the electrode. The stripping, however, is done by chemical oxidation in the solution. The potential of the electrode, when monitored as a function of time, gives an experimental curve, analogous to a normal redox titration curve that contains the qualitative and quantitative information. A sudden change in the potential occurs when all the metal deposited in the electrode has been depleted from the surface.

SV/SP technique is well-established and fast-growing area with a number of possible applications in the analysis of pharmaceutical and biological compounds. Table 4 lists the selected pharmaceutical and biological compounds that can be determined using stripping techniques together with ranges of their respective detection or determination limits.

VI. CONCLUSION

Electrochemistry is a well-established and fast-growing area with a number of possible applications in the pharmaceutical field. The improvement of quality of life has stimulated considerable research in drug design bioavailability and safety. Thus, in order to achieve these targets, highly sensitive and specific methods of analysis are necessary. The main advantage of modern voltammetric and polarographic methods is their high sensitivity, wide concentration range from 10^{-3} to 10^{-11} *M*, applicability to organic chemical pharmaceuticals, and last but not least the low-cost equipment that enables building extensive networks of analytical laboratories required for large-scale monitoring.

They are a rapid technique that has been applied successfully for trace measurements of important pharmaceutical compounds thanks to the high sensitivity and selectivity that it provides. It should be stressed that

TABLE 4
Determination of Some Selected Pharmaceutical Compounds Using by SV/SP Techniques in Pharmaceutical Formulations and Biological Fluids

Compounds	Working electrode	Detection or determination limit	Stripping Technique	References
Fluvoxamine	HMDE	$5x10^{-9}M$	AdS Square Wave	148
Fluoxetine	HMDE	$3.9x10^{-9}M$	AdS Square Wave	165
Sulpiride	SMDE	$2x10^{-10}M$	Adsorptive Linear Sweep Cathodic Stripping	166
Norfloxacin	GC	1.1 $\mu g.ml^{-1}$	AdS Square Wave	167
Fleroxacin	SMDE	$3x10^{-9}M$	Differential Pulse Cathodic Stripping	168
Rufloxacin	HMDE,DME	$9.2x10^{-9}M$	AdS	169
Nifuroxazide	HMDE,CP	10 $ng.ml^{-1}$, $5x10^{-9}M$	AdS	170,171
Lumazine	HMDE	$9x10^{-10}$ M	AdS Alternating Current	172
Phenazopyridine	HMDE	0.0299 $ng.ml^{-1}$	AdS Diffrential Pulse	173
Furazolidone	HMDE	$2x10^{-9}M$	Adsorptive Cathodic Stripping	174
Furaltodone		$1x10^{-9}M$		
Mitomycin C	HMDE	$1x10^{-8}M$	AdS	175
Ceftazidime	HMDE	$1.6x10^{-10}M$	Differential Pulse Cathodic Stripping	176
Erythromycin	GC	$5x10^{-9}M$	Second Order Differential Anodic Stripping	177
Nitrofurazone	HMDE	$1x10^{-9}M$	Cathodic Stripping	38
Cefaclor	HMDE	2.9 $ng.ml^{-1}$	Cathodic Stripping	178
Aztreonam	DME,SMDE,GC, CP, Modified CP	$2x10^{-8}M$	Differential Pulse Stripping	179
Ceftazidime	HMDE	$1x10^{-10}$ M	Cathodic Stripping	180

TABLE 4 (continued)

Cefotaxime	Silver microdisc	$1x10^{-7}$M	Differential Pulse Cathodic Stripping	181
Rifamycin SV	HMDE	$3.1x10^{-8}$M	Differential Pulse Adsorptive Stripping	182
		$1.23x10^{-8}$M	Square Wave Adsorptive Stripping	
Terbinafine	HMDE	$1.7x10^{-10}$M	AdS Square Wave	183
		$6.3x10^{-7}$M	AdS Differential Pulse	
Secnidazol	HMDE	$5x10^{-9}$M	Differential Pulse Cathodic Stripping	184
Mebendazole	HMDE	$3x10^{-11}$M	Cathodic Stripping	185
Albendazole	HMDE	$1x10^{-8}$ M	Differential Pulse Adsorptive Cathodic Stripping	186
Bleomycin	HMDE	$5x10^{-10}$ M	AdS	187
5-Fluorouracil	HMDE	$7.7x10^{-12}$ M	AdS Square Wave	152
5-Fluorouracil	SMDE	$4.6x10^{-10}$ M	Cathodic Stripping	188
Tamoxifen	GC	$4x10^{-10}$ M	Adsorptive Potentiometric Stripping	189
Paclitaxel	HMDE	$5x10^{-9}$ M	AdS	190
Mitoxantrone	Mercury Coated Carbon Fiber	$1.5x10^{-10}$ M	Differential Stripping	191
		10 nM	Cathodic Stripping	
Indomethacin	HMDE	0.5 μM	Differential Pulse Stripping	192
Indomethacin Acemethacin	HMDE	10^{-9}M	Differential Pulse Adsorptive Stripping	193
Flufenamic acid	HMDE	1.02 $ng.ml^{-1}$	Differential Pulse Stripping	194

TABLE 4 (continued)

Buprenorphine	CP	$2x10^{-8}$ M	AdS	195
Nimesulide	HMDE	$1.33x10^{-9}$ M	AdS	196
Ketorolac	HMDE	$1x10^{-11}$ M	AdS Square Wave	197
Methohexital –Na	HMDE	$2x10^{-7}$ M	Anodic AdS	198
Thiopentone-Na	HMDE	$2x10^{-9}$ M	Cathodic Stripping	199
Vitamin B_2	Activated GC	0.1 μM	AdS	200
Vitamin B_1	DME	$1x10^{-9}$ M	Linear Sweep Anodic AdS	201
Nicardipine	HMDE	$2.08x10^{-10}$ M	AdS	202
Indapamide	Modified CP	$5x10^{-9}$ M	Anodic Stripping Differential Pulse	203
Niguldipine	HMDE	6.7 $ng.ml^{-1}$	Differential Pulse Adsorptive Stripping	204
Doxazosin	Modified CP	$4.35x10^{-11}$ M	AdS Differential Pulse	205
		$5.18x10^{-11}$ M	AdS Square Wave	
Doxazosin	HMDE	$6.4x10^{-10}$ M	AdS Square Wave	206
		$2.2x10^{-11}$ M	AdS Differential Pulse	
Doxazosin	CP	$7.4x10^{-10}$ M	AdS Differential Pulse	207
		$7.7x10^{-10}$ M	AdS Square Wave	
Prazosin	Modified CP	$3.2x10^{-10}$ M	Anodic Stripping	208
Dipyridamole	Modified GC	$8x10^{-11}$ M	Anodic Stripping	209
Timolol	HMDE	$6.6x10^{-10}$ M	AdS Square Wave	158
Melatonin	CP	$1.5x10^{-7}$ M	Differential Pulse Stripping	210
Omeprazole	HMDE	$6.5x10^{-9}$ M	AdS	211
Nizatidine	HMDE	$3.0x10^{-8}$M	Cathodic AdS	212
Cisapride	SMDE	$8.4x10^{-10}$ M	AdS	213
Cinitapride		$1.8x10^{-7}$ M		

TABLE 4 (continued)

Creatine	HMDE	$6.6x10^{-8}$ M	AdS Square Wave	214
Erythropoietin	HMDE	$0.017\mu g.L^{-1}$	Cathodic Stripping Square Wave	215
Hypoxanthine	HMDE	$1x10^{-8}$ M	AdS	216
Sildenafil citrate	HMDE	$5x10^{-9}$ M	AdS Square Wave	154
Flaxedil	HMDE	$3x10^{-9}$ M	Cathodic AdS	217
Salmon calcitonin	HMDE	0.5 nM	AdS Square Wave	218
Mazindol	HMDE	$4x10^{-9}$ M	AdS	219
Phenylephrine	Modified CP	$2x10^{-6}$ M	Anodic Stripping	220
Metoclopramide	Modified GC	$8x10^{-11}$ M	Anodic Stripping	221
Nucleic acids (tRNA , ssDNA dsDNA)	HMDE	$30\ \mu g.L^{-1}$ $60\ \mu g.L^{-1}$ $2\ \mu g.L^{-1}$	Potentiometric Stripping	222

they present an independent alternative to separation and spectrometric techniques that can be used for the validation of results obtained by other techniques, and that their relationship to other methods is complimentary rather the competitive. On the other hand, it is hoped that more attention is paid to developing teaching programs dealing with modern electroanalysis, with the emphasis on instrumental design, and such as electrode shape and design. Furthermore, the voltammetric techniques are also useful for comparison purposes and for accuracy control in the context of a quality assurance system.

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