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Electrochemical methods in drug discovery and development

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A brief outline of the applications of electrochemical methods in pharmaceutical research was given. The aim of the review was not exhaustive since it would not be possible to cover such a diverse field in one review paper. Rather, several examples from the author's experience were given which demonstrate the applicability and usefulness of electrochemistry in the improving and accelerating drug design and development. The applications covered in this paper include electrochemical synthesis, electroanalytics and drug transfer across liquid/liquid interface.

Key words: electrochemical synthesis, ion transfer at liquid/liquid interface, ADME, DMPK, macrolide, azithromycin, electroanalytics.

INTRODUCTION

The main goal of pharmaceutical research revolves around design of a new drug or improving the properties or bioavailability of drugs already existing on the market. Drug discovery is a time and money consuming process which involves complex interactions among scientists of different profiles including medicinal chemists, pharmacologists, pharmaceutical scientists, biochemists, biotechnologists and physicians. Traditional trial-and-error approaches to drug discovery are nowadays increasingly replaced with modern paradigms of rational drug design such as structure-based and ligand-based drug design. Both approaches rely on the knowledge of the biological target either as its 3D structure or the interactions it elicits in the presence of other drug-like molecules. As the result of combined efforts of X-ray spectroscopy and NMR labs with molecular modelling and high-throughput screening, usually the "lead" compound(s) possessing suitable pharmacological responses are identified and isolated. Due to very high attrition rates of drugs which reached the costly clinical phases, a care is taken to optimize lead compounds in order to improve their Absorption, Distribution, Metabolism, Excretion and Toxicology (ADMET) properties as well as to assess their Drug Metabolism and Pharmacokinetics (DMPK).

Main cause of the failure of drugs in clinical phases is their adverse unfavourable biological effects or their poor absorption mostly due to the inability of drug substance to cross biological membranes and other barriers. Even if the substances possessed high affinity toward designated biological targets and had high therapeutic potential they would still be useless in case they would not be able to reach targeted biomolecule. The importance of drug absorption was thus recognized long time ago and its concept has progressed into a scientific discipline without which no contemporary pharmaceutical research could be considered. This is especially important for orally formulated drugs as the most convenient dosage forms since these drugs undergo gut and hepatic first-pass metabolism.

Among a vast variety of disciplines involved in the successful bringing the substance from the discovery of its potential therapeutic effect to the market, physical chemistry occupies a special place. Physico-chemical properties of substances are key factors determining the fate of the drug in the organism from its administration and absorption to its excretion. Not only they are responsible for successful ligand-target interactions through hydrogen bonding and hydrophobic interactions, but also four physico-chemical processes, *i.e.* ionization, solubility, lipophilicity and permeability, are of high relevance to the absorption of most orally administered drugs [1].

These processes are commonly expressed through the quantities such as ionization constant, p*K*a, intrinsic solubility, log S_0, partition coefficient, log *P* and permeability coefficient, P_e, respectively. Careful evaluation of these parameters has led to the development of Biopharma ceutical classification system (BCS) [2], which provides a framework for the division of substances according to their aqueous solubility and intestinal permeability. There were also several empirical rules of thumb developed for the prediction of

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the extent of passive permeation of drug molecules through cell membranes. The example is famous Lipinski “rule of five” [3] which identified several criteria any molecule should match to increase the chances to be absorbed by the body. Nowadays, physico-chemical parameters such as p*K*a, log *P* or log *S* are no longer perceived by medicinal chemists or formulation and pre-formulation engineers as “good” or “bad” numbers, but provide valuable prediction about the behaviour of active drug substance upon administration. Measurement of physic-chemical properties of potentially active substances has become a routine practice in the pharmaceutical research and many methods were developed for their accurate determination and prediction.

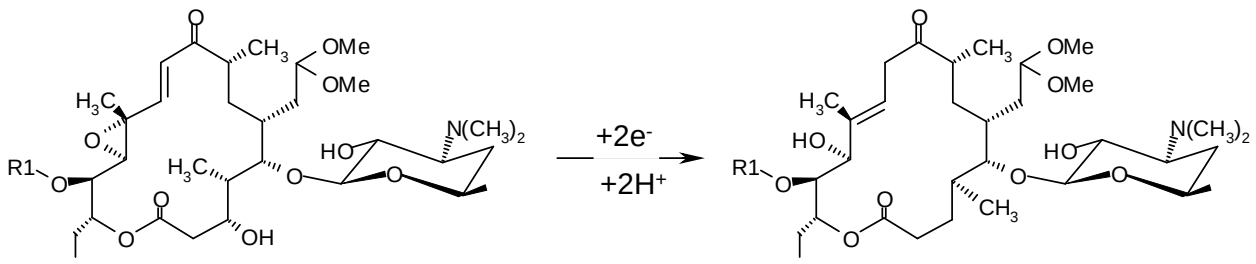
Electrochemical methods are widely used in almost all fields of pharmaceutical research. Their applications penetrate almost all labs and phases of drug development. The aim of this paper is to give an overview of the potential of electrochemistry and electrochemical methods in the synthesis and analysis of drugs. However, the subject is so broad that it would be impossible to address all the issues and applications in one review. Instead, this review is based on the author’s decade experience in dealing with electrochemistry field in pharmaceutical research and development.

ELECTROCHEMICAL SYNTHESIS OF BIOLOGICALLY ACTIVE COMPOUNDS

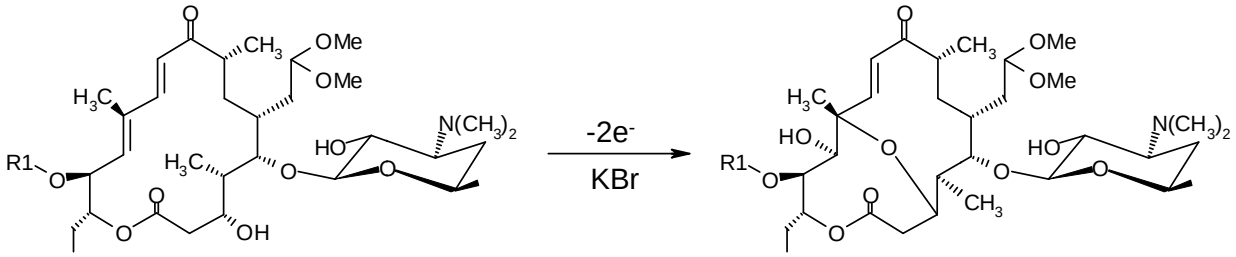
Electrochemical synthetic procedures are valuable tool for the synthesis and modifications of a large group of biologically active molecules and functional groups and as such are unavoidable techniques in medicinal and organic chemistry labs. They have proven useful not only because some products and intermediates could be obtained more easily by electrochemical means than by conventional chemical routes but also because some molecules could be synthesized almost exclusively electrochemically [4-23]. Large variety of direct and indirect electrochemical transformations of organic compounds is available to the skilful organic electrochemists which can be utilized to carry out desired chemical transformation hopefully leading to the active compounds with high biological activities. In direct electrochemical reactions, the product or reacting intermediate is formed by the electron transfer from the electrode to the reactant or vice versa, while in the indirect electrochemical reactions mediators and/or reagents are electrochemically generated to initiate the desired reaction. With the existence of a wide range of electron transfer mediators, the scope of the useful electrochemical synthetic reactions is largely extended to involve many reactions which otherwise would not be able to proceed by direct electrochemistry.

The usefulness of direct and indirect electrochemical reactions can be demonstrated with the examples of electrochemical functionalization of tylozin/desmycosin antibiotics: electrochemical opening of 12,13-oxirane desmycosin (Scheme 1) [6] and electrochemical oxidation of desmycosin (Scheme 2) [7], respectively. Electrochemical methodology can be also utilized in chiral electrosynthesis which is of high importance for pharmaceutical companies since many drugs are marketed in the enantiomerically pure forms.

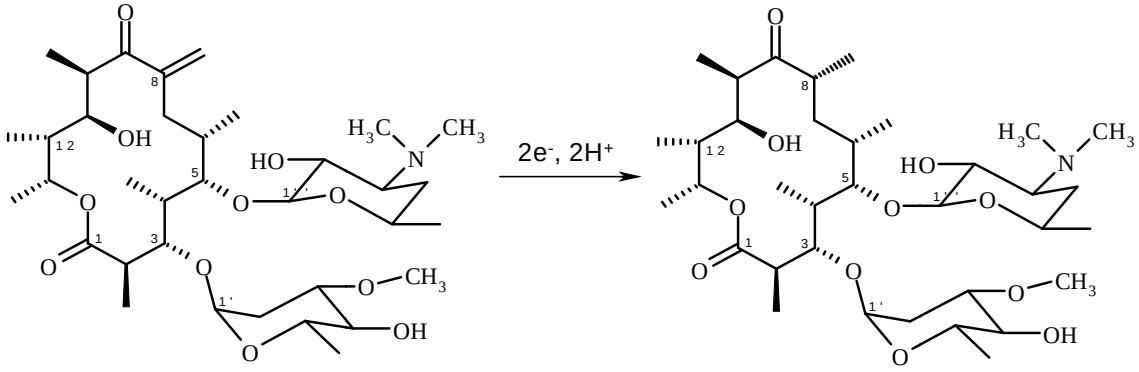
Heterogeneous nature of the electrode processes with highly structured solvent and electrolyte molecules at interphase region favours enantioselective electrochemical reactions. Relatively recent example demonstrated that exocyclic double bond of 8-methylene oleandomycin (**1**) can be reduced at mercury electrode with 67 % enantiomeric excess resulting in (*R*)-8-methyl oleandomycin (**2**) as the main product (Scheme 3) [11]. Stereoselectivity of electroreduction was explained by the approaching of the 8-methylene-oleandomycin "bottom side" at the electrode surface and exposing "top" side for the proton transfer from solution upon electron transfer.



Scheme 1. Electrochemical opening of 12,13-oxirane ring of desmycosin.



Scheme 2. Indirect electrochemical oxidation of desmycosin.



1 **2**

Scheme 3. Electrochemical reduction of 8-methylene oleandomycin at mercury electrode.

There are also other approaches for the electrochemical synthesis of chiral compounds. Electroenzymatic reactions belong to the realm of indirect electrochemical chiral transformations. They got into the focus of pharmaceutical research and development due to widespread applications of high enantio- and regioselectivity of the enzyme catalysed reactions. Electroenzymatic reactions open a route to the design of commercially attractive and environmentally friendly reactors and chemical plants. The function of redox enzymes such as, for example, dehydrogenases, oxygenases, reductases and oxidases, are dependent on either bound (flavin adenine dinucleotide (FAD), flavin mononucleotide (FMN), pyrroloquinoline quinone (PQQ)…) or freely dissolved cofactors (nicotinamide adenine dinucleotide (NAD(P)H)) redox cofactors. The use of redox enzymes suffers from several intrinsic problems which limit their widespread applications in carrying out efficient and selective chemical transformations. The most important issue is a high cost associated with the cofactors so that their use in stoichiometric amounts is not economically feasible. The solution is to use small quantities of cofactors in the reaction mixture and to apply simple and efficient methods for their regeneration. Common method is to couple another enzyme in the reaction mixture which is called regeneration enzyme in order to convert reacted cofactor back to its initial state. The complications which arise in this case are mostly connected with the complexity of reaction mixture and the necessity of subsequent separation and isolation of the product. To circumvent this problem there have been many efforts to design an electrochemical system with the suitable mediator which would be able to transfer the electrons from the electrode to cofactor with the regeneration efficiency close to 100 % (Figure 1).

The real life application of the above procedure can be demonstrated in the synthesis of antidepressant (*R*)-fluoxetine where one of the steps could be the enantiometric conversion of aromatic ketone to the corresponding alcohol using alcohol dehydrogenase and NADH as a redox system (Scheme 4).

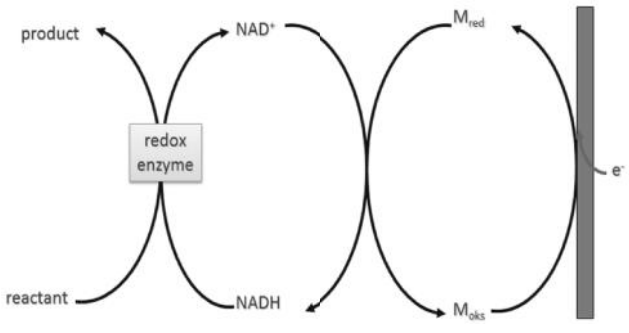
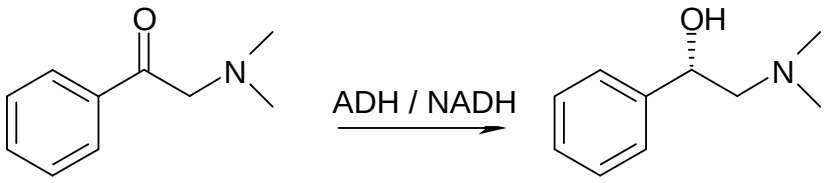


Fig. 1. The principle of indirect electrochemical regeneration system for the enzymatic reduction process.



Scheme 4. Alcohol dehydrogenase and NADH redox system have a potential to be used in the synthesis of antidepressant drug fluoxetine.

ELECTROANALYTICAL CHEMISTRY IN THE DRUG ANALYSIS

The applications of electroanalytical methods in pharmaceutical industry are so broad that it would be very difficult, if not impossible, to address them all in this review. Maybe most neglected in scientific literature are potentiometric methods of analysis. Besides their utilization for purity determination of pharmaceutical active ingredients in routine quality control laboratories [24-35], potentiometric titrations have been developed as fast and accurate methods of choice for physico-chemical profiling of drug substances. Except in the cases when the analyte is sparingly soluble or is available in limited quantities when either Yasuda-Shedlovsky cosolvent [36-40], or spectrorphotometric titrations could be ordinarily used, ionization macro- and microconstants are readily determined by potentiometric titrations [1 and references therein]. Even in the cases when p*K*as of the analyte fall in the water buffering range (pH<3 or pH>11), the ionization constants could be accurately determined if the glass electrode is appropriately calibrated and standardized in this region [1, 41, 42].

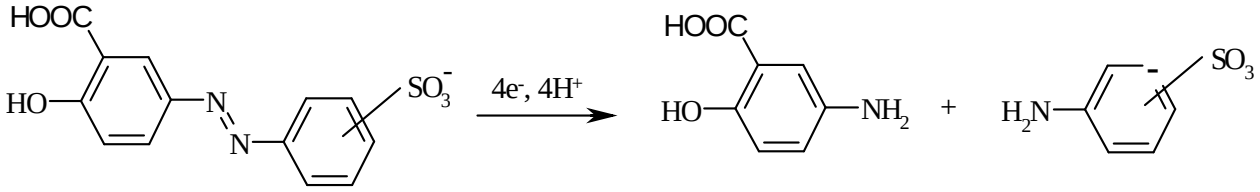
Partition coefficient log *P* as a parameter which describes affinity of neutral substance toward lipophilic environment, as well as lipophilicity profile representing a distribution coefficient, and log *D* as a function of pH, are nowadays determined more accurately and more quickly by two-phase octanol/water potentiometric titration in comparison to the traditional "shake-flask" procedures [1 and references therein]. In a typical experiment, titration curve from the two-phase octanol/water system yields pK_a^{oct}, which is compared to the p*K*a of the substance obtained in aqueous solution. From the known octanol/water ratio, log *P* could be calculated. Other methods of log *P* determination include HPLC [43-51], capillary electrophoresis [43,52,53] and centrifugal partition chromatography [54].

Potentiometric titrations are very frequently used for the determination of intrinsic solubility. Solubility determination by potentiometric titration was introduced by A. Avdeef [55-57]. The intrinsic solubility is calculated from the difference of the substance p*K*a and the apparent pK_a^{app} in the presence of the precipitate. Relatively recently faster potentiometric approach was introduced and developed by Sirius Analytical Ltd. [58-60]. The method is called Chasing equilibrium method (Cheqsol) and it is based on the back and forth titrations around equilibrium pH of the solution.

Despite the fact that polarographic and voltammetric methods of analysis provide several advantages over traditional spectrophotometric techniques such as high sensitivity, low limit of detection and reduction in cost and time of analysis, their real world applications for the qualitative and quantitative analysis of pharmaceuticals are very scarce. Up to the author's knowledge only the pulse polarographic determination of iron sucrose in injections is listed in US Pharmacopeia [61]. The main reason for the lack of electrochemical methods broader application in analytical determinations and validations of drugs is the popularity of combined separation/detection techniques such as HPLC/UV and HPLC/mass spectrometry. Only in the cases where the active substance does not possess a chromophore, but can undergo electrochemical reaction, the HPLC with the coulometric or amperometric detection could be employed. The striking example of this case is the determination of macrolide antibiotics such as erythromycin and azithromycin [62-64] with their tertiary amine groups which can undergo one- or two-electron oxidation reactions. Nevertheless, many research efforts have been made to develop and validate electroanalytical methods for almost all drug substances which can be directly oxidized or reduced at electrodes, especially for the determination of active substances in pharmaceutical formulations such as tablets [65-68,] or in bodily fluids [69 and references within].

On the other hand, electrochemical methods were widely employed for the in-vitro investigations of drug metabolism [64,70-75], ligand-protein binding interactions [76-80], drug-

DNA interactions [81-89] and anti-oxidative potential of certain compounds [90-95]. The mechanism and kinetics of the electrochemical reduction of four derivatives of 2-hydroxy-5-[(sulfophenyl)azo]benzoic acids (**3**) were investigated by cyclic voltammetry and chronoamperometry with the view on their potential application in the treatment of inflammatory bowel diseases [71]. Similarly to market medicines sulfasalazine and olsalazine, the mechanism of biological action of these compounds includes the bacterial reduction of azo bond in the gastrointestinal tract liberating active compound 5-aminosalycilic acid (5-ASA) (Scheme 5).



3 **5-ASA**

Scheme 5. Azo bond reduction follows DISP2 mechanism. The first stage in the reaction is the reduction of hydrazone tautomer giving corresponding hydrazo intermediate. The hydrazo bond cleavage is an acid catalyzed reaction and is followed by homogenous redox reaction between 5-ASA qinoneimine and parent hydrazo compound [71].

Cyclic voltammograms of these compounds are rather complex and strongly pH-dependent. On the basis of the experimental results, 2-hydroxy-5-[(2-sulfophenyl)azo]benzoic acid having sulfo group in ortho position was identified as the compound subject to the slowest rate of azo bond cleavage which in turn enables the highest efficiency to pass upper gastrointestinal tract and consequently higher biological potency for the treatment of Ulcerative colitis and Chron's disease.

THE TRANSFER OF IONISABLE DRUGS ACROSS LIQUID/LIQUID INTERFACE

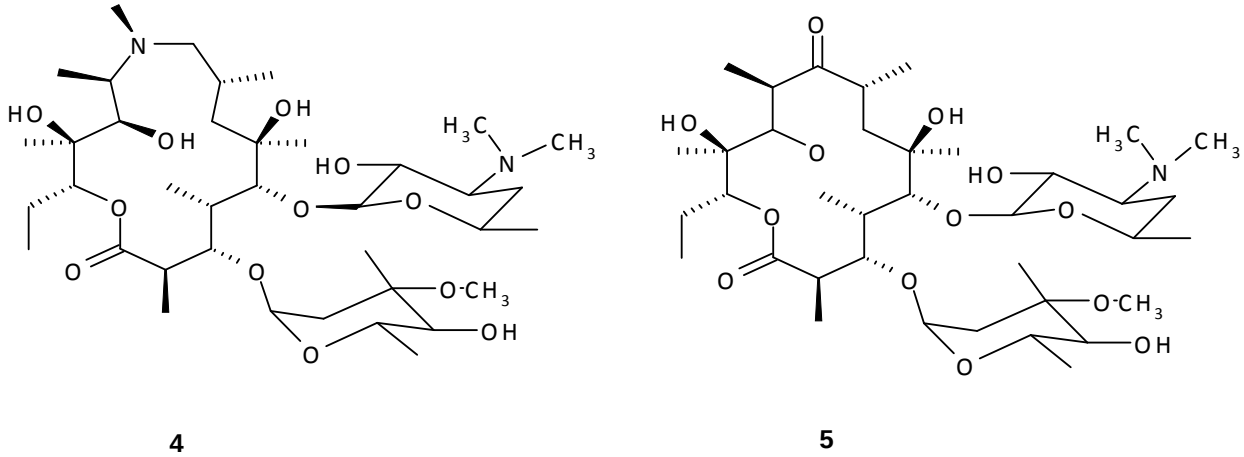
It was estimated that more than 60 % of drugs on the market exist in ionic forms in the physiological pH ranges [96]. If ionic forms are sufficiently lipophilic overall membrane transport properties of ionisable drug compounds depend not only on lipophilicity and permeability, but also on the difference between the actual membrane potential and their standard transfer potential. In order to probe the possibility of the transfer of ionisable drug compounds through the membrane, it was recognized that the liquid/liquid interface (LLI) between two immiscible solvents, one usually being water and another providing lipophilic environment, can practically mimic a biological membrane. The transfer of ionisable drug compounds through such an interface can be conveniently studied by electrochemical methods in a four-electrode electrochemical cell [97-105]. Most frequently used solvents having acceptable dielectric constants for dissolving electrolytes suitable for electrochemical measurements at their interface with water are nitrobenzene and 1,2-dichloroethane.

The electrochemical measurements at LLI can provide information about partitioning of all species present in aqueous phase. While the partitioning of neutral species does not depend on pH or Galvani potentials at LLI, ionised forms are susceptible to both quantities. The dependence of ionic partition can conveniently be represented by ionic partition diagram, i.e. plots of dependence of equilibrium Galvani potential difference between two phases on pH, which resembles well known Pourbaix diagram [106-108]. From ionic partition diagrams the predominance of species in each phase can be deducted, but also a mechanism of ionic transfer such as simple ionic transfer or proton coupled transfer can be revealed [106,109].

The establishment of correlation between electrochemical data obtain on either LLI interface or on supported liquid membranes (SLM) and pharmacological profiling of drugs has been attempted several times [110-114].

It has recently been demonstrated that cyclic voltammetry at water/nitrobenzene interface can be used as a fast in vitro method for the pharmacokinetic screening of macrolide compounds [110]. Macrolides' ability to pass through biological membranes and to accumulate in high concentrations intracellularly are of paramount importance for their pharmacokinetics, as proven by the significant amount of in vivo and in vitro data accumulated on the subject over the years [115].

Although all macrolides show similar ADME properties and pharmacokinetics, azithromycin (**4**) (Figure 2) stands out due to its ability to accumulate in 200-fold excess intracellularly than extracellularly [115]. Cyclic voltammogram of doubly protonated azithromycin taken at water/nitrobenzene interface at pHs of aqueous phase below 6 and compared to single protonated erythromycin is shown in Figure 3.



4 **5**

Fig. 2. Chemical structures of azithromycin (**4**) and erythromycin (**5**).

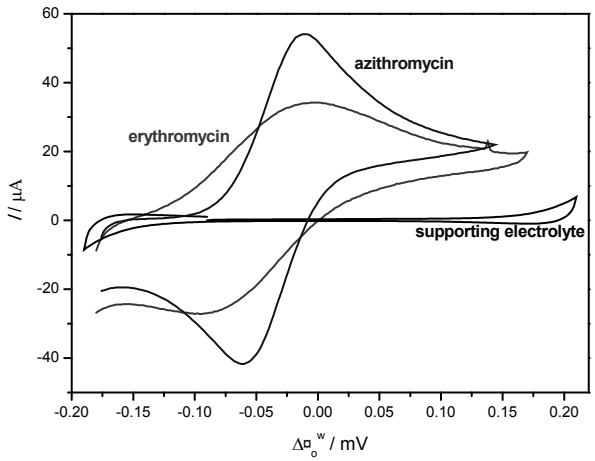


Fig. 3. Cyclic voltammograms of erythromycin and azithromycin at pH of aqueous phase 5.8 and *C*=0.2 M. Scan rate: 20 mV/s. Plot taken from [110].

While the increase of pH of aqueous phase above 6 induces only the shift of the cyclic voltammogram of erythromycin toward more positive potential, the electrochemical behaviour of azithromycin is more complex (Figure 4). Its transfer mechanism changes from simple ionic transfer of doubly protonated species at acidic pHs to the facilitated proton transfer in basic aqueous solutions [110]. The formal transfer potentials of all investigated macrolide compounds were tabulated revealing a significant difference in their values and consequently in the values of transfer free energy. Azithromycin, having the lowest standard transfer potential at water/nitrobenzene interface, stands out among investigated compounds and proofs that membrane permeation of macrolide compounds influences their overall pharmacokinetics. What is more, the results showed that cyclic voltammetry can be used in pharmaceutical research and development as a fast and simple method for screening out macrolide compounds with potentially good ADME properties.

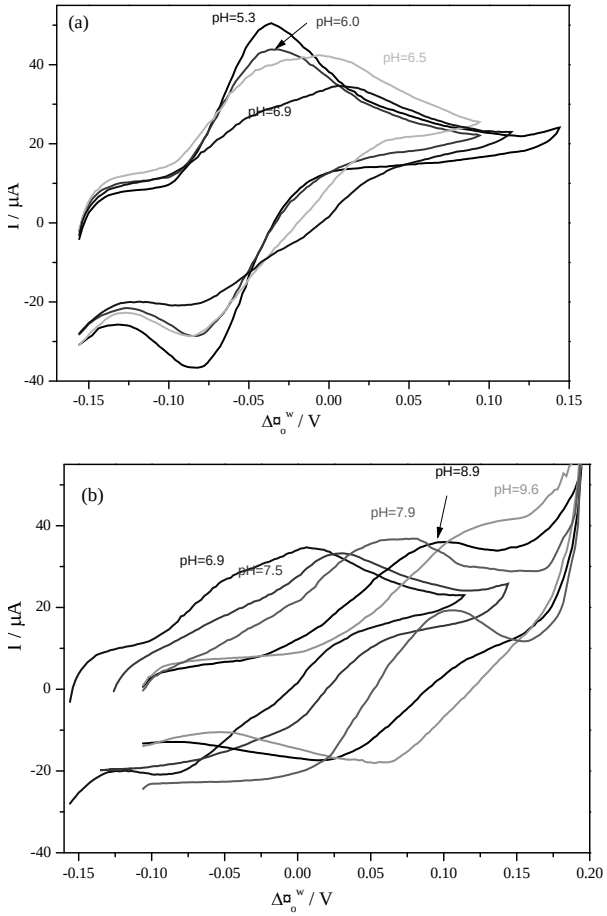


Fig. 4. Cyclic voltammograms of azithromycin at various aqueous phase pH and *C*=0.2 M. Actual pHs indicated on the graphs. Scan rate = 20 mV/s. Plots taken from [24].

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ЕЛЕКТРОХИМИЧНИ МЕТОДИ ПРИ ОТКРИВАНЕ И РАЗРАБОТВАНЕ НА ЛЕКАРСТВА

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(Резюме)

Дадено е кратко описание на приложенията на електрохимичните методи при създаване на фармацевтични продукти. Целта на обзора не е изготвянето на всеобхватен материал, тъй като не би било възможно в една обзорна статия да се покрие толкова разнообразна област. Конкретно са представени няколко примера от опита на автора, които демонстрират приложимостта и ползите от електрохимията за подобряване и ускоряване създаването и разработването на лекарства. Приложенията разгледани в тази статия включват електрохимичен синтез, електроаналитични методи и пренос на лекарствени вещества през междуфазовата граница течност/течност.