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From mercury to nanosensors: Past, present and the future perspective of electrochemistry in pharmaceutical and biomedical analysis

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ABSTRACT

Polarography was the first developed automated method of voltage-controlled electrolysis with dropping mercury electrode (DME). Then, hanging mercury drop and static mercury drop electrodes were added as an alternative indicator electrode. In this way, polarography turned formally into voltammetry with mercury electrodes in the electroreduction way. Solid electrodes such as noble metal and carbon based electrodes can be used for the investigation of the compounds for both oxidation and reduction directions, which is called voltammetry. The voltammetric and polarographic techniques are more sensitive, reproducible, and easily used electroanalytical methods that can be 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 are by far the most common use of electrochemistry for analytical pharmaceutical problems. Recent trends and challenges in the electrochemical methods for the detection of DNA hybridization and pathogens are available. Low cost, small sample requirement and possibility of miniaturization justifies their increasing development.

1. Introduction

Electroanalytical methods are routinely used in pharmaceutical and biomedical analysis. They are powerful and versatile analytical techniques that offer high sensitivity, accuracy, and precision as well as a large linear dynamic range, with relatively low-cost instrumentation. In the modern pharmaceutical and biological analysis a large number of electroanalytical applications with different techniques are available for the sensitive quantification of drugs. They have been developed for measurements in the laboratory, mostly for fundamental research. The application of electrochemical techniques in the assay of pharmaceuticals in biological materials as biosensors has increased greatly over the last few years. This requires a thorough understanding of electrochemistry, the theory and the principles of electroanalytical techniques which lay a solid foundation for appreciating many variables that are optimized during fast and effective method development and optimization.

The invention of polarography in 1922 by Professor Jaroslav Heyrovsky as a starting point of electrochemistry represented a qualitative change in electroanalytical chemistry which at that stage was restricted to potentiometry and controlled current electrolysis. He won the Nobel Prize for it in 1959. Modern electroanalytical methods resulting from the pioneering work of Professor

Abbreviations: Ab, antibody; ACP, alternating current polarography; APBA, 4-(2-(4-acetylthio)phenyl)ethynyl)benzoic acid; APTA, ptamer; AuE, gold electrode; AuSPE, gold screen printed electrode; BDDE, boron doped diamond electrode; BR, Britton-Robinson; CNT, carbon nanotube; CPE, carbon paste electrode; CV, cyclic voltammetry; DCP, direct current polarography; DME, dropping mercury electrode; DP, differential pulse; DPP, differential pulse polarography; DPV, differntial pulse voltammetry; dsDNA, double stranded deoxyribonucleic acid; ECD, electrochemical detection; EIS, electrochemical impedence spectroscopy; ESI, electrospray ionization; Fc, ferrocene; FFT, fast Fourier transformation; FIA, flow injection analysis; GCE, glassy carbon electrode; GOx, glucose oxidase; HMDE, hanging mercury drop electrode; HPLC, high performance liquid chromatography; ILMWCNTPE, ionic liquid multi walled carbon nanotube paste electrode; LOD, limit of detection; LOQ, limit of quantification; LSV, lineer sweep voltammetry; MBP, laltose binding protein; MBs, lagnetic beads; MC1R, melanocortin 1 receptor; MPTS, 3-mercaptopropyltrimethoxy silane; MS, mass spectrometry; MWCNT, multi walled carbon nanotube; NHS, *N*-hydroxy succinimide; NPP, normal pulse polarography; NPs, nanoparticles; NR, nitro reductase; n-Si, amino-functionalized silica; p-(AHNSA), poly 4-amino-3-hydroxynaphthalene sulfonic acid; PA, protective antigen; PANI, polyaniline; PGE, pencil graphite electrode; PPB, *N*-(3-pyrrol-1-ylpropyl)-4,4′-bipyridine; PPO, polyphenol oxidase; PPy, polypyrrole; PtE, platinum electrode; RuE, ruthenium electrode; SMDE, static mercury drop electrode; SPE, screen printed carbon electrode; ssDNA, single stranded deoxyribonucleic acid; SWP, square wave polarography; SWV, square wave voltammetry; TNT, 2,4,6-trinitrotoluene; UOx, uricase; ZnHCF, zinc hexacyanoferrate.

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Heyrovsky have a significant impact on the practice of many scientific and technological fields, primarily chemistry, biology, medicine, material science and environmental studies and protection. Therefore, the Nobel Prize memorial meeting is dealing with a wide range of contemporary trends in electroanalysis, from important theoretical and methodological developments to the most recent practical applications. Between 1950s and 1960s, DC polarography was one of the five most frequently used analytical techniques. After 1960s, with the advance of spectrometric and separation methods for the determination of organic compounds, DC polarography lost its importance [1–10].

In DC polarography, the spontaneously renewed pure electrode surface provided reproducible electrochemical results which enabled scientists to work out adequate theory and extensive analytical applications. The original method was then instrumentally modified in various ways. Polarography has thus gradually covered a wide field of electrolytic methods based on the use of mercury electrodes, in which it continues developing. The sensitivity of polarographic methods of analysis, enabling determination of electroactive species in concentrations down to about 10^{-5} M, was superior to most other contemporary techniques.

Renaissance of polarography was based on methods effectively eliminating the charging current and thus enabling to reach much lower limit of detection (LOD). Square wave (SWP) and differential pulse polarography (DPP), and their voltammetric variants at a hanging mercury drop electrode (HMDE), namely square wave (SWV) and differential pulse voltammetry (DPV), opened new possibilities in trace analysis. These methods can be combined with the stripping analysis, in which prior accumulation of the analyte on the electrode surface leads to the increased sensitivity by about three orders of magnitude [5–17]. Even though very successful, HMDE, consisting of a renewable drop of mercury at the end of a fine capillary, has some drawbacks mentioned in further sections. Some of these disadvantages can be successfully eliminated by using a mercury film electrode (MFE), prepared by coating a suitable substrate with a thin film of metallic mercury [15–23].

Advances since the mid-1980s, including the development of ultramicroelectrodes, the design of tailored interfaces and molecular monolayers, the coupling of biological components and electrochemical transducers, the synthesis of ionophores and receptors containing cavities of molecular size, the development of ultratrace voltammetric techniques or of high-resolution scanning probe microscopies, and the microfabrication of molecular devices or efficient flow detectors have led to a substantial increase in the popularity of electroanalysis and to its expansion into new phases and environments. Indeed, electrochemical probes are receiving a major share of the attention in the development of chemical sensors. The recent trends in the field of electroanalytical chemistry are focused on the development of "smart" electrodes modified by various chemical, biological or nanoparticles-based systems which are named as nanosensors. These electrodes usually work reasonably well in the hands of experienced electroanalytical chemist but their practical applications are limited by their low robustness and high requirements on handling analysts [24–32].

The aim of this review is to show brief overviews of electrochemistry, its past, present and the future perspectives and also the advantages and disadvantages of it. Some electrode reactions are given in order to show the interdisciplinary nature and versatility of electrochemistry and to introduce a few of the important fundamental concepts. 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 of these methods on pharmaceutical and biomedical area for various classes of drugs are presented.

2. What is electrochemistry

Electrochemistry is the branch of physical chemistry that studies chemical reactions which take place at the interference of an electrode, usually a solid metal or a semiconductor, and an ionic conductor, the electrolyte. Electrochemical processes take place at more complex interfaces such as biological membranes. Often the electrochemical charge separation leads to charge transfer, which can occur homogeneously in solution, or heterogeneously on electrode surfaces. In reality, to assure electro neutrality, two or more charge transfer half-reactions take place, in opposing directions. Except in the case of homogeneous redox reactions, these are separated in space, usually occurring at different electrodes immersed in solution in a cell. These electrodes are linked by conducting paths both in solution (via ionic transport) and externally (via electric wires etc.) so that charge can be transported. All interfaces can be harnessed for analytical measurements and most have been investigated for sensor development.

In electroanalytical methods, at least two-electrodes are used: working and reference electrodes. When it is necessary to eliminate the role of resistance between the electrodes, a third electrode is used which is called auxiliary. The solution to be analyzed is placed in an electrolytic cell into which the working electrode is immersed.

The analyzed solution, in which the indicator electrode is placed, usually contains a supporting electrolyte in addition to the sample of the working drug active compound. This added electrolyte has several functions among others such as to increase the conductivity of the solution (and decrease its resistance), eliminate transport of charged electroactive species by migration in the electric field in the cell, and to control pH or introduce suitable complexing ligands. The electroactive components present in drugs are most frequently organic compounds. For their analyses, the supporting electrolytes are usually buffers, solutions of a strong acid or of a strong base. The goal when developing an electroanalytical determination of an organic compound is to find such a supporting electrolyte in which the signals obtained in the presence of an electroactive species are best measurable and not interfering with other components of the sample.

The reactions concerned in electrochemical processes are redox reactions which involve the oxidized and reduced forms of a species be it an ion, a molecule or a biological entity. Most cases correspond to the conversion of one form into another and therefore involve the transfer of electrons across the interface. The interface may be inert and thus only provide a suitable site for the reaction and a source or sink for the electrons but more often than not the interface participates in the reaction. In localized corrosion for example the same interface holds regions of the metal undergoing oxidation and therefore metal loss to the solution while other regions promote the reduction of dissolved oxygen with electrons being transferred by conduction within the metal from the oxidation to the reduction regions. In sensor development it is common to seek an inert (i.e. not participating as reactant in the redox process), but nevertheless sufficiently catalytically active interface to speed up the reaction of interest [33–45].

The working electrodes may be passive as in potentiometry or active as in voltammetry, amperometry and impedimetry. In potentiometry, the indicator electrode is in equilibrium with the analyte while in voltammetry, amperometry or impedimetry, the working electrode drives a reduction or an oxidation. In this case the reaction at the electrode consumes species from the analyte and produces new species in the analyte; the electron involved in the electrode reaction may therefore be viewed as a reagent that can be supplied (reduction) or taken away (oxidation). In amperometry and impedimetry, the other electrode, often called the counter or secondary electrode, undergoes a reverse reaction to that on the working electrode (e.g. an oxidation if the working electrode runs

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