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APPLICATION OF MODERN ELECTROANALYTICAL TECHNIQUES: RECENT TREND IN PHARMACEUTICAL AND DRUG ANALYSIS

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ABSTRACT: The determination of drugs in pharmaceutical preparations and biological fluids is of pivotal importance in the pharmaceutical and medical sciences. Successful analysis requires sensitivities at ppb level or even less in biological fluids with high selectivity and minimal interferences from various artifacts. Till recently, biopharmaceutical analysis relied principally on spectrophotometric assay, chromatographic methods including gas-liquid chromatography (GC), high performance liquid chromatography (HPLC), GC-mass spectrometry (GS-MS), LC-MS-MS, enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA) and related techniques. Recent trends in drug analysis are the use of electrochemical detectors coupled with LC or flow injection systems. With the considerable progress in analytical instrumentation, modern electrochemical methods are gaining popularity in determination of therapeutic agents and/or their metabolites in clinical samples at extremely low concentrations (10-50 ng/ml) and yet they are highly sensitive, robust and inexpensive. The electrochemical detection offers extreme selectivity as fewer electroactive interferents and moreover, only very small volume of biological sample is needed. The present review provides comprehensive information on the literature on the application of modern electrochemical methods for pharmaceutical and drug analysis in the last two decades. The principles and theories of various modern electrochemical techniques as well as recent advancements with regard to instrumentation involving electrode surface modifications namely amperometric, nanotubes based biosensors, polymer-modified, ion selective electrodes and modified indium-tin-oxide (ITO) electrodes for the determination of drugs in pharmaceutical preparations and biological fluids are also included.

INTRODUCTION: The determination of drugs and their metabolites in biological fluids is becoming increasingly important in the pharmaceutical and biomedical sciences. Successful analyses require sensitivities at ppb level or less, high selectivity and minimal interferences from artifacts.

In order to bring a drug product from the discovery stage to the commercial market the analytical chemist develops methodology for quality control, stability testing, pharmacokinetics, identification and clinical studies.

Till recently biopharmaceutical analysis rely principally on titrations, spectrophotometric[1], chromatographic and immunochemical methods [2]. A review by Sandor Gorog outlines the changes in the field of pharmaceutical analysis in the past two decades [3]. The most demanding of the pharmaceutical analytical assays require high specificity and determining drugs with subnanogram detection limit in biological fluids [4].

Gas-liquid Chromatography (GLC) with electron capture, nitrogen flame ionization or mass spectrometric detection, HPLC coupled with mass spectroscopy [5, 6], LC with ultraviolet or fluorescence detection and radioimmunoassay are the commonly used procedures in measuring trace level concentration of drug in biological fluids [7]. More recently modern electroanalytical techniques coupled with TLC or LC are extremely useful in measuring blood levels and urinary excretion of drugs in low doses (up to 50-100 ng/ml) [8].

Recent advances in electrochemical instrumentation make electroanalytical methods an appealing choice in pharmaceutical analysis [9]. Modern electrochemical techniques have excellent limits of detection and a wide dynamic range [10]. The selectivity of electrochemical detection in complex samples is excellent. Furthermore, the application of electroanalytical methods enables the analysis of materials with colored or solid particles dispersed. Direct analysis is analytically very convenient without the need to step in to separation or pre-treatment whereas the use of spectroscopic techniques and optical methods require preliminary separation in most cases.

Further, electroanalytical techniques require only very small sample volumes, often in the microlitre range, coupled with the low detection limits allowing analysis on subpicogram amounts of drug products and metabolites [11]. For these reasons and also for their simplicity and rapidity, electrochemistry is uniquely suited for clinical and bioanalysis where small volumes of blood or urine are analyzed for low concentrations of drug products and metabolites [12].

In comparison to other *in vivo* analytical techniques, the instrumentation required for electrochemical methods is so simple and inexpensive even to the point of having disposable electrochemical cells.

With the advent of micromachining technologies and the improvement in the designs of electrochemical cells, the detection and quantification of different drugs in biological fluids and pharmaceutical preparations using electrochemical methods is the latest trend. Although a great deal of work has been done in the last few years for trace level determination of various drugs in biological fluids and in pharmaceutical dosage form using electroanalytical techniques but no review summarizes developments in electroanalytical methods in terms of electrode modifications and their application in recent years.

The present review provides comprehensive information on the literature on the application of modern electrochemical methods for pharmaceutical and drug analysis in the last two decades. The principles and theories of various modern electrochemical techniques as well as recent advancements with regard to instrumentation in terms of use of ultra-microelectrodes and electrode surface modifications are also included. A comprehensive coverage is given to various types of modified working electrodes namely nanotubes based biosensors, polymer-modified electrodes, ultra microelectrodes and ion selective electrodes and their application in determination of various drugs in pharmaceutical preparations and biological fluids.

This article covers the basics of different electroanalytical techniques useful in pharmaceutical analysis and most importantly, directs the reader to their current pharmaceutical applications in the literature.

THEORY AND INSTRUMENTATION: Electro-analytical chemistry implies to the analysis of chemical species through the use of electrochemical methods, in other words a study of the chemical response of a system to an electrical stimulation. In an electrochemical experiment, one or more of the four parameters-potential (E), Current (I), Charge (Q) and Time are measured. The response of a system depends on which parameter is used as the excitation signal. The different combinations of parameters and working electrode type make a long list of techniques like voltammetry, polarography (dc, fast-scan and differential pulse), linear sweep voltammetry, cyclic voltammetry, hydrodynamic voltammetry, differential pulse, square wave voltammetry and stripping voltammetry [13].

Fundamentals and application of various electrochemical methods have been compiled by Bard & Faulkner [14].

Generally, alteration in the concentration of a chemical species is monitored by measuring changes in current in response to an applied voltage with respect to time. According to Faraday's law, the charge is directly proportional to the amount of species undergoing a loss (oxidation) or gain (reduction) of electrons.

$$Q = n F e$$

Q is the total charge generated (coulombs), e is the number of electrons per molecule lost or gained. n is the number of moles of a species undergoing oxidation or reduction, F is Faraday's constant (96,487 C/mol) and current (I) is the change in charge as a function of time.

$$I = dQ / dt$$

Thus, the current response with respect to time (voltammogram) gives information about changes in the concentration of the species of interest. A great deal of good literature is available on fundamentals of electroanalytical chemistry for analysis of organic compounds [15, 16]**.** Since the voltammetric techniques demonstrate a large linear dynamic range (10^{-3}-10^{-10} M), solid electrode voltammetry (which exclude polarography) is limited to application for a detection limit of approximately 10^{-4}-10^{-5} M.

Small amplitude polarographic techniques (ac and pulse) can be applied to the measurement of drugs in bulk and dosage form and to the assay of drugs and metabolites in biological fluid, when concentrations are at least 10^{-6} M. Only the techniques of fast scan polarography, differential pulse polarography and stripping voltammetry are capable of determining drugs in biological fluids with the limits of detection of approximately 100-200 ng/ml, 10-20 ng/ml and less than 10 ng/ml of biological fluid respectively [17].

Many analytical techniques at varying level of sensitivities are required to solve analytical-pharmaceutical problems**.** Voltammetry is particularly valuable technique for the determination of polar metabolites that cannot be readily derivatized for gas chromatography [6].

Various electrochemical techniques currently in use in clinical and biomedical analysis are discussed by KI Ozomwna in his book [18]**.**

MODERN VOLTAMMETRIC TECHNIQUES:

1. **Rapid Scan Linear Sweep Voltammetry (LSV)**: It is the simplest technique in which a rapid potential scanning is applied in one direction at the working electrode that varies linearly (20-100 mV/s) with time.

2. **Fast Cyclic Voltammetry (FCV)** is a type of potentiodynamic electrochemical technique in which the working electrode potential is ramped linearly with time but in contrast to linear sweep voltammetry on reaching a set potential, ramp potential is inverted to the initial potential. During the potential sweep, the current at the working electrode is plotted versus the applied potential to give the cyclic voltammogram. In this technique the background subtracted voltammogram gives additional information about the behavior of the redox couples in electrolyzed species. The current response over a range of potentials is measured, making it a better technique to discern additional current contributions from other electroactive species. Fast cyclic voltammetry is a relatively fast technique with single scans typically recorded every 100 ms, however, the fast scan rates decrease the signal to noise ratio.

3. In **Normal Pulse Voltammetry** (NPV), a series of periodical constant pulse of potential is superimposed to a linear scanning; a consistent enhancement of the signal is achieved. The difference between the current just before and at the end of the pulse is measured, so that the reading is less influenced by the capacitive current.

4. **Differential Pulse Voltammetry** (DPV) is a hybrid form of linear sweep and pulsed voltammetry. It is a very sensitive technique enabling a detection limit in ppb or lower. It has found excellent usage in analytical determination of trace level of organic species. However, multiple pulses in the waveform make it a relatively slower technique with individual scans taking minutes to complete.

5. **Square Wave Voltammetry** (SWV) is a newer and popular pulse technique for analytical work. It is further development of pulse technique, a rapid step scanning of potential is applied to the electrode and moreover on each step is superimposed a high frequency square wave (20-100 Hz). Its common form used is Osteryoung square wave. In this form the current response to the potential excitation is sampled once on each forward pulse and once on each reverse pulse.

   The two currents are then summed up thereby remarkably increasing sensitivity. As SWV effectively removes the background current from the measurement, it has advantage over CV because of its speed, sensitivity and dynamic range of detection. It can respond to both high and low concentrations of electroactive species. It can detect micromolar concentration of analyte in contrast to CV which can detect only millimolar concentration.

6. In **Constant Potential Amperometry**, a uniform potential is applied and the change in current is monitored as a function of time. The advantage of this technique is that the time resolution is limited only by the data collection frequency of the instrument. On the other hand, its primary disadvantage is the low chemical selectivity. For example, all species with oxidation potentials below the applied voltage will be oxidized and contribute to the current.

7. **Chronopotentiometry** is a technique in which a constant current or a current step is applied to the electrode and the resulting potential change is plotted versus time. It is advantageous over the more common polarographic/ voltammetric methods due to its ability to measure higher concentrations.

8. **Chronoamperometry** is a square wave pulsed voltammetric technique. Limited information about the identity of the electrolyzed species can be obtained from the ratio of the peak oxidation current versus the peak reduction current. However, as with all pulsed techniques, chronoamperometry generates high charging currents, which decay exponentially with time. It takes approximately one second to complete a scan in the delayed pulse mode which is necessary to prevent fouling of the electrode and as the current is integrated over relatively longer time intervals, chronoamperometry gives a good signal to noise ratio. The recent developments and application of direct and stripping SWV for drug compounds in their dosage forms and biological samples as reported in the period from the year, 1997 till 2010 are scrutinized by Dogan-Topal *et al* [19].

   Use of numerous ion selective electrodes, surface modified solid electrode, ultra microelectrodes and screen printed electrode is also highlighted in the review. The most recent methods and materials for the construction, validation, analysis, and design of electrochemical sensors for bioanalytical, clinical, and pharmaceutical applications for in vivo and in vitro diagnosis are covered in a book by Xueji Zhang, Huangxian Ju and Joseph Wang [20].

9. **Adsorptive stripping voltammetry** is the most effective electroanalytical technique for trace measurement of drugs and other compounds of biological significance. In this technique, the analyte is pre-concentrated first by adsorption onto the working electrode, followed by voltammetric measurement of the surface species. The resulting voltammetric response is significantly larger than the solution-species alone. Hence, the detection limits are improved to nanomolar concentration level [21].

   Depending upon the redox properties of the analyte, the accumulated species can be quantified by scanning the potential in the cathodic or anodic directions. A variety of voltammetric waveforms have been used in stripping voltammetry, including linear scan, differential pulse, square wave, staircase, as or subtractive mode [22]. The differential pulse stripping mode has been widely used because of its correction for the charging current and its commercial availability.

   A brief review by Vire JC, Kauffmann JM and Patriarche GJ presents the principles, instrumentation and advantages of adsorptive stripping voltammetry for drug analysis in complex media [23]. It also discusses application of modified electrodes to enhance selectivity.

Most adsorptive stripping procedures utilize the hanging mercury drop electrode (HMDE) for measuring reducible species. Because of lower background current level, self-cleaning properties, reducible surface area and automatic control, mercury electrodes offer lower detection limits (10^{-10}-10^{-11}M) as compared to solid electrodes (10^{-8}-10^{-9} M). A detailed review on applications of polarography in pharmaceutical, biomedical as well as in industrial and agriculture field has been presented [24].

The low potential of evolution of hydrogen, which initiates the decomposition of water, is another advantage, since it allows measurement in various media in a wide range of potential. All these advantages make the mercury electrode the most versatile and used for detection of pharmaceuticals in different matrices. However, apart from being highly toxic, its use is limited to the range of negative potential [25]. This limitation of the range of potential precludes its use in monitoring of oxidizable compounds. Solid electrodes that have a window of good potential are of considerable applicability for throughput screening of drug compounds. Thin film mercury electrodes (TFME) on glassy carbon, carbon paste, wax-impregnated graphite, platinum and gold electrodes are used for oxidizable analytes.

The nature of the stages of electrochemical pre-treatment depends on the types of materials involved in the construction of electrodes. As the responses obtained are related to redox reactions that occur on electrode surface or the electrode-solution interface, the choice of the material of working electrode is very important. However, if the transfer of electrons is very slow, does not occur or occurs at a value of potential outside the window of the electrode potential, it is possible to change the surface electrodic by immobilization of functional groups, incorporation of inorganic and organic catalysts (enzymes and antibodies), deposition of polymer films, modified with silica and deposition of biological membranes [26].

Chemically modified electrode (CME) made of a conducting or semiconducting material that is coated with a selected monomolecular, multimolecular, ionic, or polymeric film of a chemical modifier exhibits chemical, electrochemical, and/or optical properties of the film [27].

These microelectrodes are more selective and more sensitive, because the amendment allows controlling the physico-chemical nature of the electrode-solution interface as a way to change the reactivity and selectivity of the electrode base favoring the development of electrodes for different analytical applications.

Besides the commonly used modified platinum, gold, glassy carbon and carbon paste electrodes, ultra-microelectrodes with dimensions smaller than 10 µM are promising. The use of Ultra- microelectrodes (UMEs) greatly enhances the quality of experimental data by providing better resolution of the voltammetric profile, higher-current density and decreases the effects of the resistance of the solution [28].

So, the use of modified electrode is fast replacing mercury electrodes and inert metals. B Uslu and SA Ozkan summarize recent progress in the development and application of all forms of solid electrodes to the screening of pharmaceutical dosage form and biological fluids [29].

Various chemically modified electrodes used in drug analysis include:

Modified carbon paste electrodes: This simplest type of modified electrode consists of a mixture of graphite powder with 'Nujol' to form a stiff paste which is then placed into an electrode holder. A modifying component, which is electroactive or which can extract an electroactive analyte into the surface of the paste, is mixed with the paste. Carbon paste electrodes have been used in determination of drugs like Dipyrone [30], Dipyridamole [31], central nervous system agents Diazepam, Oxazepam, Tamzepam [32] and chemotherapeutic agents like Azithromycin [33] and Cefataxime [34].

Polymer modified electrodes: Electrode surfaces are modified by coating them with different types of polymers mainly conducting polymer, ion exchange and redox polymers. Often chemical groups are attached to these coatings in order to introduce particular electrochemical effects. Conducting polymers like polyacetylene, polypyrrole, polyaniline or polythiophene are easily prepared by electrochemically oxidizing the substrate on the electrode surface.

Various polymer modified electrodes found application in analysis of Acetaminophen [35], Chlorprothixene [36], Isoniazid [37], chemotherapeutic agents like Amoxicillin [38], Tinidazole [39] in biological fluids and drug formulations.

During the last several years, Indium-tin-oxide (ITO) films on glass or quartz substrates have been increasingly employed as an electrode surface because it has prominent characteristics such as a good electrical conductivity, wide electrochemical working window, and high optical transparency. Modified indium-tin-oxide (ITO) electrodes have been used for the determination of drugs like Paracetamol [40], Atenolol [41], and CNS agent like Imipramine [42].

In recent years, boron doped diamond electrodes are also utilized in analysis of pharmaceuticals like Paracetamol and Cafeine [43], Fluvastatine [44], Perfloxacin [45], Tetracycline [46], Sulfadiazine and Sulfamethoxazole [47] etc.

Ion selective electrodes: They are based on an ion selective membrane that separates the sample from the inner electrolyte. The nature of the membrane determines the selectivity of the electrode. A membrane is considered to be any material that separates two solutions. It is across this membrane that the charge develops. Several types of sensing electrodes are commercially available. They are classified by the nature of the membrane material used to construct the electrode. It is this difference in membrane construction that makes an electrode selective for a particular ion.

Determinations using ion selective electrodes are less expensive and are not subject to interferences such as color in the sample [48]. There are few matrix modifications needed to conduct these analyses. This makes them ideal for clinical use where they are most popular [49].

Nanotubes based electrodes: Nano materials have become an extremely popular theme in recent electrochemical sensing research due to their electrical conductivity, unique structural and catalytic properties, high loading of biocatalysts, good stability and excellent penetrability [50]. Carbon nanotubes (CNTs) are used as electrode materials with useful properties for various potential applications including miniature biological devices.

The subject of electrochemical sensing utilizing CNTs including CNTs paste electrodes has been extensively studied and reviewed by various authors. Carbon nanotubes paste electrodes are new alternative for the development of electrochemical sensors [51]**.** A review covers the development of electrochemical sensors and biosensors using nanowires as sensing material [52]**.** These sensors achieved higher response current, low work potential and low interference. Drugs of diverse therapeutic classes have been investigated using nanomaterial based carbon and gold electrodes.

Analgesics like Paracetamol [53], Mefenamic acid [54] anticancer drugs like Noscapine [55], Quercetin and Rutin [56], cardiovascular agents like Procaine [57], chemotherapeutic agents Acyclovir [58], Lincomycin [59], Metronidazole [60], Norfloxacin [61], central Nervous system agents like Bisoprolol fumerate [62], Dopamine [63], Trifluperazine [64] and many more have been quantified using modified carbon nanotube based electrodes. Electrochemical biosensors have been studied for a long time. A review is presented by Wang Y and *et al*., on electrochemical sensors used for clinical analysis [65]**. A**nother review by Miroslav Pohanka and Petr Skladal describes their principles and applications [66].

Use of electrochemical detectors along with Flow Injection Analysis also has applications in pharmaceutical determination [67]. Electrochemical detection in liquid chromatography was introduced in 1973 for the assay of catecholamines and other neurotransmitters and continues to grow in popularity for the determination of trace amounts of biologically active compounds in complex samples in biology and medicine**.** Application of electrochemical detection in high performance LC to the assay of biologically active compounds is reviewed by Toshiharu Nagatu and Kohichi Kojima [68].

A great deal of work has been done in the last few years for trace level determination of various drugs in biological fluids and in pharmaceutical dosage form using electroanalytical methods. An overview on pharmaceuticals assayed by electroanalytical techniques covers the period between 1987 and 1990 [69]**.** NA El-Maali presented a survey of the use of voltammetry for drug analysis in the period from 1998 till 2002 along with rules that must be considered for drug analysis [70].

Some good reviews on analysis of pharmaceuticals and biological fluids using modern electroanalytical techniques that covers the principles as well as various selected studies on the subject are also available [71, 72].

In comparison to other *in vivo* analytical techniques, instrumentation required for electrochemical analysis is simple and inexpensive even to the point of having disposable electrochemical cells and thus biomedical aspects of electrochemical methods of analysis is now widely explored [73].

PRESENT AND FUTURE TRENDS IN PHARMACEUTICAL DRUG ANALYSIS: Recent achievements in electrochemical analysis of pharmaceutical and biomedical chemistry include its role in drug development, metabolite determination, oxidative stress, and electrochemical therapy. The consistent efforts to improve the critical parameters such as stability, accuracy and reliability due to rapid progress in development of biosensors would further enhance the application of electrochemical analysis of drugs and/or their metabolites in pharmaceutical dosage forms and biological fluids [74].

With the considerable progress in electrode surface modification, the use of numerous ion selective electrodes, microelectrodes and screen printed electrodes has considerable applicability for throughput screening of drug compounds as they are specific to a particular type of analyte and promote a high degree of selectivity, enabling the development of sensors for easy handling and construction, low cost, potential for miniaturization and rapid detection.

With the advent of micromachining technologies and advancement in the designs of electrochemical cells, the detection and quantification of different drugs in biological fluids and pharmaceutical preparations using ultramicroelectrodes (UMEs) would undoubtedly be the method of choice in future [75]. These electrochemical sensors will undoubtedly play an important role in future for analysis of drug compounds [76].

Sensor arrays for detecting multi-analyte will be required and the densities of arrays for more complete and rapid information need to increase microfluidic sensor systems, which are capable of expanding sizes of arrays while reducing sample volume, as well as non-invasive biosensors, will revolutionize the sensor techniques and technology. Electrochemical techniques in trace level determination of biologically active compounds will bring sophisticated analytical capabilities to the non-specialist and general public alike in the near future.

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