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Voltammetric analysis of class II antiarrhythmic drugs propranolol and acebutolol

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Abstract

Antiarrhythmic agents are used to suppressing abnormal rhythms of the heart. Class II antiarrhythmic agents are beta-blockers used to treat supraventricular tachycardias. Voltammetric analysis of class II antiarrhythmic drug active ingredients propranolol and acebutolol carried out with various modified/non-modified electrodes using cyclic voltammetry (CV), linear sweep voltammetry (LSV), differential pulse voltammetry (DPV) and square wave voltammetry (SWV) were compiled from the literature. The effect of supporting electrolyte and pH was interpreted. Scan rate results obtained with the voltammetric methods showed whether the redox process of the drug active ingredient diffusion or adsorption controlled on the electrode used in the selected supporting electrolyte. Results of the quantitative analysis of these drugs were evaluated in terms of parameters such as linearity range, the limit of detection, stability, robustness, repeatability, reproducibility, and sensitivity. Accuracy and precision of the validated methods were compared by combining the results obtained from the pharmaceutical dosage forms of the drug active ingredients. Finally, the analytical application of the drugs in real samples such as human serum and urine was evaluated and it was examined whether the analysis results were affected by the other substances in real samples.

Keywords: Beta-blockers, acebutolol, propranolol, antiarrhythmic drug, modified electrode, voltammetry

1. Introduction

Hypertension is one of the most common diseases detected in over 60% of people over 60 years old [1,2]. Although hypertension is not controlled, it is a complex disease that seriously affects the structure and function of many organs in the body, but the prevalence of hypertension in society is quite high [3-5]. It might also cause chronic kidney failure [6-8]. Beta-adrenergic receptor antagonists (β-blockers) used in the treatment of hypertension cause significant effects and side effects in order to eliminate/decrease the sympathetic muscle tone in various organs and structures, primarily the heart, and in proportion to the degree of this tone [9-12].

Antiarrhythmic agents are used to suppressing abnormal rhythms of the heart [13]. According to Vaughan Williams classification introduced in 1970 [14-17], antiarrhythmic agents are classified as Class I as sodium channel blockers, Class II as beta-blockers, Class III as potassium channel blockers, Class IV as calcium channel blockers and Class V with variable mechanisms [18].

Today, the increasing use of beta-blockers has enabled analysis to become very important and many chemical analysis methods are used for this purpose. There are many studies in the literature using spectroscopic [19-22], chromatographic [23-28], and electrochemical methods for the quantitative analysis of propranolol and acebutolol. Electroanalytical methods are more advantageous than other methods due to their fast, good repeatability rate, high stability, low cost, low detection limit features. In addition, the sample does not have to be pretreated separately, which increases the use of these methods in drug analysis. In recent years, the widespread use of voltammetric methods in the determination of electrochemically active substances is noteworthy [29-33]. In the voltammetric methods, a three-electrode system is used and the selection of working electrodes is very important for precise and effective

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analysis. Especially carbon and metal-based working electrodes are widely used because they are easy to find, relatively inexpensive and can be easily modified. In recent years, studies in which the working electrodes used have been modified with various electroactive materials, and their sensitivity and selectivity have been very popular. For this purpose, a wide variety of materials are used, such as carbon nanotubes, electroactive polymers, and metal nanoparticles. Numerous studies with modified electrodes are available in the literature, reporting that more sensitive results are obtained than bare electrodes [34-41].

In this review, electrochemical analysis studies of beta-adrenergic receptor antagonists acebutolol and propranolol were compiled and gathered. Analyzes made by using linear, cyclic, square wave, differential pulse, and adsorptive stripping voltammetric methods with these active substances were interpreted. It was aimed at this review to determine the electrochemical qualitative and quantitative analysis of these drug active substances selected from beta-blockers by using variously modified and/or unmodified electrodes and voltammetric methods.

1.1. Beta-adrenergic receptor blockers

Beta-adrenergic receptor blockers antagonize the effects of catecholamines on beta-adrenergic receptors [42-44]. Beta-blockers are used in the treatment of hypertension, angina, long-term treatment of heart failure, supraventricular tachyarrhythmia, acute myocardial infarction, migraine, hyperthyroidism, social phobia, essential tremor [44-49]. When beta-adrenergic receptor antagonists were used for the first time, it was not expected to show antihypertensive effects in patients with a primary indication of angina. However, later, all beta-adrenergic receptor antagonists have also been found to reduce arterial blood pressure in hypertensive patients with angina pectoris [17,50,51].

Beta-blockers are divided into two groups: Non-selective, i.e. those that competitively block both β1 and β2 adrenergic receptors, and are generally called β1 selectors and show more affinity for β1 receptors than β2 receptors [44].

Non-selective beta-blockers, such as propranolol, block both β1 adrenergic receptors, which are found in heart cells and enable the sympathetic effect to reach the heart, as well as β2 adrenergic receptors, which are found in the vascular, bronchus, gastrointestinal tract and relax.

Cardio selective beta-blockers such as acebutolol, atenolol, and metoprolol show selectivity to the β1 receptor, and because of these properties, they can be used safely in asthma patients where bronchospasm is contraindicated [18,44,52].

Beta-adrenergic receptor blockers are also frequently used in glaucoma treatment [53]. However, since non-selective agents cause more pronounced decreases in pulmonary function tests, pulse, and systolic blood pressure compared to selective ones, it is recommended to prefer selective ones in those with cardiac and respiratory problems [44].

Propranolol is seen as a standard that needs to be compared to newly developed drugs for systemic use. It has been used extensively for many years and has been found to be safe and effective for many indications [51,54].

The antagonization of beta-adrenergic receptors is effective in regulating circulation as a result of different mechanisms including myocardial contraction, cardiac contraction and decreased cardiac output. As a result of the use of beta-adrenergic receptors, beta receptors are blocked, thereby decreasing the release of renin and decreasing circulating angiotensin II production. In addition, beta-blockers act by increasing the sensitivity of baroreceptors to blood pressure [17,51].

1.2. Effect mechanisms and pharmacokinetic properties of beta-blockers

The antagonization of beta-adrenergic receptors is effective in regulating circulation as a result of different mechanisms including myocardial contraction, cardiac contraction, and decreased cardiac output. As a result of the use of beta-adrenergic receptors, the beta receptors are blocked, thereby decreasing the release of renin and decreasing circulating angiotensin II production. In addition, beta-blockers act by increasing the sensitivity of baroreceptors to blood pressure [17,51,55-57].

Absorption rates of beta-blockers are generally high, reaching maximum concentration 1-3 hours after ingestion. Propranolol has a lower bioavailability as it is exposed to the common first-pass effect. The rate of drugs reaching the systemic circulation is dose-dependent and increases with increasing dose [55,58,59].

Beta-antagonists are rapidly dispersed and have a large distribution volume. Since propranolol and lindolol are lipophilic, they quickly cross the blood-brain barrier. The half-life of most beta antagonists is 2-5 hours. Propranolol and metaprolol are metabolized in the liver; very few unchanged drugs

are found in the urine. Elimination of drugs such as propranolol may take longer in cases of liver disease, decreased hepatic blood flow, or inhibition of hepatic enzymes [55,60]. Side effects of beta-blockers are fatigue, weight gain, cold hands and feet, headache, depression, and trouble sleeping [61,62].

Beta-receptor blockers have different effects on different systems such as cardiovascular, respiration, and endocrine as below:

1.2.1. Effects on the cardiovascular system

When beta-blocking drugs are taken chronically, they reduce blood pressure in patients with hypertension. These drugs do not hypotension in healthy volunteers with normal doses of blood pressure. Beta receptor antagonists have pronounced effects on the heart such as negative inotropic and chronotropic effects.

1.2.2. Effects on the respiratory system

Blockade of β2 receptors in the bronchial smooth muscle increases the resistance of the respiratory tract, especially in patients with asthma. Although this problem is solved with the use of β1 selective antagonists, there are currently no β1 selective antagonists that do not affect β2-adrenoreceptors.

1.2.3. Eye effects

Some beta-blocking drugs have been found to decrease intraocular pressure, especially in the eye with glaucoma.

1.2.4. Metabolic and endocrine effects

Beta-antagonists such as propranolol cause inhibition of lipolysis stimulated by the sympathetic nervous system. Chronic use of beta-adrenoreceptor antagonists caused an increase in VLDL (Very Low-Density Lipoprotein) concentrations and a decrease in HDL (High-Density Lipoprotein) concentration. This event is undesirable in terms of the risk of developing cardiovascular disease [44,60].

1.3. Propranolol

Propranolol (PRP, Fig. 1) is a prototype of beta-blocking drugs. It is a non-selective beta-blocker used in the treatment of various cardiovascular disorders such as hypertension, angina pectoris, pheochromocytoma, cardiac arrhythmia, myocardial infarction, and dysfunctional birth. As with all non-selective blockers, it should be used with caution in patients with diabetes as hypoglycemia improves in patients with diabetes and suppresses symptoms of hypoglycemia such as tachycardia, sweating, and tremor. It is PRP causing the most side effects related to the central nervous system such as sedation, memory impairment, and fatigue [44].

Since PRP has been abused in many sports in recent years to control stage fear, the International Olympic Committee has accepted PRP as doping and included it in the category of banned substances. As a result of the studies conducted in the World Anti-Doping Agency analysis laboratories, it has determined the maximum amount of the drug in the urine as 0.5 μg mL^{-1} [63].

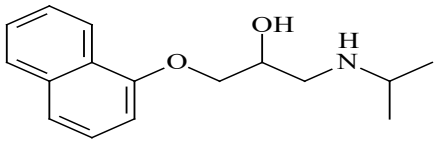

Figure 1. Structure of propranolol

1.4. Acebutolol

Acebutolol hydrochloride (ACB, Fig. 2) is a hydrophilic-adrenoreceptor blocking agent with cardio selective, mild intrinsic sympathomimetic activity. It slows the heart rate, prevents hand tremors, increases athletic performance (physical condition, abilities, and muscle strength), and has a calming effect. Therefore, determining this drug used by athletes in urine is of great importance [64].

Acebutolol has a lipophilic character and when taken orally, its absorption in the gastrointestinal tract is complete or nearly complete. Approximately 80% is excreted in urine and 20-30% in bile. It forms the active metabolite of diacetol in the body [44,65].

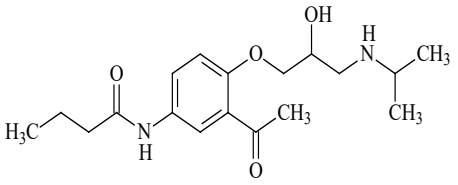

Figure 2. Structure of acebutolol

2. Electrochemical behavior of beta-blockers

Some studies presenting the electrochemical analysis of PRP and ACB carried out using various electrochemical sensors are available in the literature. The electroanalytical determination studies of PRP and ACB are described below and the results obtained using validated voltammetric methods are listed in Table 1.

2.1. Electroanalytical determination of PRP

Gaichore and Srivasta [66] prepared a modified carbon paste electrode based on γ-cyclodextrin carbon nanotube composite (γ-CD-CNT-CME) and used for the determination of PRP. Electrochemical analysis of PRP was checked out with cyclic voltammetry (CV) and differential pulse adsorptive stripping voltammetry (DPAdSV). CV results indicated that the electrooxidation of PRP was irreversible and adsorption controlled on γ-CD-CNT-CME. 0.04 M Britton Robinson buffer (BRB) solution at pH 1.5 was selected as supporting electrolyte in PRP determination. Under optimum experimental conditions, the peak current of PRP increased linearly with its concentration from 0.142 to 47.6 μM with a detection limit (LOD) of 40.19 nM by DPAdSV. The repeatability, reproducibility, precision, and accuracy of the selected method were detected by performing five replicate measurements for PRP with satisfactory results. Stability results indicated that the electrode was stable for about 6 months. The proposed method was used for the determination of PRP in pharmaceutical formulations, urine, and blood serum samples without any interference from other species.

p-(Melamine) film-coated edge plane pyrolytic graphite electrode (EPPG) was used as a sensitive electrochemical sensor for the determination of PRP by Raj et al. [67]. The p-(melamine)/EPPG sensor demonstrated excellent electrocatalytic activity for the oxidation of PRP with a significant increase in the peak current and a shift in the peak potential towards less positive potentials. Cyclic voltammograms of PRP showed a single irreversible oxidation peak at pH 7.4 on the p-(melamine)/EPPG sensor. Square wave voltammetry (SWV) was used for the detection of PRP as it has several advantages including excellent sensitivity and low background currents. Under optimum experimental conditions, the calibration plot of the peak current versus the concentration was found to be linear in the range of 0.1 to 800 μM. The limit of detection (LOD) and limit of quantification (LOQ) values were calculated as 9 nM and 30 nM, respectively. Interference studies were checked out to investigate the influence of some common interfering species (metabolites in biological fluids) in the determination PRP. It was observed no interference in the determination of PRP with the common metabolites in biological fluids. The modified sensor and the proposed method were applied to the determination of PRP in pharmaceuticals, human urine, and plasma samples with good recovery results.

A sensor-based on 8-hydroxy-8-propoxycalix [8] arene and multi-walled carbon nanotubes modified glassy carbon electrode (HPC-8/MWCNT/GCE) was prepared for the determination of PRP [63]. This modified electrode caused an increase in the peak current and the electrocatalytic activity on PRP electrooxidation. CV and DPV methods were used to investigate the electrooxidation behavior of PRP. The oxidation process of PRP was diffusion-controlled and irreversible on HPC-8/MWCNT/GCE. Oxidation peak currents were obtained linearly with PRP concentrations ranging from 0.338 to 54.1 μM with a detection limit of 135 nM in phosphate buffer solution (PBS) at pH 7.0. The results of the stability studies for HPC-8/MWCNT/GCE were stable for over 2 weeks and remained 91.7% reproducible when stored at 4 °C. The modified electrode was successfully used for the determination of PRP in pharmaceutical dosage forms.

In another study, a graphene and conductive polymer (poly-1,5-diaminonaphthalene) modified edge plane pyrolytic graphite (GR/PDAN/EPPG) electrode was used for the sensitive determination of PRP [68]. Cyclic voltammograms showed that the electrochemical oxidation of PRP was irreversible. The authors proposed a possible $2e^-/2H^+$ oxidation mechanism. The SWV method was applied to detect PRP over the concentration of 0.1 - 750 μM with a detection limit of 20 nM in PBS at pH 7.2. The results of reproducibility studies revealed that the sensor had excellent reproducibility with a relative standard deviation of 3.2%. The developed method was applied to detect PRP in pharmaceuticals, human urine, and blood plasma samples with good recoveries.

The electrochemical oxidation behavior of PRP was analyzed with CV and DPV methods using platinum nanoparticles doped multi-walled carbon nanotubes modified GCE (PtNPs/MWCNTs/GCE) by Kun et al. [69]. The oxidation reaction of PRP on PtNPs/MWCNTs/GCE was irreversible and diffusion controlled. The peak current response of PRP was linear in the concentration range of 0.676 to 38.0 μM with a LOD of 84.5 nM with DPV in PBS at pH 7.0. PtNPs/MWCNTs/GCE was found to be stable for two weeks. The prepared PtNPs/MWCNTs/GCE was used for the determination of PRP in its pharmaceutical dosage forms with reliable results.

A carbon paste electrode incorporated with nanosized propranolol-imprinted polymer (nanoMIP-CPE) was developed for the determination of N-nitrosopropranolol as a carcinogenic metabolite of PRP by Alizadeh and Allahyari [70]. Oxidation of

the hydroxyl group in N-nitrosopropranolol was used to monitor the target molecule. Under optimized conditions, the concentration of N-nitrosopropranolol ranged linearly from 0.1 to 10.0 μM with a LOD of 80.0 nM in acetate buffer solution at pH 4.5 by DPV method. The sensor and method developed for the determination of N-nitrosopropranolol were applied in plasma and gastric juice samples. The results clearly showed that the developed sensor and validated method could be applicable to detect N-nitrosopropranolol in real samples.

A reduced graphene oxide modified carbon paste electrode (rGO-CPE) was used to sensitively determine PRP by CV, DPV, and SWV methods [71]. The oxidation process of PRP was irreversible and diffusion controlled on rGO-CPE. The authors proposed that the electrooxidation of PRP involved $2H^+/2e^-$ transfer process. Under optimized conditions, the oxidation peak of PRP increased proportionally in the concentration range of 0.1 to 2.5 μM for DPV and 0.1 to 5.0 μM for SWV in BRB at pH 7.0. LOD values for DPV and SWV were calculated as 40.0 nM and 2.0 nM, respectively. The proposed sensor was successfully used to determine the amount of PRP in the pharmaceuticals, artificial urine, and serum samples with SWV.

Mohammadi and his colleagues developed a simple and sensitive method for PRP analysis using the magnetic core-shell manganese ferrite nanoparticles modified screen-printed carbon electrode (MCSNP/SPCE) [72]. CV and DPV methods were used for the electrochemical measurements of PRP. The oxidation reaction of PRP was irreversible and diffusion controlled on MSPCE/SPCE. DPV parameters were optimized for the quantitative determination of PRP. Under optimized conditions, the PRP peak current changed linearly with a concentration of 0.4 to 200.0 μM in PBS at pH 7.0. The detection limit was obtained as 80 nM. The developed method was applied for the measurement of PRP concentration in pharmaceutical dosage form and urine samples with good analytical performance.

Łuczak prepared a nanogold supported inorganic/organic hybrid 3D sensor (3D Au-NPs-Au electrode) for the electrochemical oxidation and quantitative determination of PRP [73]. The results of the scan rate study indicated that the irreversible oxidation process of PRP was controlled by diffusion in PBS at pH 7.4. The prepared sensor showed reliable results in the PRP concentration range from 0.1 to 20.0 μM with a detection limit of 0.0675 nM using the DPV method. The prepared voltammetric sensor and the proposed method were applied to detect PRP in dosage forms without any interference.

Nateghi developed the $(Ti_{0.5}V_{0.5})_3C_2$ modified carbon paste electrode (CPE) and used it for the detection of PRP in its pharmaceutical dosage form and neutral solution by voltammetric methods [74]. According to the voltammetric analysis, it was proposed that the possible oxidation mechanism of PRP was over $2H^+/2e^-$. Linear PRP concentration range 0.5 - 5.0 μM, LOD value was obtained as 160.0 nM in BRB solution at pH 7.0 using DPV. The accuracy of the proposed method was demonstrated by the successful determination of PRP from its pharmaceutical dosage form.

In another study, the electroanalytical determination of PRP was carried out using a cathodically pretreated boron-doped diamond electrode (BDD) by the SWV method [75]. Cyclic voltammograms of PRP in 0.1 M H_2SO_4 showed one irreversible anodic peak with a diffusion-controlled process. The SWV method validated in the range of 0.2 - 9.0 μM for PRP in 0.1 M H_2SO_4. The LOD value for PRP was obtained as 180.0 nM. The proposed method was used for the determination of PRP in pharmaceutical formulations with good results.

Electroanalysis of PRP was investigated by CV and DPV methods using platinum nanoparticle doped multiwalled carbon nanotube-modified GCE (PtNPs/MWCNTs/GCE) in 0.1 M PBS at pH 7.4 [76]. PtNPs/MWCNTs/GCE showed electrocatalytic activity to the oxidation of PRP. Under optimized conditions, the linear range of PRP was 0.2 - 50 μM with a detection limit of 150.0 nM for the DPV method. The practical applicability of the developed modified electrode for the selective and sensitive determination of PRP was tested in serum samples and good recovery results were obtained.

When the studies in the literature described above were evaluated, it was seen that the electrochemical analysis of PRP was performed for the anodic behavior of PRP. Various modified or unmodified electrodes were used in the studies and it was found that PRP generally had a diffusion-controlled process. For this reason, DPV and SWV techniques could be used for the sensitive determination of PRP, except for a study done with DPAdSV due to the adsorption-controlled process of PRP [66]. The widest linearity ranges were obtained with p-(melamine) film-coated edge plane pyrolytic graphite electrode [67] and the graphene/conductive polymer (poly-1,5-diaminonaphthalene) modified edge plane pyrolytic graphite electrode [68]. Although the lowest LOD value was seen with the reduced graphene

oxide modified carbon paste electrode and SWV method [71], the linearity range of this study was narrow. The subsequent lowest LOD values were obtained for the studies with the widest linearity ranges [67,68]. Inter-day and intra-day repeatability values were obtained as RSD% and between 0.33% and 3.5%. Accuracy studies were carried out and recovery values were obtained in the range of 90.0% and 107.0% for pharmaceutical dosage forms, urine, serum, and gastric juice. Precision and accuracy studies showed that all electrodes and methods developed gave satisfying results and were suitable for the determination of PRP without any interference of excipients.

The possible oxidation mechanism of PRO has also been discussed in some studies, and two oxidation pathways have been proposed: The hydroxyl group in one of them and the secondary amine group in the other is thought to be oxidized. On both pathways, the redox mechanism proceeds over 2 electrons and 2 protons [63,66-69,71,76].

2.2. Electroanalytical determination of ACB

Al-Ghamdi et al. [77] investigated the cathodic electrochemical behavior of ACB using voltammetric methods with a hanging mercury drop electrode (HDME). The experimental results of ACB indicated an irreversible and adsorption controlled cathodic process of ACB. The reduction peak current was linear in proportion to the concentration of ACB in the range of 0.5 to 6.0 μM in BRB solution at pH 7.5 by square wave adsorptive stripping voltammetry (SWAdSV) under optimized conditions. LOD and LOQ values were obtained as 170.0 nM and 500.0 nM, respectively. The validated method was applied to direct analysis of ACB from its pharmaceutical dosage forms, human plasma, and human urine samples, with satisfying recovery results.

An electrochemical method for the determination of ACB was developed based on the pencil graphite electrode (PGE) by Levent [78]. ACB showed a reversible and adsorption controlled oxidation peak by CV method. The electrochemical oxidation mechanism of ACB was suggested to be via $2e^-/2H^+$. The oxidation peak current indicated a linear relationship between 0.0004 and 0.007 μM with a LOD of 0.09 nM in BRB solution at pH 10.0 by SWAdSV under the specified conditions. The proposed method was successfully applied for the ACB determination in pharmaceutical dosage forms and urine samples.

In another study, Yamuna et al. [79] investigated the electrochemical oxidation of ACB using screen-printed carbon electrodes (SPCE) with CV and DPV methods. SPCE was activated by electrochemical pretreatment prior to experiments. The authors reported that the activated SPCE (aSPCE) revealed a better performance than inactivated SPCE. ACB had an irreversible and diffusion-controlled electrooxidation process on aSPCE. The linear range was found to be 0.01 to 200 μM with a LOD of 6.0 nM in PBS at pH 7.0 with DPV. The results of the interference study indicated that aSPCE could be applicable for the determination of ACB in practical applications.

Detection of ACB was achieved using a simple and economic graphite pencil electrode (GPE) by Bagoji et al. [80]. Oxidation signals of ACB were measured by CV, DPV, and SWV methods. According to the results, the electrochemical oxidation process of ACB was irreversible and was defined as diffusion controlled. Oxidation peak currents increased linearly with an increase of ACB concentration in the range of 1.0 to 15.0 μM for DPV and SWV in PBS at pH 7.0. LOD values were obtained as 0.126 nM and 0.128 nM for DPV and SWV, respectively. The validated DPV method was applied for the detection of ACB in human urine samples.

Silva et al. [81] prepared a sensor based on a carbon paste electrode modified with amino-functionalized mesostructured silica (NH_2/HMS/CPE) for the simultaneous determination of ACB, pindolol, and metoprolol in waters by voltammetric methods. Two anodic and one cathodic peak were obtained for ACB using NH_2/HMS/CPE in 0.1 M PBS at pH 4.0. The first anodic peak and cathodic peak were attributed to a quasi-reversible redox process. The second irreversible anodic peak was used for the measurements of the experiments because it was more intense than the first oxidation peak. Scan rate studies indicated that the electrooxidation process of ACB on NH_2/HMS/CPE was adsorption controlled. The calibration curve obtained for ACB demonstrated a linear relationship in the concentration range of 0.5 - 50 μM. LOD and LOQ values were obtained with DPV as 58.0 and 190.0 nM, respectively. The proposed method was successfully applied for the determination of ACB, pindolol, and metoprolol in drinking water, environmental and wastewater samples.

Table 1. Validation data for the analysis of PRP and ACB (p=plasma, u=urine, ph= pharnaceut., w=real water sample, b=buffer, gj=gastric juice, hp=human plasma, hu=human urine)

Propranolol

Electrode Type	Method	Medium	Linear Range	LOD	LOQ	Precision (RSD%) Intra-day	Precision (RSD%) Inter-day	Recovery (%)	Ref.
γ-CD-CNT-CME								99.5-99.8 (ph)	[66]
	DPAdSV	BRB, pH 1.5	0.142-47.60 μM	0.0401 μM	-	1.84	1.99	98.2-100.7 (u) 98.8-100.4 (s)	
p-(melamime)/ EPPGE	SWV	PBS, pH 7.4	0.1-800 μM	9 nM	30 nM	0.89	-	98.55-101.21 (u) 98.63-101.62 (p)	[67]
HPC-8/MWCNT/GCE	DPV	PBS, pH 7.0	0.338-54.10 μM	0.135 μM	-	3.2	-	99.4 (ph)	[63]
GR/PDAN/EPPG	SWV	PBS, pH 7.2	0.1-750 μM	20 nM	-	3.2	-	97.75 (ph)	[68]
PtNPs/MWCNTs/GCE	DPV	PBS, pH 7.0	0.676-38.0 μM	0.0845 μM	-	2.74	-	99.2 (ph)	[69]
nanoMIP-CPE	DPV	$HClO_4$, pH 4.5	0.1-10.0 μM	0.08 μM	-	-	-	90.0-106.0 (s) 91.0-107.0 (gj)	[70]*
rGO-CPE	DPV	BRB, pH 7.0	0.1-2.5 μM	0.04 μM	-	-	-	-	[71]
	SWV		0.1-5.0 μM	0.002 μM	-	-	-	100.0-100.34 (ph) 100.0 (u) 102.0 (s)	
MCSNP/SPCE	DPV	PBS, pH 7.0	0.4-200 μM	80 nM	-	-	-	97.8-103.9 (ph) 97.0-102.5 (u)	[72]
3D Au-NPs-Au electrode	DPV	PBS, pH 7.4	0.0001-0.02 mM	$6.75x10^{-5}$ mM	-	-	2.9	97.0-105.0 (ph)	[73]
$(Ti_{0.5}V_{0.5})_3C_2$ modified CPE	DPV	BRB, pH 7.0	0.5-5.0 μM	0.16 μM	-	-	-	94.0 (ph)	[74]
BDD	SWV	0.1 M H_2SO_4	0.2-9.0 μM	0.18 μM	-	0.33	3.5	93.3-105.0 (ph)	[75]
PtNPs/MWCNTs/GCE	DPV	PBS, pH 7.4	0.2-50 μM	0.15 μM	-	2.44	-	99.0-103.2 (s)	[76]

Acebutolol

Electrode Type	Method	Medium	Linear Range	LOD	LOQ	Precision (RSD%) Intra-day	Precision (RSD%) Inter-day	Recovery (%)	Ref.
HDME	SWAdSV	BRB, pH 7.5	0.5-6.0 μM	0.17 μM	50 μM	2.9-3.2 (hp) 3.3-2.8 (hu)	3.4-3.8 (hp) 3.3-1.7 (hu)	101.6 (ph.) 97.0-103 (p) 96-104 (u)	[77]
PGE	SWAdSV	BRB, pH 10.0	0.4-7.0 nM	0.09 nM	0.30 nM	4.82 (b)	-	103.9 (ph) 90.6-109.1 (u)	[78]
aSPCE	DPV	PBS, pH 7.0	0.01-200 μM	0.006 μM	-	-	-	-	[79]
GPE	DPV	PBS, pH 7.0	1.0-15.0 μM	0.0126 μM	0.0418 μM	3.01	-	95.4-101 (u)	[80]
	SWV			0.0128 μM	0.0427 μM	-	-	-	
NH_2/HMS/CPE	DPV	PBS, pH 4.0	0.5-50 μM	0.058 μM	0.19 μM	3.8	4.0	99-108 (w)	[81]

* In this study, N-nitrosopropranolol was detected as the metabolite of propranolol.

In the literature, studies achieved for the electrochemical analysis of ACB were usually performed on the oxidation peak of ACB, except for a study with a hanging mercury drop electrode [77]. The studies were carried out using modified and unmodified electrodes, and the process of ACB on the electrodes was adsorption controlled for some studies [77,78] and diffusion controlled for other studies [79-81]. The widest linearity range and the lowest LOD value were obtained with the pretreated screen-printed electrode [79]. Inter-day and intra-day repeatability values were between 0.78% and 4.825% and were given as RSD%. Accuracy studies were achieved with recovery values, and the results were between 90.6% and 109.0% for pharmaceutical dosage forms, urine, serum, and real water samples. Recovery values showed that the electrodes and the developed methods could be used for the sensitive determination of ACB without any interference of the excipients.

Possible oxidation and reduction mechanisms of ACB have been discussed in some studies. It has been suggested that the cathodic mechanism of ACB is due to the reduction of the carbonyl group between the methyl and phenyl groups [77]. In the oxidation mechanism of ACB, two different mechanisms have been proposed for the two anodic peaks of ACB. Accordingly, oxidation for the semi-reversible redox mechanism is thought to proceed with the hydroxyl group with 2 electrons and 2 protons. For the other

irreversible redox mechanism, it has been suggested that oxidation results from the breakdown and subsequent oxidation of the molecule [80,81].

3. Conclusions

Propranolol and acebutolol as class II antiarrhythmic agents are beta-blockers and are used in the treatment of supraventricular tachycardias. Voltammetric analysis of propranolol and acebutolol studied with various modified/non-modified electrodes were compiled from the literature. After the supporting electrolyte was selected for the voltammetric analysis of PRP and ACB, scan rate studies were achieved in the studies and it was observed that the redox process of PRP and ACB was generally diffusion-controlled on the electrodes used. Quantitative analysis of drug active ingredients was investigated in terms of some parameters such as linearity range, the limit of detection, stability, repeatability, reproducibility, and sensitivity. The accuracy and precision of the methods were studied using the pharmaceutical dosage forms of propranolol and acebutolol and the results were analyzed. Finally, the voltammetric determination of this drug's active ingredients was carried out using some real samples such as human serum and urine. The results showed that other excipients in real samples did not affect the quantitative analysis of propranolol and acebutolol.

References

[1] J.E. Bager, P. Hjerpe, K. Manhem, S. Bjorck, S. Franzen, A. Rosengren, S.A. Eryd, Treatment of hypertension in old patients without previous cardiovascular disease, J Hypertens, 37, 2019, 2269-2279.

[2] P.K. Whelton, N.R.C. Campbell, D.T. Lackland, G. Parati, C.V.S. Ram, M.A. Weber, X.H. Zhang, Strategies for prevention of cardiovascular disease in adults with hypertension, J Clin Hypertens, 22, 2020, 132-134.

[3] J. Naish, D.S. Court, Medical Sciences, 2. edition, Saunders Ltd, London, 2014, 562.

[4] N.R. Poulter, D. Prabhakaran, M. Caulfield, Hypertension, Lancet, 386, 2015, 801-12.

[5] R. McManus, M. Constanti, C.N. Floyd, M. Glover, A.S. Wierzbicki, Managing cardiovascular disease risk in hypertension, Lancet, 395, 2020, 869-870.

[6] V.P. Arcangelo, A.M. Peterson, Pharmacotherapeutics for Advanced Practice: A Practical Approach (4. edition), 2016, Philadelphia, Lippincott Williams & Wilkins.

[7] T.I. Chang, M.J. Sarnak, Intensive blood pressure targets and kidney disease, Clin J Am Soc Nephro, 13, 2018, 1575-1577.

[8] A. Duni, E. Dounousi, P. Pavlakou, T. Eleftheriadis, V. Liakopoulos, Hypertension in chronic kidney disease: Novel insights, Curr Hypertens Rev, 16, 2020, 45-54.

[9] A.V. Chobanian, G.L. Bakris, H.R. Black, W.C. Cushman, L.A. Green, J.L. Izzo, D.W. Jones, B.J. Materson, S. Oparil, J.T. Wright, E.J. Roccella, Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure, Hypertension, 42, 2003, 1206-1252.

[10] A.S. Go, M.A. Bauman, S.M. Coleman King, G.C. Fonarow, W. Lawrence, K.A. Williams, E. Sanchez, An effective approach to high blood pressure control: A science advisory from the American Heart Association, the American College of Cardiology, and the Centers for Disease Control and Prevention, Hypertension, 63, 2014, 878-85.

[11] C.S. Wiysonge, H.A. Bradley, J. Volmink, B.M. Mayosi, L.H. Opie, Beta-blockers for hypertension, Cochrane Db Syst Rev 1, 2017, CD002003.

[12] S.W. Chan, M. Hu, B. Tomlinson, The pharmacogenetics of beta-adrenergic receptor antagonists in the treatment of hypertension and heart failure, Expert Opin Drug Met, 8, 2012, 767-790.

[13] Y. Agrawal, J.K. Kalavakunta., V. Gupta, Antiarrhythmic agent induced ventricular tachycardia, Am J Ther, 24, 2017, E487-E487.

[14] E.M. Vaughan Williams, A classification of antiarrhythmic actions reassessed after a decade of new drugs, J Clin Pharmacol, 24, 1984, 129-147.

[15] P. Brugada, The Vaughan-Williams classification of antiarrhythmic drugs - Why don't we find its clinical counterpart pace, Pace, 13, 1990, 339-343.

[16] J. Ritter, R. Flower, G. Henderson, H. Rang, Rang and Dale's Pharmacology (7. Edition), 2011, London, Churchill Livingstone.

[17] M. Lei, D.L. Wu, D.A. Terrar, C.L.-H. Huang, Modernized Classification of cardiac antiarrhythmic drugs, Circulation, 138, 2018, 1879-1896.

[18] D.P. Zipes, A consideration of antiarrhythmic therapy, Circulation, 72, 1985, 949-956.

[19] A.A. El-Emam, F.F. Belal, M.A. Moustafa, S.M. El-Ashry, D.T. El-Sherbiny, S.H. Hansen, Spectrophotometric determination of propranolol in formulations via oxidative coupling with 3-methylbenzothiazoline-2-one hydrazone, Farmaco, 58, 2003, 1179-1186.

[20] A. Gölcü, C. Yücesoy, S. Serin, Spectrophotometric determination of some beta-blockers in dosage forms based on complex formation with Cu(II) and Co(II), II Farmaco, 59, 2004, 487-492.

[21] A. Gölcü, New, simple, and validated UV-spectrophotometric method for the estimation of some beta blockers in bulk and formulations, J Anal Chem, 63, 2008, 538-543.

[22] J.M.M. Junior, A.L.H. Muller, E.L. Foletto, A.B. da Costa, C.A. Bizzi, E.I. Muller, Determination of propranolol hydrochloride in pharmaceutical preparations using near infrared spectrometry with fiber optic probe and multivariate calibration methods, J Anal Methods Chem, 2015, 795102.

[23] R. Ghanem, M.A. Bello, M. Callejon, A. Guiratum, Determination of beta-blocker drugs in pharmaceutical preparations by non-suppressed ion chromatography, J Pharmaceut Biomed, 15, 1996, 383-388.

[24] M. Delamoye, C. Duverneuil, F. Paraire, P. de Mazancourt, J.-C. Alvarez, Simultaneous determination of thirteen β-blockers and one metabolite by gradient high-performance liquid chromatography with photodiode-array UV detection, Forensic Sci Int, 141, 2004, 23-31.

[25] H.-B. Lee, K. Sarafin, T.E. Peart, Determination of β-blockers and β2-agonists in sewage by solid-phase extraction and liquid chromatography-tandem mass spectrometry, J Chromatogr A, 1148, 2007, 158-167.

[26] S.A.B. Salman, S.A. Sulaiman, Z. Ismail, S.H. Gan, Quantitative determination of propranolol by ultraviolet HPLC in human plasma, Toxicol Mech Method, 20, 2010, 137-142.

[27] M. Caban, P. Stepnowski, M. Kwiatkowski, N. Migowska, J. Kumirska, Determination of β-blockers and β-agonists using gas chromatography and gas chromatography-mass spectrometry - A comparative study of the derivatization step, J Chromatogr A, 1218, 2011, 8110-8122.

[28] A.A. Salem, I.A.Wasfi, S.S.Al-Nassibi, Trace determination of β-blockers and β2-agonists in distilled and waste-waters using liquid chromatography-tandem mass spectrometry and solid-phase extraction, J Chromatogr B, 908, 2012, 27-38.

[29] S.A. Özkan, B. Uslu, H.Y. Aboul-Enein, Analysis of pharmaceuticals and biological fluids using modern electroanalytical techniques, Crit Rev Anal Chem, 33, 2003, 155-181.

[30] V.K. Gupta, R. Jain, K. Radhapyari, N. Jadon, S. Agarwal, Voltammetric techniques for the assay of pharmaceuticals-A review, Anal Biochem, 408, 2011, 179-196.

[31] O.A. Farghaly, R.S.A. Hameed, A.-A.H. Abu-Nawwas, Electrochemical analysis techniques: A review on recent pharmaceutical applications, Int J Pharm Sci Rev Res, 25, 2014, 37-45.

[32] F. Scholz, Voltammetric techniques of analysis: The essentials, ChemTexts, 1, 2015, 17.

[33] O. Inam, E. Demir, B. Uslu, Voltammetric pathways for the analysis of ophthalmic drugs, Curr Pharm Anal, 16, 2020, 367-391.

[34] A. Vulcu, C. Grosan, L.M. Muresan, S. Pruneanu, L. Olenic, Modified gold electrodes based on thiocytosine/guanine-gold nanoparticles for uric and ascorbic acid determination, Electrochim Acta, 88, 2013, 839-846.

[35] D. Kul, C.M.A. Brett, Electrochemical investigation and determination of levodopa on poly(Nile blue-a)/multiwalled carbon nanotube modified glassy carbon electrodes, Electroanal, 26, 2014, 1320-1325.

[36] P. Krzyczmonik, E. Socha, G. Andrijewski, Determination of ascorbic acid by a composite-modified platinum electrode, Anal Lett, 50, 2017, 806-818.

[37] S. Palanisamy, S.K. Ramaraj, S.-M. Chen, V. Velusamy, T.C.K. Yang, T.-W. Chen, Voltammetric determination of catechol based on a glassy carbon electrode modified with a composite consisting of graphene oxide and polymelamine, Microchim Acta, 184, 2017, 1051-1057.

[38] I. Zablocka, M. Wysocka-Zolopa, K. Winkler, Electrochemical detection of dopamine at a gold electrode modified with a polypyrrole-mesoporous silica molecular sieves (MCM-48) film, Int J Mol Sci, 20, 2019, 111.

[39] H. Sarıoğulları, A. Şenocak, T. Basova, E. Demirbaş, M. Durmuş, Effect of different SWCNT-BODIPY hybrid materials for selective and sensitive electrochemical detection of guanine and adenine, J Electroanal Chem, 840, 2019, 10-20.

[40] E.S. Gomes, F.R.F. Leite, B.R.L. Ferraz, H.A.J.L. Mourão, A.R. Malagutti, Voltammetric sensor based on cobalt-poly(methionine)-modified glassy carbon electrode for determination of estriol hormone in pharmaceuticals and urine, J Pharm Anal, 9, 2019, 347-357.

[41] A. Şenocak, A. Khataee, E. Demirbas, E. Doustkhahd, Ultrasensitive detection of rutin antioxidant through a magnetic micro-mesoporous graphitized carbon wrapped Co nanoarchitecture, Sensor Actuat B-Chem, 312, 2020, 127939.

[42] J.W. Upward, D.G. Waller, C.F. George, Class II antiarrhythmic agents, Pharmacol Therapeut, 37, 1988, 81-109.

[43] W.H. Frishman, β-Adrenergic Blockers, Hypertension (2. edition), A Companion to Brenner and Rector's The Kidney, 2005, Amsterdam, Elsevier Inc.

[44] A.J. Trevor, B.G. Katzung, M. Kruidering-Hall, Katzung & Trevor's Pharmacology Examination & Board Review, 11. edition, 2015, New York, McGraw-Hill Education.

[45] N. Freemantle, J. Cleland, P. Young, J. Mason, J. Harrison, Beta blockade after myocardial infarction: systematic review and meta regression analysis, BMJ, 318, 1999, 1730-1737.

[46] P.A. James, S. Oparil, B.L. Carter, W.C. Cushman, C. Dennison-Himmelfarb, J. Handler, D.T. Lackland, M.L. LeFevre, T.D. MacKenzie, O. Ogedegbe, S.C. Smith, L.P. Svetkey, S.J. Taler, R.R. Townsend, J.T. Wright, A.S. Narva, E. Ortiz, 2014 evidence-based guideline for the management of high blood pressure in adults: Report from the panel members appointed to the Eighth Joint National Committee (JNC 8), JAMA, 311, 2014, 507-520.

[47] E.A. Ushkalova, S.K. Zyryanov, K.E. Zatolochina, A.P. Pereverzev, N.A. Chukhareva, Antiarrhythmic drugs use in elderly patients. Vaughan Williams class I and II drugs, Ration Pharmacother Cardiol, 12, 2016, 471-478.

[48] C. Hocht, F.M. Bertera, J.S. Del Mauro, Y.S. Plantamura, C.A. Taira, A.H. Polizio, What is the real efficacy of beta-blockers for the treatment of essential hypertension?, Curr Pharm Desing, 23, 2017, 4658-4677.

[49] J.M. Cruickshank, The Role of Beta-Blockers in The Treatment of Hypertension, Hypertension: From Basic Research to Clinical Practice, Advances in Experimental Medicine and Biology, Editor: M.S. Islam, 956, 2016, Springer, Cham.

[50] T.K. Morgan, R. Lis, W.C. Lumma, R.A. Wohl, K. Nickisch, G.B. Phillips, J.M. Lind, J.W. Lampe, S.V. Di Meo, H.J. Reiser, T.M. Argentieri, M.E. Sullivan, E. Camtor, Synthesis and pharmacological studies of N-[4-[2-hydroxy-3-[[2-[4-(1H-imidazol-1-Yl)phenoxy]ethyl]amino]propoxy]phenyl] methanesulfonamide, a novel antiarrhythmic agent with class II and class III activities, J Med Chem, 33, 1990, 1087-1990.

[51] L.L. Brunton, J.S. Lazo, K.L. Parker, The pharmacological basis of therapeutics (11. edition), 2006, New York, McGraw-Hill Education.

[52] D. Ladage, R.H.G. Schwinger, K. Brixius, Cardio-selective beta-blocker: Pharmacological evidence and their influence on exercise capacity, Cardiovasc Ther, 31, 2013, 76-83.

[53] K.Y. Xu, E.D.P. Campbell, S.S. Gill, R. Nesdole, R.J. Campbell, Impact of combination glaucoma therapies on beta-blocker exposure, J Glaucoma 26, 2017, E107-E109.

[54] A.V. Srinivasan, Propranolol: A 50-year historical perspective, Ann Indian Acad Neur, 22, 2019, 21-26.

[55] P.R. Kowey, Pharmacological effects of antiarrhythmic drugs, Arch Intern Med, 158, 1998, 325-332.

[56] R. Mehvar, D.R. Brocks, Stereospecific pharmacokinetics and pharmacodynamics of beta-adrenergic blockers in humans, J Pharm Pharm Sci, 4, 2001, 185-200.

[57] W.H. Frishman, M. Alwarshetty, Beta-adrenergic blockers in systemic hypertension - Pharmacokinetic considerations related to the current guidelines, Clin Pharmacokinet, 41, 2002, 505-516.

[58] B. Terhaag, Clinical pharmacokinetics of the beta-receptor blockers propranolol and talinolol, Z Klin Med, 44, 1989, 119-124.

[59] A. Corletto, H. Frohlich, T. Tager, M. Hochadel, R. Zahn, C. Kilkowski, R. Winkler, J. Senges, H.A. Katus, L. Frankenstein, Beta blockers and chronic heart failure patients: Prognostic impact of a dose targeted beta blocker therapy vs. heart rate targeted strategy, Clin Res Cardiol, 107, 2018, 1040-1049.

[60] B.G. Katzung, Basic and Clinical Pharmacology (4. edition), Editors: M. Weitz and P. Boyle 2020, New York, McGraw-Hill Education.
[61] J.B. Schwartz, D. Keefe, D.C. Harrison, Adverse effects of antiarrhythmic drugs, Drugs, 21, 1981, 23-45.
[62] W. Amjad, W. Qureshi, A. Farooq, U. Sohail, S. Khatoon, S. Pervaiz, P. Narra, S.M. Hasan, F. Ali, A. Ullah, S. Guttmann, Gastrointestinal side effects of antiarrhythmic medications: A review of current literature, Cureus, 9, 2017, e1646.
[63] Z. Kun, Y. Shuai, T. Dongmei, Z. Yuyang, Electrochemical behavior of propranolol hydrochloride in neutral solution on calixarene/multi-walled carbon nanotubes modified glassy carbon electrode, J Electroanal Chem, 709, 2013, 99-105.
[64] N.A. Alarfaj, M.F. El-Tohamy, Construction and validation of new electrochemical carbon nanotubes sensors for determination of acebutolol hydrochloride in pharmaceuticals and biological fluids, J Chin Chem Soc, 61, 2014, 910-920.
[65] J.S. Choi, J.P. Burm, Pharmacokinetics of acebutolol and its main metabolite, diacetolol after oral administration of acebutolol in rabbits with carbon tetrachloride-induced hepatic failure, Arch Pharm Res, 25, 2002, 541-545.
[66] R.R. Gaichore, A.K. Srivastava, Electrocatalytic determination of propranolol hydrochloride at carbon paste electrode based on multiwalled carbon-nanotubes and c-cyclodextrin, J Incl Phenom Macro, 78, 2014, 195-206.
[67] M. Raj, P. Gupta, N.R. Goyal, Poly-Melamine film modified sensor for the sensitive and selective determination of propranolol, a β-blocker in biological fluids, J Electrochem Soc, 163, 2016, H388-H394.
[68] P. Gupta, K.S. Yadav, B. Agrawal, N.R. Goyal, A novel graphene and conductive polymer modified pyrolyticgraphite sensor for determination of propranolol in biological fluids, Sensor Actuat B-Chem, 204, 2014, 791-798.
[69] Z. Kun, H. Yi, Z. Chengyun, Y. Yue, Z. Shuliang, Y. Yuyang, Electrochemical behavior of propranolol hydrochloride in neutral solution on platinum nanoparticles doped multi-walled carbon nanotubes modified glassycarbon electrode, Electrochim Acta, 80, 2012, 405-412.
[70] T. Alizadeh, L. Allahyari, Highly-selective determination of carcinogenic derivative ofpropranolol by using a carbon paste electrode incorporated withnano-sized propranolol-imprinted polymer, Electrochim Acta, 111, 2013, 663-673.
[71] H.T. Purushothama, Y.A. Nayaka, Electrochemical determination of propranolol using reduced graphene oxide modified carbon paste electrode, Anal Bioanal Electrochem, 11, 2019, 1575-1589.
[72] S.Z. Mohammadi, S. Tajik, H. Beitollahi, Electrochemical determination of propranolol by using modified screen-printed electrodes, Indian J Chem Techn, 27, 2020, 73-78.
[73] T. Łuczak, A nanogold supported inorganic/organic hybrid 3D sensor for electrochemical quantification of propranolol-effective antagonist of β-adrenergic receptors, Ionics, 25, 2019, 5515-5525.
[74] M.R. Nateghi, Synthesis of (Ti0.5V0.5)3C2 as novel electrocatalyst to modify carbon paste electrode for measurement of propranolol in real samples, Russ J Electrochem, 55, 2019, 106-115.
[75] E.R. Sartori, R.A. Medeiros, R.C. Rocha-Filho, O. Fatibello-Filho, Square-wave voltammetric determination of propranolol and atenolol in pharmaceuticals using a boron-doped diamond electrode, Talanta, 81, 2010, 1418-1424.
[76] Z. Kun, C. Hongtao, Y. Yue, B. Zhihong, L. Fangzheng, L. Sanming, Platinum nanoparticle-doped multiwalled carbon-nanotube-modified glassy carbon electrode as a sensor for simultaneous determination of atenolol and propranolol in neutral solution, Ionics, 21, 2015, 1129-1140.
[77] A.F. Al-Ghamdi, M.M. Hefnawy, A.A. Al-Majed, F.F. Belal, Development of square-wave adsorptive stripping voltammetric method for determination of acebutolol in pharmaceutical formulations and biological fluids, Chem Cent J, 6, 2012, 15.
[78] A. Levent, Voltammetric behavior of acebutolol on pencil graphite electrode: Highly sensitive determination in real samples by square-wave anodic stripping voltammetry, J Iran Chem Soc, 14, 2017, 2495-2502.
[79] A. Yamuna, P. Sundaresan, S.M. Chen, S.R.M. Sayed, T.W. Chen, S.P. Rwei, X. Liu, Electrochemical determination of acebutolol on the electrochemically pretreated screen printed carbon electrode, Int J Electrochem Sc, 14, 2019, 6168-6178.
[80] A.M. Bagoji, S.M. Patil, T.S. Nandibewoor, Electroanalysis of cardioselective betaadrenoreceptor blocking agent acebutolol by disposable graphite pencil electrodes with detailed redox mechanism, Cogent Chem, 2, 2016, 1172393.
[81] M. Silva, S. Morenta-Zarcero, D. Pérez-Quintanilla, I. Sierra, Simultaneous determination of pindolol, acebutolol and metoprolol in waters by differential-pulse voltammetry using an efficient sensor based on carbon paste electrode modified with amino-functionalized mesostructured silica, Sensor Actuat B-Chem, 283, 2019, 434-442.