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Review

Voltammetric analysis of drugs

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Abstract

A review on the voltammetric analysis of drugs is presented. The review includes a summary of the rules that must be considered for drug analysis and a survey of the use of voltammetry for drug analysis in the period from 1998 till 2002.

Keywords: Drug management; Drug analysis; Voltammetry

1. Introduction

Drug analysis is undertaken during various phases of pharmaceutical development [1], such as formulation and stability studies, quality control (QC) and toxicology and pharmacological testing in animals and man [2,3]. In hospitals, drug analysis is performed on patients samples in support of clinical trials, i.e. bioavailability and pharmacokinetic studies and in monitoring therapeutic drugs and drugs abuse [4–8].

All these investigations require reliable and validated analytical methods in order to measure drugs in complex media such as formulation and biofluids.

1.1. Drug management

1.1.1. Quality management in drug analysis

Quality management in drug analysis covers a wide range of quality improving activities designed to ensure the reliability of the analytical data. These activities include ensuring that the samples are properly collected and preserved prior to analysis, that the analysis is carried out using the appropriate techniques and that the results are properly recorded and reported. The aim of this review is to focus on the voltammetric analysis of drugs. Before applying the technique for analysis, guidelines on the quality management aspects of routine quality control (QC) work should be available [9]. This section is especially aimed at young workers and laboratory managers wishing to introduce quality management systems into their laboratories.

1.1.2. Validation

Once the analytical method has been developed, it has to be validated before or during its use. Validation of the method establishes that its performance characteristics are adequate for the intended use. It builds quality and reliability into the method. In the pharmaceutical industry, validation of analytical methods is required in support of product registration application [10].

Validation is performed by conducting a series of experiments using the specific conditions of the method and the same type of matrix as the intended samples. The definitions and procedures used to calculate the parameters concerning the linearity range, recovery, etc., are adequately described in many publications related to pharmaceutical [10–20] and biomedical [21–28] analysis.

The International Conference on Harmonisation (ICH) has produced guidelines [29] on the validating of analytical procedures for pharmaceutical product registration applications.

Validation does not imply that the method is free from errors. It only confirms that it is suitable for the purpose [30]. Any modification of a method during its use requires its revalidation. For example, if a new instrument or a different type of electrode, etc., is brought into use, or the method is applied to a different type of sample, it will require revalidation. Some revalidation may also be required when transferring the method between laboratories or when changes are made in the manufacturing process for the drug. Other factors, which can be considered when validating a

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method are the cost per analysis, the lake of difficulty, the rate of the operations and the potential for their automation.

Once the method has been developed and validated, it is thus fully documented and approved for use. It should be then described in sufficient detail to allow any analyst to use it without difficulty.

Tentative recommendations required for validation in drug electroanalysis [31] are given in Table 1.

1.1.3. Method comparison

The accuracy of a newly developed or modified method can be assessed by comparing the results obtained using it with these obtained using a reference method of known accuracy and precision using a linear regression analysis [32–34]. A reasonable number of samples (10–20) evenly spaced over a concentration range of interest must be analyzed by both the candidate method and the reference method. Results must be plotted as pointed with one axis (usually the abscissa) for the reference method and the other for the candidate method.

Simple linear regression is a widely used statistical approach for assessing systematic and random errors associated with the new method. It involves relatively simple calculations and provides reliable estimates of intercept and slope. However, if an appropriate computer program is available for statistical calculations, it is more appropriate to use weighted linear regression since this compensates for the change in variance across the concentration range.

1.1.4. Solutions, reagents and samples

Standard solutions of drugs in water or methanol must be used during many stages of analysis such as calibration, validation, etc. In bioanalytical work, although stock solutions can be prepared in water or methanol, standard solutions for calibration and other experiments should be prepared by dilution of the stock solutions with a relevant biological fluid. Indeed behaviour of the drug in pure aqueous solutions can greatly differ from the behaviour in the complex biological fluids. Drug and reagent solutions must be stored in such a way as to maintain their integrity. Prior to analysis their stabilities should be tested by comparison with freshly prepared solutions.

Table 1
Tentative recommendations for electroanalysis of drugs

Identification of the electroactivity of the molecule
Identification and study of the degradation product(s)
Identification and study of the metabolite(s)
Selectivity towards structurally related drugs
Influence of the components of the matrix on the EC response
Influence of the side products on the EC response
Comparison with a non-electrochemical method
Calibration curve versus standard addition method
Internal standard (recovery test)
Reproducibilty and repeatability of the response (+blank)
Linearity (range and slope)
Detection limit

In general, solutions of drugs and chemicals are more stable at low temperatures (4 or −20 °C) than at room temperature.

Samples to be analyzed must be handled in accordance with the approved procedures [35], since any deviance to the procedure will be a major contributor to measurement errors. The biofluids most commonly analyzed for drugs and/or metabolites are blood (plasma or serum) and urine. Blood should be centrifuged to retain either the plasma, if an anticoagulant such as heparin is added to the sample, or the serum, if the blood is coagulated. For urine, usually a midstream sample is collected for most analyses. However, in a urinary excretion study, sampling is performed quantitatively, *i.e.* the volume of urine is also measured at such collection. The laboratory in which analysis takes place must have a reliable system for the documentation of the samples, from sample receipt to the disposal of the sample excess.

1.1.5. Analysis

All analyses must be carried out in accordance with written procedures. Assays should preferably be performed in duplicate each time using a separate portion of the sample rather than repeating the determination on the final solutions, e.g. the repeated addition into the cell (in voltammetric analysis) or the repeated injection into the flow injection cell (in the FIA). This gives confidence in results and serves to check on the homogeneity of the sample and the random variation in the instruments response [36].

Quality control and laboratory accreditation are next steps in the quality management [37–45].

Many reviews related to environmental analysis [46], trace metal ions determination [46,47], pharmaceuticals and biomedical analysis [48], chemical sensors for radiopharmaceuticals [49] have been reported in the literature. Application of polarography and/or voltammetry in analysis of drugs has been also reviewed in many citations [31,48,50–53].

The aim of the current review is to survey the voltammetric analysis of drugs, which were published between 1998 and 2002 since many reviews have discussed previous periods. It deals with only the voltammetric analysis of drugs.

2. Instrumentation

Voltammetry can be carried out using commercially available polarographic instruments employing the classical polarographic method (DC polarography) as well as pulse methods (e.g. DPP). Modern voltammetric instruments with automatic timing of the individual operations are useful for controlling the individual steps in AdSV measurements (accumulation time, solution stirring, rest period, initiation of polarization); a computerized instrument is useful for this purpose. Square-wave voltammetry (SWV) has become more widely accessible.

2.1. Electrodes

Voltammetry can be carried out practically at all types of electrodes designed for voltammetry and for which a completely reproducible constant surface area can ensure reproducible results over the whole measuring period or during a series of measurements.

2.2. Types of electrodes used in voltammetry

The working electrode is the electrode at which the reaction of interest occurs. Generally, the working electrode in voltammetry is characterized by its small surface area, which enhances polarization. Another reason for using very small electrodes is to minimize depletion (by electrolysis) of the analyte. The choice of the working electrode is very important for the sensitivity and reproducibility of stripping analysis. Stationary working electrodes used in stripping measurement fall into two large groups, mercury electrodes and inert solid electrodes. There are two types of mercury electrodes that have gained wide acceptance for stripping analysis: the hanging mercury drop electrode (HMDE) or static mercury drop electrode (SMDE) and the mercury-film electrode (MFE). There are several kinds of solid electrodes, e.g. glassy carbon electrode (GCE), graphite electrode, carbon paste electrode (CPE), platinum electrode (Pt), gold electrode, etc.

2.3. Methodology

In drug analysis, adsorptive stripping voltammetry (AdSV) is popular because of the low limit of determination (reaching few ppb concentrations) its accuracy and precision, as well as the low cost of instrumentation relative to other analytical methods of analysis.

Adsorptive stripping voltammetry (AdSV) comprises a variety of electrochemical approaches, having a step of preconcentration onto the electrode surface prior to the voltammetric measurement. The major advantage of SV compared with direct voltammetric measurements is the preconcentration factor [54–57]. For trace analysis of organic compounds, the accumulation of the compound to be determined on the working electrode will be followed by voltammetric oxidation of the accumulated substance (anodic stripping voltammetry, ASV) or by voltammetric reduction (cathodic stripping voltammetry, CSV). The stripping technique can be achieved by using different types of electrodes e.g. hanging mercury drop electrode (HMDE), static mercury drop electrode (SMDE) or the more recent mercury electrode called controlled growth mercury electrode (CGME). This accumulation step can also occur at many other types of solid electrodes, e.g. platinum electrodes, carbon paste electrode (CPE), glassy carbon electrode (GCE), wax-impregnated graphite electrode (WIGE) or the chemically modified electrode (CMCPES). The process at CME is not purely adsorptive accumulation, but also chemisorption through specific reactions at CME under controlled conditions. The applications of CME's to the determination of trace amount of organic analytes have been reviewed [58].

To achieve maximum sensitivity with AdSV 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 materials, accumulation time, accumulation potential, solvent, surface properties of the compound, electrode area, ionic strength, pH and temperature [59,60].

2.4. AdSV at a hanging mercury drop electrode (hmde)

The HMDE is used to study substances that are accumulated by adsorption on the electrode and then reduced during a scan to more negative potentials. The supporting electrolyte is usually a buffer solution, but hydroxide solutions can also often be used. Not only Hg electrodes could be used for the determination of reducible compounds, but also for those that are polarographically inactive [61].

Alternating voltage or DP signals are usually superimposed for the determination of non-reducible compounds. The surface activity of these compounds leads to the formation of characteristic peaks called tensammetric maxima [61] at the adsorption/desorption potential. For this type of analysis, the name "Adsorption Stripping Tensammetry" (AdST) has been proposed [61].

2.5. AdSV at solid electrodes

Both the carbon paste and the platinum electrode are useful for studying substances that are oxidized at the electrode after adsorptive accumulation, during scanning toward positive potential values. The accumulation is carried out either at a set E_{acc} value or with an open circuit. In order to eliminate the effect of accompanying substances in the analyzed sample, accumulation should be carried out by immersing the electrode in a stirred solution for a given t_{acc}, then rinsed, and transferred to the pure base electrolyte in which the actual voltammetric determination is carried out.

Chemically modified electrodes (CME's) correspond to a relatively modern approach to electrode systems that find utility in:

(1) a wide spectrum of basic electrochemical investigations and
(2) the design of electrochemical devices and systems for applications in chemical sensing. Compared to other electrode concepts in electrochemistry, the distinguishing feature of a CME is that a generally quite thin film (from a molecular monolayer to perhaps a few micrometers-thick multiplayer) of a selected chemical is bonded to or coated on the electrode surface to endow the electrode with the chemical, electrochemical, etc.,

Table 2
Voltammetric analysis of drugs

Generic Name	Medium	Method	Working electrode	D.L.	Ref.
(I) Analgesic drugs					
Buprenorphine	–	LSV	CPE	0.2 μM	[69]
Etodolac	BR., pH 2.15	CV, LS, DP, SWV	GCE	68 μM	[70]
Ketodolac	Acetate buffer, pH 5	AdSV, CV	HMDE	0.1 pM	[71]
Phenazopyridine	BR., pH 11	DPV	HMDE	0.099 ng/ml	[72]
(II) Anesthetics					
Cisatracurium	–	CV, DPV	CPE	0.38 μg/ml	[73]
(III) Anti-angenal drugs					
Nifedipine	pH 1.5	LS, CV	GCE	–	[74]
(IV) Anti-asthmatic drugs					
Isoxsuprine, Fenoterol	BR. buffer	DC, DPP, AC	Hg	0.02, 0.01 μg/ml	[75]
(V) Antibacterial drugs					
Sulfadiazine, sulfamerazine, sulfamethazine	–	FIA, HPLC, amperometry, CV	Diamond electrode	50 nM	[76]
(VI) Antibiotics					
Amoxicillin	0.1 M–H_2SO_4	SV	MCPE	–	[77]
Aztreonam	0.03 M acetate buffer, pH 2.0	DPSV, OSWSV	DME, SMDE, GCE, CPE, MCPE	20, 80 nM aqu., urine samples, res	[78]
Ceftazidime	0.1 M H_3PO_4, pH 2.5	CV, DPV, OSWV	SMDE, CGME, GCE, CPE	0.2 nM	[79]
Cephalexin, Ampicillin	–	CV	Four electrode system	–	[80]
Enrofloxacin, Sparfloxacin, Fleroxacin	Britton-Robinson buffer, pH 4–11.98	DC, DPP, AC	Hg electrode	0.1 μM	[81]
Fleroxacin	Britton-Robinson buffer, pH 8.5	DC, DPP, AdSV	HMDE	~ 1 ng/ml	[82]
Ofloxacin	B.R. buffer, pH 4.1–10.3	DC, DPP	Hg-electrode	–	[83]
(VII) Antidepresents, anticycotics, neuroleptics					
(i) Antidepresents					
Fluoxetine	Buffer, H_2O/acetonitrile	SWV, CV, LSV, DPV	HMDE	0.39 nM	[84]
Imipramine, Trimipramine, Thioridazine	–	AdSV	MCPE	Down to 1 nM	[85]
Trazodone	0.2 M KCl, 0.2 M acetate/phosphate buffer	DPV	Pt	2.5 μM	[86]
(ii) Anticycotics					
Chlorpromazine, Promethazine	BR. buffer pH 9	DPSV	GCE	Down to 1mg/ml	[87]
Flunarizine	–	–	GCE	–	[88]
Pimozide	BR. buffer, pH 2.1	DPV	GCE	0.27 nM	[89]
(iii) Neuroleptic					
Zuclopenthixol	Phosphate buffer, pH 5.2	CV, LSV, DPV	GCE	–	[90]
(VIII) Anti-histamines					
Terbutaline	Phosphate buffer, pH 6.0	LSV	GCE	–	[91]
(IX) Antihypertensive drugs					
Doxazosin	PH 6.8	AdSV, SWV	MCPE	0.233 ppm	[92]
Lacidipine	BR buffer, pH 6.0	DPV	GCE	3.52 μM	[93]
(X) Anti-infective, amoebicides					
Metronidazole	BR buffer, pH 10	LSV	GCE	–	[94]
(XI) Anti-inflammatory					
Tenoxicam	Phosphate buffer, pH 5.3	DPV	SMDE	–	[95]
(XII) Cytostatics					
Daunomycin	–	CV	RdE	μg/ml	[96]
Nogalamycin	–	CAdSV	HMDE	ng/ml	[97]

Table 2 (*continued*)

Generic Name	Medium	Method	Working electrode	D.L.	Ref.
(XII) Cytostatics					
Adriamycin		–	CME	–	[98]
Daunomycin	–	CV	–	2.4 μg/ml	[99]
Echinomycin	–	CPSA	HMDE	–	[100]
Echinomycin	–	CV	HMDE	–	[101]
Lumazine	–	DPV, CV	HMDE	–	[102]
Mitomycin	Acid activated MC, pH 3.9	CV	HMDE	–	[103]
Nogalamycin	–	CV, DPV	HMDE	–	[104]
(XIII) Diuretic drugs					
Indapamide	pH 4.0	CV, DPV, ASV	MCPE	5 nM	[105]
(XIV) Neurotransmitters					
Dopamine	–	CV, CA, FIA	Carbon–Fiber micrelectrodes	–	[106]
Dopamine	HEPES, pH 7.4	AdSV	Graphite carbon fibre microelectrode	–	[107]
Dopamine	Physiological buffer, 37 °C	AdSV	Rotating disk GCE	Down to 10 nM	[108]
Dopamine	–	LSV	Au ME	–	[109]
Dopamine	–	–	Rotating disk electrode	–	[110]
(XV) Nutrient supplements					
Histidine	Clark-Lubs buffer, pH 9.6	CV, CC	SMDE	0.12–50 μM	[111]
(XVI) Sympathomimetic and parasympathomimetic drugs					
Catechols	0.3 M, pH 4.0	CV	MCPE	60 nM, 80nM, 40 mM	[112]
(XVII) Tranquilizers					
Benzodiazapines	H_2O-1,2-dichloroethane interface	CV	–	–	[113]
Chlordiazepoxide	0.1M–HCl and 0.5 ml 0.2% SDS	CSV	Mixed binder CPE	0.5 nM	[114]
(XVIII) Vitamins					
Ascorbic Acid	0.15 M-KH_2PO_4, pH 4	Laser ablation Voltammetry	Pt disk	–	[115]
Menadione	Phosphate buffer, pH 11.5	CV	Au or Pt IDA	234 nM	[116]
(XIX) Miscellaneous					
Caffeine	0.05 $MHClO_4$	SWV	CME	2 μM	[117]
Cimetidine (anti-H_2)	0.1 M NaOH	CV, DPV	GCE	Down to 0.3 μg/ml	[118]
Melatonin (hormone)	–	oxidation	CPE, GCE	2.3 μM	[119]

Abbreviations: CPE = carbon paste electrode, MCPE = modified carbon paste electrode, SMDE = static mercury drop electrode, HMDE = hanging mercury drop electrode, DME = dropping mercury electrode, GCE = glassy carbon electrode, CGME = controlled growth mercury electrode, CME = chemically modified electrode, IDA = Au or Pt interdigitated array electrode, SV = stripping voltammetry, Semi DAdV = Semi differential adsorptive voltammetry, AdSV = adsorptive stripping voltammetry, DPSV = differential pulse stripping voltammetry, DCSV = direct current stripping voltammetry, DPV = differential pulse voltammetry, CV = cyclic voltammetry, DPAdSV = differential pulse adsorptive stripping voltammetry, LSV = linear sweep voltammetry, ACSV = alternating current stripping voltammetry, OSWSV = Osteryoung square wave stripping voltammetry, DPCSV = differential pulse cathodic stripping voltammetry, DCP = direct current polarography, CC = chronocoulometry, DPP = differential pulse polarography, OSWV = Osteryoung square wave voltammetry, CSV = cathodic stripping voltammetry, DSV = differential pulse stripping voltammetry, FIA = flow injection analysis, LV = linear sweep voltammetry, SWAdSV = square wave adsorptive stripping voltammetry, ASV = anodic stripping voltammetry, SSP = single sweep polarography, CPSA = chronopotentiometric stripping analysis. BR. = Britton–Robinson buffer.

and other desirable properties of the film in a rational chemically designed manner.

2.6. Terminology and definitions

Chemically modified electrode-(CME)-according to the IUPAC Compendium of Chemical Terminology, is defined as an electrode made of a conducting or semi conducting material that is coated with a selected monomolecular, multimolecular, ionic or polymeric film of a chemical modifier, that by means of faradic (charge transfer) reactions or interfacial potential differences (no net charge transfer) will exhibit chemical, electrochemical, and/or optical property changes in the presence of specific substance.

Electrodes are usually chemically modified by one of four approaches:

(1) Chemisorption–adsorption in which the forces involved is the valence forces of the same kind as these operating in the formation of chemical compounds [62]. The chemical film is strongly and, ideally, irreversibly adsorbed (chemisorbed) onto the electrode surface. This approach usually yields monolayer (or less) coverage.
(2) Covalent bonding-linking agents are used to covalently attach from one to several monomolecular layers of the chemical modifier to the electrode surface.
(3) Polymer film coating-electron conductive and nonconductive polymer films are held on the electrode surface by some combination of chemisorption and low solubility in the contacting solution or by physical anchoring in the porous electrode. The polymer film can be organic, organometallic or inorganic; it can already contain the desired chemical modifier or that chemical can be added to the polymer in a second, functionalizing step. It can contain the equivalent of a few up to many thousands of monomolecular layers of the chemical modifier.
(4) Composite—the chemical modifier is simply mixed with an electrode matrix material, electron-transfer mediator or electrocatalyst, combined with the carbon particles of a carbon paste electrode. Alternatively, intercalation matrices such as certain Langmuir-Blodgett films, zeolites, clays and molecular sieves can be used to contain the modifier.

2.7. AdSV in flowing systems

The combination of the effect of spontaneous adsorption of the analyte with the medium-exchange principle [59] led to the application of AdSV in flowing systems. In this technique, accumulation is carried out during the interval (t_{acc}) when the carrier solution with the injected sample flows through the detector. When the sample plug leaves the detector, the stripping process is started either without interrupting the flow or after stopping the flow.

The detectors used are either mercury film, carbon or carbon paste electrodes, which are often employed for the electrochemical detection in HPLC or an amperometric detector.A higher selectivity is achieved automatically in flowing systems as the electroactive compounds whose faradic responses could interfere in the signal recording are removed from the vicinity of the electrode by the carrier stream during the reduction step. Also, the time interval between the moment when the sample plug leaves the detector and the polarization scan is started ''Washing period''—can be prolonged to several seconds without significant decrease in the current value, this ''Washing period'' further decreases the interferences from other surface-active substances [63]. The flow through AdSV methods has been described for the determination of some drugs (see Table 2).

Flow systems have been described for quantifying by AdSV. A review is given for the principles, key developments and representative applications of small electrodes in flow solutions using voltammetry [64]. The analytical applications of the adsorptive voltammetry of biological molecules, e.g. nucleic acids, proteins have been reviewed [65].

There have also been reviews discussing the instrumentation, interferences and advantages of the applications of AdSV in pharmaceutical analysis [66,67]. The improvement of the quality of drug activity requires efficient research in drug design, i.e. high activity and low dose, bioavailability and safety. The design and application of disposable, screen-printed electrochemical sensors for biomedical, environmental and industrial analyses has been reviewed by Hart et al. [68]. AdSV could be, therefore, used to determine drugs with marked adsorbability on the electrode surface, especially those, which are less polar than the solvent. If the drug contains a group subjected to a faradic process at the electrode, reduction or oxidation occurs during recording of the voltammetric curve. For electroinactive drugs, a tensammetric peak is formed on the curve in the region of desorption of the accumulated drug. Thus, in order to achieve these targets, highly sensitive and specific methods of the drug analysis are always required. Voltammetry is found to fulfill these conditions. As the aim of this review is to list the drugs detectable (and their concentration measurable) using voltammetry, tabulation of these drugs was classified according to their therapeutic categories.

2.8. Survey of drugs investigated by voltammetry

Table 2 lists these drugs using a classification based on their therapeutic categories. The mediums, the method, the working electrode with the achieved detection limits are listed in the table.

In this report, we have attempted to identify and list the drugs, as well as the rules that should be considered for drug analysis. The report concerns with the use of voltammetry—as a precise, accurate and low cost technique—for drug analysis with more than 119 references covering the period from 1998 till 2002.

The decline in the number of papers cited in this table in the period from 2000–2002 may be attributed to the fact that voltammetry is now directed to the DNA biosensors for environmental monitoring and control.

References

[1] J.C. Berridge, Pharmaceutical analysis in a multidisciplinary development environment, J. Pharm. Pharmacol. 45 (1993) 361.
[2] J. Chamberlain, The Analysis of Drugs in Biological Fluids, 2nd ed., CRC Press, Boca Raton, FL, 1995.

[3] R.C. Baselt, R.H. Cravey, Disposition of toxic drugs and chemicals in man, 4th ed., Chemical Toxicology Institute, Foster City, CA, USA, 1995.
[4] R.C. Baselt, Analytical Procedures for Therapeutic Drug Monitoring and Emergency Toxicology, 2nd ed., PSG, Littleton, MA, USA, 1987.
[5] A.C. Mehta, Analytical issues in the chemical stability testing of drugs in solution, Anal. Proc. 32 (1995) 347.
[6] C.K. Lai, T. Lee, K.M. Au, A.Y.W. Chan, Uniform solid-phase extraction procedure for toxicological drug screening in serum and urine by HPLC with photodiode array detection, Clin. Chem. 43 (1997) 312.
[7] A. Cringauz, Introduction To Medical Chemistry, How Drugs Act and Why, Wiley-VCH, New York, 1997.
[8] Ruth, R.L., Carol, T.W., Rochelle, D.S., Pharmacology, Drug Actions and Reactions, Fifth ed. The Parthenon Publishing Group, International Publishers in Medicine, Science and Technology, 1996.
[9] G.J. Sewell, Hospital pharmacy quality control services, J. Clin. Pharm. Ther. 20 (1995) 149.
[10] M.E. Swartz, I.S. Krull, Analytical Method Development and Validation, Mercel Dekker, New York, 1997.
[11] G.P. Carr, J.C. Wahlich, Practical approach to method validation in pharmaceutical analysis, J. Pharm. Biomed. Anal. 8 (1990) 613.
[12] P.A.D. Edwardson, G. Bhaskar, J.E. Fairbrother, Method validation in pharmaceutical analysis, J. Pharm. Biomed. Anal. 8 (1990) 929.
[13] J.M. Green, What is this thing called ‘‘control’’? Birth 26 (1) (1999) 51–52.
[14] T.D. Wilson, Liquid chromatographic methods validation for pharmaceutical products, J. Pharm. Biomed. Anal. 8 (1990) 389.
[15] D.R. Jenke, Development and validation of an ion-exclusion chromatographic method for the quantitation of organic acids in complex pharmaceutical products, J. Chromatogr. Sci. 36 (4) (1998) 179–186.
[16] D.R. Jenke, Chromatographic method validation: a review of current practices and procedure: I. Ruggedness, revalidation and system suitability, J. Liq. Chromatogr. Relat. Technol. 19 (1996) 737.
[17] D.R. Jenke, Chromatographic method validation: a review of current practices and procedure: II. Ruggedness, revalidation and system suitability, J. Liq. Chromatogr. Relat. Technol. 19 (1996) pp. 1873.
[18] A.C. Mehta, The validation criteria for analytical methods used in pharmacy practice research, J. Clin. Pharm. Ther. 14 (6) (1989) 465–473.
[19] I. Molnar, Computerized design of separation strategies by reversed-phase liquid chromatography: development of Dry Lab Software, J. Chromatogr., A 965 (1–2) (2002) 175.
[20] L. Lugosi, I. MolnarI, Statistically validated evaluation of clinical trials, Orv. Hetil. 140 (41) (1999) 2303–2307.
[21] Analytical method validation: bioavailability, bioequivalence, and pharmacokinetic studies, Conference report, J. Pharm. Sci. 81 (1992) 309.
[22] A.R. Buick, M.V. Doig, S.C. Jeal, G.S. Land, R.D. McDowall, Method validation in the bioanalytical laboratory, J. Pharm. Biomed. Anal. 8 (1990) 629.
[23] L.J. Phillips, J. Alexander, H.M. Hill, in: E. Reid, I.D. Wilson (Eds.), Analysis for Drugs and Metabolites Including Anti-Infective Agents, Royal Society of Chemistry, Cambridge, 1990, pp. 23–36.
[24] R.J.N. Tanner, in: E. Reid, I.D. Wilson (Eds.), Analysis for Drugs and Metabolites Including Anti-infective Agents, Royal Society of Chemistry, Cambridge, 1990, pp. 57–63.
[25] A.C. Mehta, Drug determination in biological fluids—approaches to method validation, Talanta 34 (1987) 609.
[26] J.R. Lang, S.A. Bolton, Comprehensive method validation strategy for bioanalytical applications in the pharmaceutical industry: 1. Experimental considerations, J. Pharm. Biomed. Anal. 9 (5) (1991) 357–361.
[27] J.R. Lang, S.A. Bolton, Comprehensive method validation strategy for bioanalytical applications in the pharmaceutical industry: 2. Statistical analyses, J. Pharm. Biomed. Anal. 9 (4) (1991) 35–42.
[28] D. Dadger, P.E. Burnen, Issues in evaluation of bioanalytical method selectivity and drug stability, J. Pharm. Biomed. Anal. 14 (1995) 23–31.
[29] International Conference on Harmonisation (ICH): Validation of Analytical Procedures. Note for Guidance. Commission of the European Communities, Brussels, 1995.
[30] A.C. Mehta, Quality management in drug analysis, Analyst 122 (1997) 83R–88R.
[31] J.-M. Kauffmann, J.-C. Vire, Pharmaceutical and biomedical applications of electroanalysis, Anal. Chim. Acta 273 (1993) 329.
[32] J.N. Miller, Basic statistical methods for analytical chemistry: Part 2. Calibration and regression mettreds, Analyst 116 (1991) 3.
[33] J.C. Miller, J.N. Miller, Statistics for Analytical Chemistry, 2nd ed., Ellis Horwood, Chichester, 1988.
[34] M.T. Gilbert, I. Barinov-Colligon, J.R. Miksic, Cross-validation of bioanalytical methods between laboratories, J. Pharm. Biomed. Anal. 13 (4–5) (1995) 385.
[35] R.D. McDowall, Sample preparation for biomedical analysis, J. Chromatogr. 492 (3) (1989) 58.
[36] N.T. Crosby, Review of current and future analytical methods for the determination of mycotoxins, Food Addit. Contam. 1 (1984) 39.
[37] A.G. Causey, H.M. Hill, L.J. Phillips, Evaluation of criteria for the acceptance of bioanalytical data, J. Pharm. Biomed. Anal. 8 (1990) 625.
[38] M.D. Erlo Roth, The Line on Laboratory Accreditation South of the Border, Laboratory Accreditation Newsletter, June 2001, Originally published in *CAP TODAY.*
[39] E. Mullins, Introduction to control charts in the analtical laboratory, Analyst 119 (3) (1994) 369.
[40] D. Burnett, J. Williams, in: A.C. Moffat (Ed.), Clarke’s Isolation and Identification of Drugs, 2nd ed., Pharmaceutical Press, London, 1986, pp. 118–127.
[41] L.M. Tsanaclis, J.F. Wilson, Intra- and interlaboratory sources of imprecision in drug measurements by different techniques, Clin. Chem. 39 (5) (1993) 851.
[42] L.M. Tsanaclis, J.F. Wilson, Comparison by external quality assessment of performance of analytical systems for measurement of therapeutic drugs in serum, Ther. Drug Monit. 19 (4) (1997) 420.
[43] J.F. Wilson, L.M. Tsanaclis, K. Barnett, External quality assessment of Syva Emit and Abbott TDx II assays for methotrexate in serum, Ther. Drug Monit. 18 (6) (1996) 721.
[44] K. Davies, D. Burnett, Quality and accreditation in clinical chemistry laboratories analysis in the national health service, Analyst 122 (3) (1997) 297.
[45] E.J. Newman, Quality in the Analytical Laboratory, Wiley, Chichester, 1995.
[46] P.M. Bersier, J. Howell, J.C. Bruntlett, Advanced electroanalytical techniques versus atomic absorption spoctrometry, inductively coupled plasma atomic emission spectrometry and inductively coupled plasms mass spectrometry in environmental analysis, Analyst 119 (2) (1994) 219.
[47] R. Kalvoda, Review of adsorptive stripping voltammetry-assessment and prospects, Fresenius J. Anal. Chem. 349 (1994) 565.
[48] A.Z. Abu Zuhri, W. Voelter, Applications of adsorptive stripping voltammetry for the trace analysis of metals, pharmaceuticals and biomolecules, Fresenius J. Anal. Chem. 1 (1998) 360.
[49] W.R. Heineman, Biosensors based on polymer networks formed by gamma irradiation crosslinlcing, Appl. Biochem. Biotechnol. 41 (1993) 87.
[50] G.J. Patriarche, J.-C. Vire, Applications of polarography and voltammetry in analysis for drugs, Anal. Chim. Acta 196 (1987) 193.
[51] L.G. Chatten, Recent applications of electrochemical techniques to the analysis of pharmaceuticals, J. Pharm. Biomed. Anal. 1 (4) (1983) 491.

[52] W.F. Smyth, A.D. Woolfson, Drug assays—the role of modern voltammetric techniques, J. Clin. Pharm. Ther. 12 (1987) 117.
[53] P.M. Bersier, J. Bersier, Polarographic adsorption analysis and tensammetry: toys or tools for day-to-day routine analysis? Analyst 113 (1988) 3.
[54] Z. Galus, Fundamentals of Electrochemical Analysis, second ed., Polish Scientific PWN, Warsaw, 1994.
[55] J. Wang, B.A. Freiha, Selective voltammetric detection based on adsorptive preconcentration for flow injection analysis, Anal. Chem. 55 (1983) 1285.
[56] L.N. Rodringues, M.V. Zanoni, A.G. Fogg, Indirect polarographic and cathodic stripping voltammetric determination of cefaclor as an alkaline degradation product, J. Pharm. Biomed. Anal. 21 (1999) 497.
[57] J. Wang, D.B. Luo, P.A. Farias, J.S. Mahmoud, Adsorptive stripping voltammetry of riboflavin and other flavin analogues at the static mercury drop electrode, Anal. Chem. 57 (1985) 158.
[58] G.J. Patriarche, New trends on modified electrodes: application to drug analysis, J. Pharm. Biomed. Anal. 4 (1986) 789.
[59] J. Wang, Stripping Analysis: Principles, Instrumentation and Application, VCH, Deerfield Beach, 1985.
[60] J. Wang, Analytical Electrochemistry, 2nd ed., Wiley-VCH, New York, 2000.
[61] G. Hong, H. Naifei, L. Shuchang, Adsorptive stripping voltammetric properties of fentanyl at Hg electrode, Talanta 41 (1994) 1929.
[62] V. Gold, K.L. Loening, A.D. McNaught, P. Sehmi, Compendium of Chemical Terminology, IUPAC Recommendation, Blackwell, Oxford, 1987.
[63] M. Kopanica, V. Stará, Voltammetric determination of Cyadox using adsorptive accumulation in a flow-through system, J. Electroanal. Chem. 214 (1986) 115.
[64] P. Gratteri, E.S. Furlanetto, S. Pinzauti, E. La Porta, P. Mura, G. Santoni, Adsorptive stripping voltammetry for thiomersal assay, J. Pharm. Biomed. Anal. 12 (1994) 273.
[65] D.C. Johnson, S.G. Weber, A.M. Bond, R.M. Wightman, R.E. Shoup, I.S. Krull, Electroanalytical voltammetry in flowing solutions, Anal. Chim. Acta 180 (1986) 187.
[66] J.-C. Vire, J.M. Kauffmann, G.J. Patriarche, Adsorptive stripping voltammetry applied to drug analysis: a powerful tool, J. Pharm. Biomed. Anal. 7 (1989) 1323.
[67] P. Gratteri, S. Pinzauti, E. La Porta, P. Mura, G. Papeschi, G. Santoni, Determination of flubendazole in pharmaceutical dosage forms by differential pulse polarography and UV spectroscopy, Farmaco 45 (1992) 707.
[68] J.P. Hart, S.A. Wring, Recent developments in the design and application of screen-printed electrochemical sensors for biomedical, environmental and industial analyses, Trends Anal. Chem. 16 (1997) 89.
[69] M.A. Garca-Fernandez, M.T. Fernandez-Abedul, A. Costa-Garca, Voltammetric study and determination of buprenorphine in pharmaceuticals, J. Pharm. Biomed. Anal. 21 (1999) 809.
[70] S. Yilmaz, B. Uslu, S.A. Ozkan, Anodic oxidation of etodolac and its square wave and differential pulse voltammetric determination in pharmaceuticals and human serum, Talanta 54 (2001) 351.
[71] A. Radi, A.M. Beltagi, M.M. Ghoneim, Determination of ketorolac in human serum by square wave adsorptive stripping voltammetry, Talanta 54 (2001) 283.
[72] S.M. Sabry, Adsorptive stripping voltammetric assay of phenazopyridine hydrochloride in biological fluids and pharmaceutical preparations, Talanta 50 (1999) 133.
[73] R. Fernandez Torres, M. Callejon, J.C. Jimenez Sanchez, M.A. Bello Lopez, A. Guiraum Perez, Electrochemical oxidation of cisatracurium on carbon paste electrode and its analytical applications, Talanta 53 (2001) 1179.
[74] Z. Senturk, S.A. Ozkan, Y. Ozkan, Electroanalytical study of nifedipine using activated glassy carbon electrode, Pharm. Biomed. Anal. 16 (1998) 801.
[75] F. Belal, H. Al-Malaq, A.A. Al-Majed, Voltammetric determination of isoxsuprine and fenoterol in dosage forms and biological fluids through nitrosation, J. Pharm. Biomed. Anal. 23 (2000) 1005.
[76] T.N. Rao, B.V. Sarada, D.A. Tryk, A. Fujishima, Electroanalytical study of sulfa drugs at diamond electrodes and their determination by HPLC with amperometric detection, J. Electroanal. Chem. 491 (2000) 175.
[77] B. Uslu, I. Biryol, Voltammetric determination of amoxicillin using a poly (N-vinyl imidazole) modified carbon paste electrode, J. Pharm. Biomed. Anal. 20 (1999) 591.
[78] N. Abo EL-Maali, Electrochemical behaviour of the monobactam antibiotic aztreonam at different electrodes and in biological Fluids, Bioelectrochem. Bioenerg. 45 (1998) 281.
[79] N. Abo EL-Maali, Voltammetric analysis of ceftazidime after preconcentration at various mercury and carbon electrodes. Application to sub-ppb level determination in urine samples, Talanta 51 (2000) 957.
[80] L. Basaez, P. Vanýsek, Transport studies of β-lactam antibiotics and their degradation products across electrified water/oil interface, J. Pharm. Biomed. Anal. 19 (1999) 183.
[81] M. Rizk, F. Belal, F. Ibrahim, S. Ahmed, N.M. El-Enany, Voltammetric analysis of certain 4-quinolones in pharmaceuticals and biological fluids, J. Pharm. Biomed. Anal. 24 (2000) 211.
[82] V. Kapetanovic, L. Milovanovic, M. Aleksic, L. Ignjatovic, Voltammetric methods for analytical dtermination of fleroxacin in quinodis® Tablets, J. Pharm. Biomed. Anal. 22 (2000) 925.
[83] M. Rizk, F. Belal, F.A. Aly, N.M. El-Enany, Differential pulse polarographic determination of ofloxacin in pharmaceuticals and biological fluids, Talanta 46 (1998) 83.
[84] A.M.S. Roque da Silva, J.C. Lima, M.T. Oliva Teles, A.M. Oliveira Brett, Electrochmical studies and square wave adsorptive stripping voltammetry of the antidepressant fluoxentine, Talanta 49 (1999) 611.
[85] A. Ferancova, E. Korgova, R. Miko, J. Labuda, Determination of tricyclic antideprssants using a carbon paste electrode modified with β-cyclodextrin, J. Electroanal. Chem. 492 (2000) 74.
[86] D. Dogrukol-Ak, V. Zaimoglu, M. Tuncel, Voltammetry of trazodone by platinum electrode and its determination in tablets using DP technique conditions, Eur. Pharm. Sci. 7 (1999) 215.
[87] N. Yongnian, I. Wang, K. Serge, Voltammetric determination of chlorpromazine hydrochloride and promethazine hydrochloride with the use of multivariate calibration, Anal. Chim. Acta 439 (2001) 159.
[88] B. Uslu, N. Yilmaz, N. Erk, S.A. Ozkan, Z. Senturk, I. Biryol, The study of the voltammetric behaviour of flunarizine, J. Pharm. Biomed. Anal. 21 (1999) 215.
[89] S.A. Ozkan, Y. Ozkan, Z. Senturk, Electrooxidation of pimozide and its differential pulse voltammetric and HPLCEC determination, Anal. Chim. Acta 453 (2002) 221.
[90] Z. Senturk, S.A. Ozkan, Y. Ozkan, H.Y. Aboul-Enein, Voltammetric investigation of oxidation of zuclopenthixol and application to its determination in dosage forms and in drug dissolution studies, J. Pharm. Biomed. Anal. 22 (2000) 315.
[91] N. Yilmaz, S.A. Ozkan, B. Uslu, Z. Senturk, I. Biryol, Determination of terbutaline based on oxidation by voltammetry, J. Pharm. Biomed. Anal. 17 (1998) 349.
[92] S. Fdez de Betono, A.A. Garcia, J.F.A. Valentin, UV-spectrophotometry and square wave voltammetry at nafion-modified carbon-paste electrode for the determination of doxazosin in urine and formulations, J. Pharm. Biomed. Anal. 20 (1999) 621.
[93] J.A. Squella, A.E. Iribarren, J.C. Sturm, L.J. Nunez-Vergara, Electrochemical determination of lacidipine, J. AOAC Int. 82 (1999) 1077.
[94] S.A. Ozkan, Y. Ozkan, Z. Senturk, Electrochemical reduction of metronidazole at activated glassy carbon electrode and determination in pharmaceutical dosage forms, J. Pharm. Biomed. Anal. 17 (1998) 299.

[95] N. Ozaltin, Differential pulse polarographic determination of tenoxicam in pharmaceuticals and added to blood, Anal. Chim. Acta 406 (2000) 183.
[96] X. Chu, G.-L. Shen, J.-H. Jiang, T.-F. Kang, B. Xiong, R.-Q. Yu, Voltammetric studies of the interaction of daunomycin anticancer drug with DNA and analytical applications, Anal. Chim. Acta 373 (1998) 29.
[97] M.S. Ibrahim, Voltammetric behaviour and determination of the anthracycline antitumor drug nogalamycin, Anal. Chim. Acta 409 (2000) 105.
[98] A.M. Oliveira-Brett, M. Vivan, I.R. Fernandes, J.A.P. Piedade, Electrochemical detection of in situ adriamycin oxidative damage to DNA, Talanta 56 (2002) 959.
[99] C. Xia, S. Guo-Li, J. Jian-Hui, K. Tian-Fang, X. Bin, Y. Ru-Qin, Voltammetric studies of the interaction of daunomycin anticancer drug with DNA and analytical application, Anal. Chim. Acta 373 (1998) 29.
[100] S. Hasoa, J. Dvorak, F. Jelen, V. Vetterl, Interaction of DNA with echinomycin at the mercury electrode surface as detected by impedance and chronopotentiometric measurements, Talanta 56 (2002) 905.
[101] F. Jelen, A. Erdem, E.P. Palecek, Cyclic voltammetry of echinomycin and its interaction with double-stranded and single-stranded DNA adsorbed at the electrode, Bioelectrochemistry 5 (2002) 165.
[102] M.S. Ibrahim, I.S. Shehatta, A.A. Al-Nayeli, Voltammetric studies oof the interaction of lumazine with cyclodextrins and DNA, J. Pharm. Biomed. Anal. 28 (2002) 217.
[103] D. Marin, P. Perez, C. Teijeiro, E. Palecek, Interaction of surface-confined DNA with acid-activated mitomycin C, Biophys. Chem. 75 (1998) 87.
[104] M.S. Ibrahim, Voltammetric studies of the interaction of nogalamycin antitumor drug with DNA, Anal. Chim. Acta 443 (2001) 63.
[105] A. Radi, Stripping voltammetric determination of indapamide in serum at castor oil-based carbon paste electrodes, J. Pharm. Biomed. Anal. 24 (2001) 413.
[106] B.D. Bath, D.J. Micheal, B.J. Trafton, J.D. Joseph, P.L. Runnels, R.M. Wightman, Subsecond adsorption and desorption of dopamine at carbon-fiber microelectrodes, Anal. Chem. 72 (2000) 5994.
[107] K.D. Kozminski, D.A. Gutman, V. Davila, D. Sulzer, A.G. Ewing, Voltammetric and pharmacological characterization of dopamine release from single exocytotic vents at rat pheochromocytoma (PC12) cells, Anal. Chem. 70 (1998) 3123.
[108] C. Earles, J.O. Schenk, Rotating disk electrode voltammetric measurements of dopamine transporter activity: an analytical evaluation, Anal. Biochem. 264 (1998) 191.
[109] R.R. Chellappan, O. Takeo, Electroanalysis of ascorbate and dopamine at a gold electrode modified with a positively charged self-assembled monolayer, J. Electroanal. Chem. 496 (2001) 44.
[110] C. Nianhang, C.G. Towbridge, J.B. Justice, Voltammetric studies on mechanisms of dopamine efflux in the presence of substrates and cocaine from cells expressing human norepinepherine, J. Neurochem. 71 (1998) 653.
[111] G.C. Nan, W.X. Ping, D.J. Ping, C.H. PingQing, A study on electrochemistry of histidine and its metabolites based on the diazo coupling reaction, Talanta 49 (1999) 319.
[112] Y. Bai, J.Y. Mo, Q. Cheng, S.H. Chen, Determination of catechols on heme modified electrode by electrocatalytic oxidation, Fenxi Shiyanshi 17 (1998) 5.
[113] L.M.A. Monzon, L.M. Yudi, Voltammetric analysis of lipophilicity of benzodiazepine derivatives at the water|1,2-dichloroethane interface, J. Electroanal. Chem. 495 (2001) 146.
[114] M.M. Hefnawy, Analysis of certain tranquilizers in biological fluids, J. Pharm. Biomed. Anal. 27 (2002) 661.
[115] R.P. Akkermans, M. Wu, C.D. Bain, M. Fidel-Suarez, R.G. Compton, Electroanalysis of ascorbic acid: a comparative study of laser ablation voltammetry and sonovoltammetry, Electroanalysis 10 (1998) 613.
[116] Z.M. Liu, J. Li, T.Y. You, X.R. Yang, E.K. Wang, Voltammetric study of vitamin K_3 at interdigitated array microelectrodes, Electroanalysis 11 (1999) 53.
[117] M. Zen, Y.-S. Ting, Y. Shih, Voltammetric determination of caffeine in beverages using a chemically modified electrode, Analyst 123 (1998) 1145.
[118] Y.F. Yang, Determination of cimetidine by glassy carbon electrode, Fenxi Kexue Xuebao 14 (1998) 301.
[119] A. Radi, G.E. Bekhiet, Voltammetry of melatonin at carbon electrodes and determination in capsules, Bioelectrochem. Bioenerg. 45 (1998) 275.