Journal of Scientific Perspectives

Volume **4,** Issue **4,** Year **2020**, pp. **223-236**
E - ISSN: **2587-3008**
URL: https://journals.gen.tr/jsp
DOİ: https://doi.org/10.26900/jsp.4.019
Research Article

DEVELOPMENT OF ELECTROCHEMICAL SENSORS FOR QUANTITATIVE ANALYSIS OF METHYLDOPA AT MODIFIED-GCE AND PGE ELECTRODES BY VOLTAMMETRY

Suzan YANIK* & Saliha B. KURT & Betul ARI*** & Sahin DEMIRCI**** & Selehattin YILMAZ*****

**Department of Chemistry, Faculty of Science and Arts, Canakkale Onsekiz Mart University, TURKEY e-mail: suzan.yanik@gmail.com ORCID ID: https://orcid.org/0000-0002-0532-4149*

***Department of Chemistry & Nanoscience and Technology Research and Application Center, Canakkale Onsekiz Mart University, TURKEY, e-mail: salihakurt49@gmail.com ORCID ID: https://orcid.org/0000-0003-0346-441X*

****Department of Chemistry & Nanoscience and Technology Research and Application Center, Canakkale Onsekiz Mart University, TURKEY, e-mail: betullcan@gmail.com ORCID ID: https://orcid.org/0000-0003-3557-3055*

*****Department of Chemistry & Nanoscience and Technology Research and Application Center, Canakkale Onsekiz Mart University, TURKEY, e-mail: sahindemirci@gmail.com ORCID ID: https://orcid.org/0000-0001-7083-1481*

******Department of Chemistry, Faculty of Science and Arts, Canakkale Onsekiz Mart University, TURKEY, e-mail: seletyilmaz@hotmail.com ORCID ID: https://orcid.org/0000-0003-4607-3523*

Received: 14 September 2020, Accepted: 9 October 2020

ABSTRACT

Methyldopa is one of the important drugs used in the treatment of high blood pressure (hypertension). In addition to various methods such as chromatographic and spectrophotometric methods, electrochemical methods are used for the determination of methyldopa. However, poly (p-aminobenzene sulfonic acid), pen-tip graphite electrode (PGE) study was not found in the literature search. Modified electrodes are important because they increase the sensitivity of the analysis. Furthermore, electrochemical methods have advantages such as being faster and cheaper than other instrumental analysis methods, being more sensitive, not requiring long pretreatments in the preparation of samples. In this study, the glassy carbon electrode (GCE) was modified with poly(p-

aminobenzene sulfonic acid) to prepare poly (p-aminobenzene sulfonic acid) -modified glassy carbon electrodes. Cyclic voltammetry (CV) technique was used for the electropolymerization process. Methyldopa was selected in various concentrations of phosphate pH 7.40 buffer, anodic and cathodic voltamograms were taken and oxidation and reduction properties were investigated. Measurements were taken at different scanning rates by CV technique and the current type of methyldopa was determined. Peak flow-concentration graphs were drawn from the measurements taken by Differential Pulse Voltammetry (DPV) technique and the linearity range was 0.020- 2.500 µM for modified-GCE and 0.020-2.820 µM for PGE. The limit of detection (LOD) was calculated as 0.006 µM for modified-GCE, 0.012 µM for PGE. The limit of quantification (LOQ) was calculated as 0.020 µM for modified-GCE and 0.040 µM for PGE.

Keywords: *methyldopa, voltammetry, modified electrode, pen tip graphite electrode, glassy carbon electrode.*

1. INTRODUCTION

Methyldopa, a catechol derivative, is an ancient antihypertensive agent. It has been used to treat high blood pressure since the 1960s. It is a structural analogue of the anti-Parkinsonism drug dopa (dihydroxyphenyl alanine). It has a catechol group and an amino acid skeleton with a methyl group and α-carbon of the side chain on it. Methyldopa converts to methyl norepinephrine through biotransformation at adrenergic nerve terminals. L-DOPA recognized as levo-dopa and ʟ-3,4-Dihydroxyphenylalanine is an amino acid and can be produced in human body (Bastide et. al., 2015; De Deurwaerdere et. al., 2017). L-DOPA is an endogenous precursor for dopamine which is a neurotransmitter and moreover, L-DOPA produced by biosynthesis of L-tyrosine (De Deurwaerdere et. al., 2017; Hauser, 2009; Mercuri and Bernardi, 2005). L-DOPA is highly hydrophilic due to its hydroxyl and amino groups (Azari and Zou, 2012; Mu et. al., 2017). Because of this unique feature it can be utilize for modification reactions (Di Giovanni et. al., 2019), (Gholivand and Amiri, 2009).

Methyldopa is one of the anti-hypertensive agents, especially during the pregnancy period (Figure 1.). It has been also found that methyldopa would inhibit the enzyme DOPA decarboxylase that consequently would convert L-DOPA into dopamine precursor of epinephrine and norepinephrine. Thus, determination of methyldopa in pharmaceutical and biological samples is very important.

Various techniques have been used to detect methyldopa in bulk and drug preparation like spectrophotometric (Norouzi et al., 2009) and chromatography (Fouladgar and Karimi, 2013) methods. Such methods need mathematical analysis, utilization of the organic solvents, costly tools, and laborious procurement process of the samples. Put differently, researchers considerably attended the electrochemical procedures owing to simplified operations, satisfactory accuracy, inexpensiveness, environmental-friendly, quickness, and higher sensitivity for detecting methyldopa, and diverse analytes free from other difficult pre-treatments.

Undesirable events of the electrode can be controlled by changing the chemical structure of the electrode surface. Electroanalytical chemists have been used to carbon, gold, platinum and mercury electrodes until the mid-1970s (Stradiotto *et. al.,* 2003).

In the literature, some chemical reagents were chemically bonded to electrode surface to improve electrode properties with the unique properties of chemical reagents (Murray *et al.,* 1987). Electrodes are usually prepared by modifying a conductive substrate. Thus, modified

substrate possessed desirable functions which is different from the unmodified substrate. The substrate surfaces are prepared by changing them in many different ways as adsorption, chemically modification, and so on (Stradiotto *et al.,* 2003).

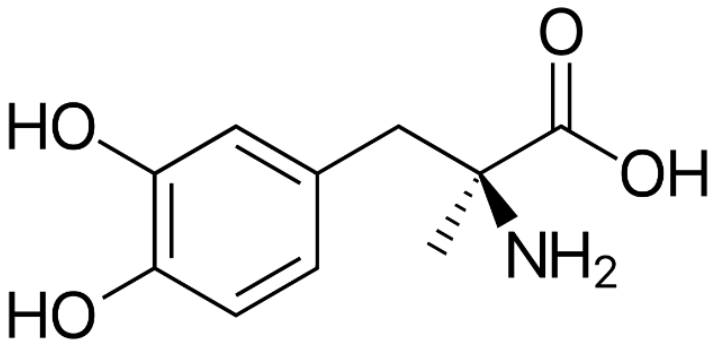
All electrodes are primarily electronically conductive materials they are modified. Carbon, metals, semiconductors, a conductive polymers and organometals can be use as a substratematerial (Ozdemir, 2006). In making electrodes covered with polymer film, either pre-coat with chemically synthesized polymers or directly monomer polymerized at the electrode surface (Murray *et al.,* 1987).

Due to the limited number of electrodes used in electroanalytical chemical analysis working conditions by changing the chemical or electrochemical properties of the electrodes developed. The desired reaction on the carbon electrode may be blocked after a while due to oxidation and contamination on the surfaceor different mechanisms. Top revent this, the surfaces of the solide electrodes are changed by modification (Shahrokhian and Ratsgar, 2011). Fabrication of modified electrodes their controllable morphology and better surface functionalization offer ultra sensitive and selective analysis for electrochemical detection.

The aim of this study is to determine the sensitivity of methyldopa in low concentration by developing electrochemical nanobiosensors (Shahrokhian and Ratsgar, 2011). Electrochemical methods are faster, cheaper and more sensitive than their methods such as Chromatography and UV. In addition, It has advantages such as not requiring long pre-treatment in preparation.

In this study, GCE was modified with poly (p-aminobenzene sulfonic acid) and p-ABSA modified glassy carbon electrodes were prepared. Electrochemical behavior of the active substance has been examined in PGE, modified-GCE electrode. The stability and repeatability of the electrodes were investigated. Current type of oxidation of methyldopa in the chosen supporting electrolyte system determined. The lower limit of detection (LOD) and the quantitative limit of detection (LOQ) were calculated. The accuracy of the two electrodes can be restored with methyldopa obtained from commercially available tablets. The recovery values were determined by calculating the results.

Figure 1. Chemical formula of *Methyldopa*



2. MATERIAL AND METHOD

2.1 Apparatus

AUTOLAB 12 potentiostat/galvanostat device (EcoChemie, Netherlands) was used for all electrochemical measurements and raw voltammograms were treated with a Savicky and Golay algorithm using GPES 4.9 software program by moving average method (peak width 0.01 V). The three electrode system was comprised of a pencil graphite electrode (PGE), Ag/AgCl/3M KCl reference electrode and a platinum wire as the auxiliary electrode. The

Tombow 2B pencil lead of 0.5 mm diameter and length of 60 mm was used as PGE for the investigation. GCE as working electrode (GCE; ∂ = 3 mm, Metrohm), a platinum wire as auxiliary electrode and Ag/AgCl (KCl 3M, Metrohm) as reference electrode. The GCE electrode was polished with alumina (prepared from ∂ = 0.01 µm aluminum oxide) on an alumina polish pad before each experiment and then rinsed with ultra-pure deionized water and ethanol. All experiments were performed at room temperature (22.0-25.0˚C).

2.2 Reagents and materials

Acetate and phosphate buffers were used as buffer solutions in the experiments. 1 M acetic acid solution was prepared for the acetate buffer and reached the desired pH values with 5 M NaOH. pH 3.50 - 5.50 has been studied with this buffer.

Preparation of 0.50 M acetate buffer solution (ABS) (pH 4.50):To prepare of 0.50 M ABS (pH 4.50) 0.2722 g (0.002 mol) sodium acetate per liter of 0.50 M ABS used acetate trihydrate and 0.1154 mL acetic acid. The pH of the solution is adjusted to 4.80 by pH meter using 0.1 N NaOH or 0.1 N HCl. To provide ionic strength 1.168 g of NaCl was added to solution.

Preparation of PBS (pH 7.40): To prepare of PBS firstly 0.2 M $NaH_2PO_4.2H_2O$ and 0.2 M Na_2HPO_4 aqueous solutions were prepared and suitable for the desired pH adjusted with conjugated base solutions.

Electrode surface was cleaned with 0.3 µm, 0.1 µm and 0.05 µm alümina (Al_2O_3) before modification. Later alumina residues remaining on the electrode surface were also cleaned with HNO_3 (1:1), acetone and distilled water. GCE was modified by electropolymerization technique in 0.1 M NaH_2PO_4-Na_2HPO_4 (pH 7.40) buffer containing p-aminobenzene sulfonic acid. The coated surface was activated by cylic voltammetry technique and methyldopa analysis was carried out in 0.1 M NaH_2PO_4-Na_2HPO_4 (pH 7.40) buffer solution.

The activation process for the PGE was performed in pH 4.70 ABS in volving 0.5 M glacial acetic acid.

Methyldopa stock solution and support electrolyte were prepared in PBS at pH 7.40. All aqueous solutions have prepared by using TKA2 Smart (0.055 µS/cm conductivity) distilled water.

In this study, methyldopa active substance and drug form was procured from the pharmaceutical company (İ.E Ulugay) (alfamet®).

2.3 Calibrationgraph for the quantitative determination of methyldopa

The diluted methyldopa solutions were prepared by using diluting with Britton-Robinson (B-R) buffer solution from the stock solution (Reddaiah *et al.*, 2012). A linear calibration curve was created in the B-R buffer solution (pH 7.40) with the DPV method in the concentration range of 0.020 µM and 70 µM methyldopa.

2.4 Recovery works

Five tablets were weighed and powdered in a mortar to determine the amount of methyldopa in Alfamet® tablets. The 30.4 mg of each tablet contains 20 mg methyldopa An appropriate amount of each sample was dissolved and sonicated for one hour to prepare equivalent molar stock solutions. So that check the validity of the developed method, the amount of methyldopa in alfamet® tablet forms by determining the recovery studies were performed in accordance with the linear response of the calibration graphs.

2.5 Preparation of sensor

The graphite pencil electrode used in the studies was prepared by cutting Tombo brand pen tips to a size of 3.0 cm. The pen tips were placed in the pen so that they were 1 cm inside the electrochemical cell. The 1.0 cm surfaces of the electrodes were activated in PBS under the application of +1.40 V potential for 30 seconds. (Subak and Ozkan, 2018). With this process, the groups on the surface of carbon electrodes was oxidized to carboxyl groups.

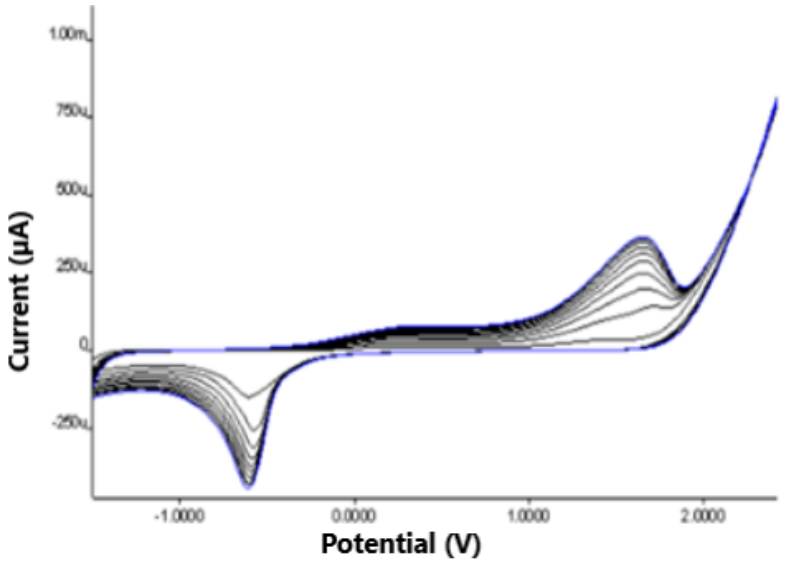
GCE: Before starting the modification, the first electrode was cleaned with 0.1 μm and 0.3 μm diamond paste and 0.05 μm alumina on cleaning pads. Then washed in an ultrasonic bath with HNO_3: distilled water (1:1 by the volume) and finally acetone and distilled water. After cleaning the electrode surface, it was prepared based on the method given in the literature (Mo and Ogorevc, 2005), (Sağlıkoğlu, 2011), (Yang *et al.*, 2006). GCE was modified with $2.0x10^{-3}$M p-aminobenzene sulfonic acid at 200 mVs^{-1} in the potential range of -1.5 V and +2.4 V in the phosphate buffer solution by electropolymerization technique (Jin *et al*., 2005). It was coated, taking 10 cycles at scan speed. Coated surface conversion voltammetry technique and analysis of methyldopa was made after the activation process.

3. RESULTS AND DISCUSSION

3.1 Modification and Activation of Glassy Carbon Electrode

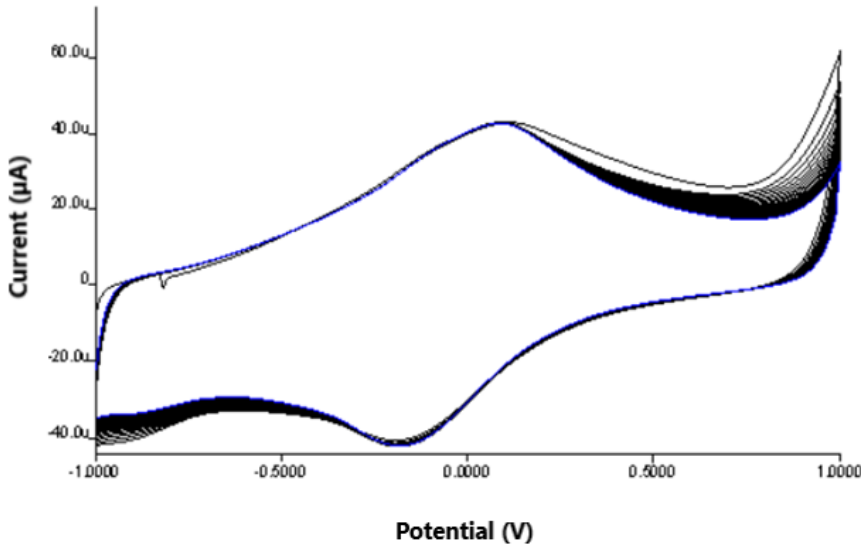
First of all, the surface of electrode 1 was cleaned before modification, after cleaning by cleaning pads with 3 μm diamond paste and 0.05 μm alumina (Al_2O_3), respectively. HNO_3 was washed in an ultrasonic bath with acetone and distilled water (1: 1 by volume). The electrode was cleaned in this way, the surface electrode was coated using the method in the literature (Huang *et al.*, 2008). GCE was covered by electropolymerization technique in 0.1 M PBS tampon solution (pH=7.4) that contained $2x10^{-3}$ M aminobenzene sulfonic acid at the potential range -1.5 V and +2.4 V at 200 mVs^{-1} at scan rate for 10 cycles in Figure 2.

Figure 2. The electrochemical polymerization of $2x10^{-3}$ M p-aminobenzene sulphonic acid in 0.1 M PBS (pH 7.40) on GCE surface, 200 mVs^{-1}voltammogram at scan rate.



The modified electrode was activated with 20 cycles in the range -1 / + 1V (Figure 3).

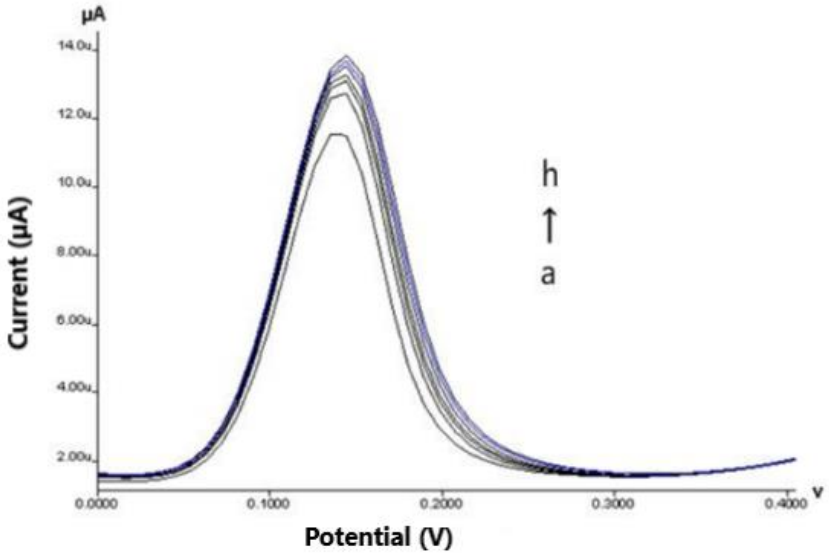
Figure 3. Voltammogram of the activation of the modified- GCE (scanning rate = 200 mVs^{-1}).



3.2 The Analysis of Methyldopa at Glassy Carbon Working Electrode

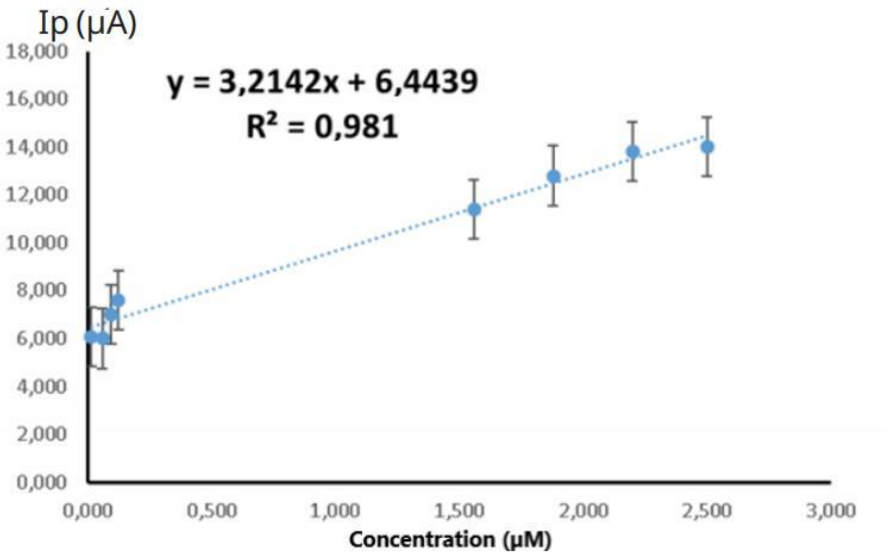
The modified electrode was actived at pH 7.40 according to the method given in the literature (Mo and Ogorevc, 2005). It was calibrated due to the standard addition method of methyldopa at pH 7.40 in PBS. The voltammograms of the calibration are shown in Figure 4.

Figure 4. Voltammograms for calibrations of methyldopa at poly ABSA modified-GCE (a: 0.015µM, b: 0.06 µM, c: 0.094 µM, d: 0.125 µM, e: 1.56 µM, f: 1.88 µM, g: 2.20 µM, h: 2.50 µM) (scanning rate: 200 mVs^{-1})



In phosphate buffer (pH 7.40) peak of current-concentration (C-Ip) graph is shown in Figure 5.

Figure 5. Graph of peak current vs concentration (C-Ip) of methyldopa in PBS (pH 7.40) at poly ABSA modified GCE

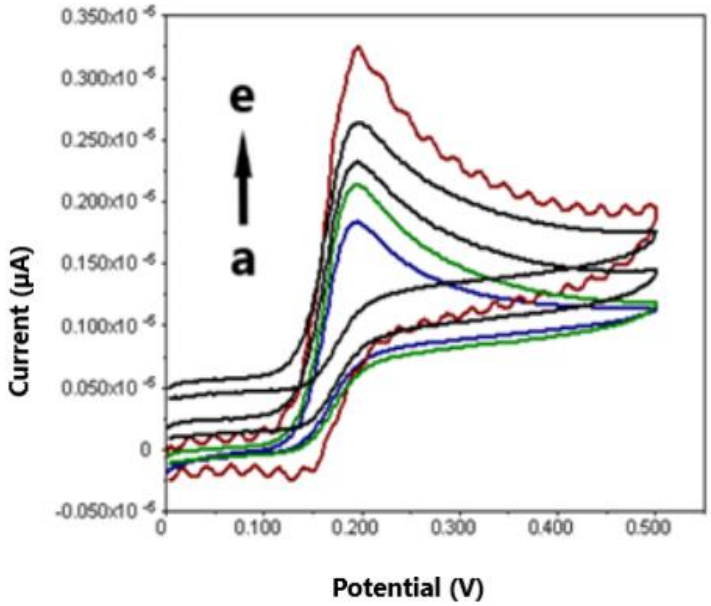


As a result, the calibration graph has been drawn based on outcomes. The slope of the graph was determined as 3.2142 and the regression coefficient was found as 0.981. The linearity of calibration was determined between 0.015µM-2.50 µM from the equation of the graph.

3.3 Analysis of Methyldopa Using Pen Tip Graphite Electrode

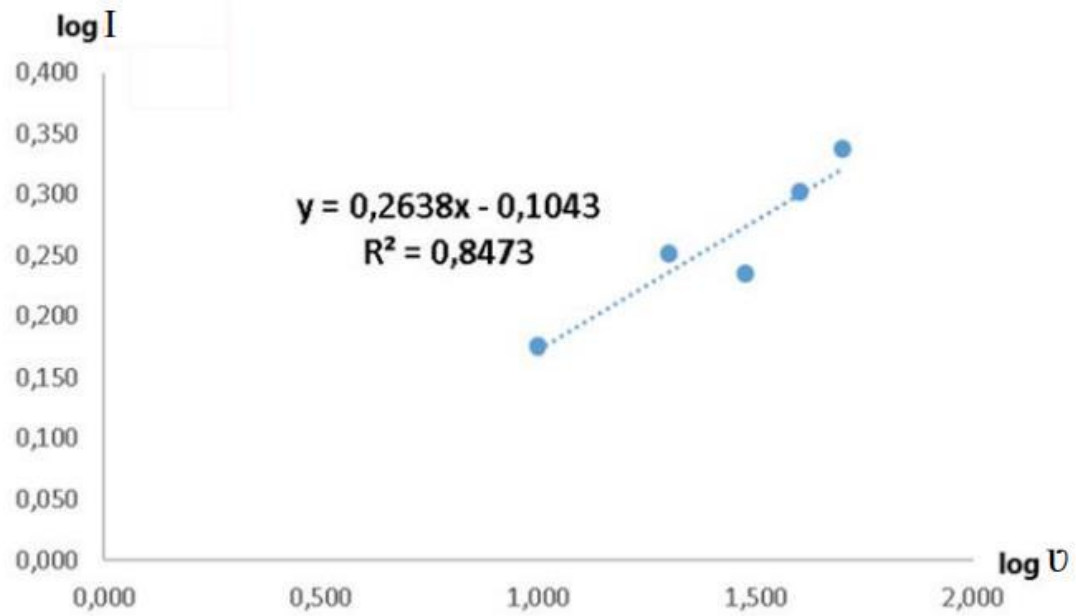
Scanning rates study was done between 10-50 mV/s to determine the current type of methyldopa at activated electrodes (Figure 6).

Figure 6. Voltammogram of scanning rates study of methyldopa at PGE (Scan rate = a) 10; b) 20; c) 30; d) 40; e) 50 mVs^{-1}**)**



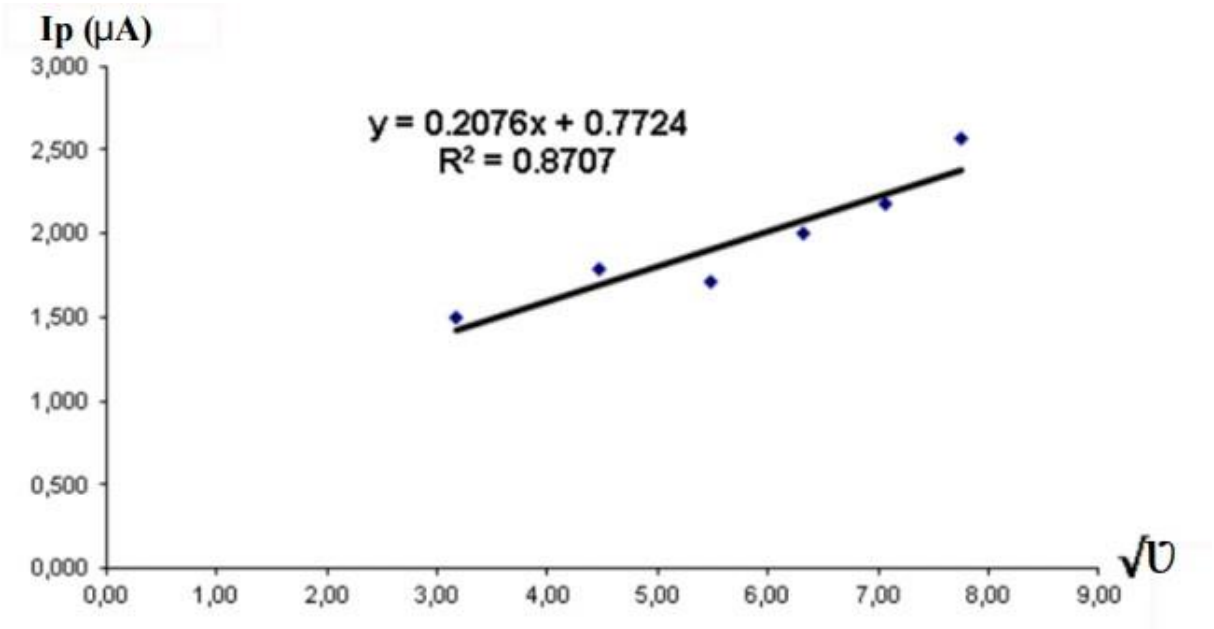
In order to determine the type of current in the oxidation reaction of methyldopa, voltammograms were taken at different scanning rates by cyclic voltammetry technique. This scan rate of voltammograms were (a) 10; b) 20; c) 30; d) 40; e) 50 mVs^{-1})). The graph of logarithm of the current vs log scan rate was given in Figure 7. According to this, slope of the graph was found far from 0.5, indicating that shows the current adsorption was controlled (Rezaei, *et al.*, 2013).

Figure 7. Log scan rate-log peak current obtained by cyclic voltammetry technique of methyldopa using PGE current (logv-logI_P) graph.



It is also obtained from the increase of the oxidation peak current linearly with the square root of the scan rate vs current was that was given Figure 8. Correlation coefficient (R^2) was obtained 0.8473 (far from 1). It is an important indicate or that the current was controlled by adsorption (Skrzypek et al, 2005).

Figure 8. Peak current vs square root of scan rate of methyldopa at PGE



For methyldopa, whose current type is determined with adsorption control, DPV measurements in anodic direction between 0.0 V-0.45 V by accumulating 100 seconds before each analysis has been taken. Voltammograms of the calibration where linearity was determined in Figure 9. and Figure 10. Graph of peak current-concentration (C-Ip) in the phosphate (pH 7.40) buffer solution of methyldopa in 4.9. specified.

Figure 9. Voltammograms of calibration of PGE and methyldopa (a: 0.002µM, b: 0.005 µM, c: 0.007 µM, d: 0.010 µM, e: 0.012 µM, f: 0.034 µM, g: 0.060 µM, h: 0.100 µM) (scanning rates: 16 mVs^{-1})

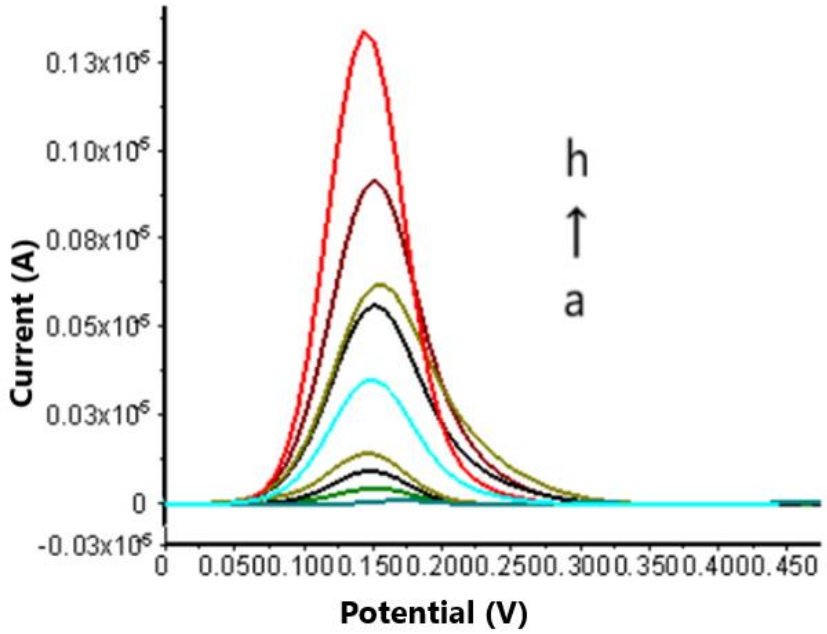
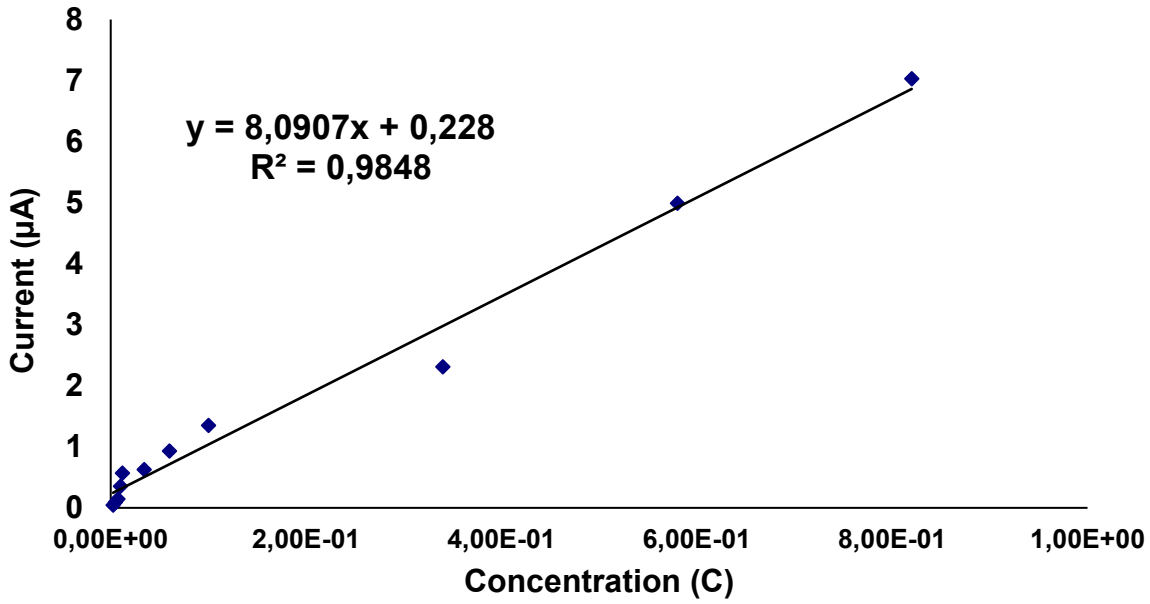


Figure 10. The graph of peak current vs concentration (C-Ip) of methyldopa in PBS (pH 7.40) at PGE.



As a result, the calibration graph has been drawn based on outcomes. The slope of the graph was determined as 8.0917 and the regression coefficient as 0.9848. The linearity was determined from the equation of the graph between 0.02µM-0.820µM. For quantitative analysis of methyldopa, obtained using modified- GCE and PGE electrodes. Comparison of the analytical determination parameters with those given in Table 1.

Table 1. The Comparison of parameters to determination of methyldopa at modified-GCE and PGE electrodes

PARAMETERS	MODIFIED - GCE	PGE
Potential, V	0.144	0.151
Linearity range of concentration, µM	0.020-2.500	0.020-0.820
Slope, µAM	3.214	8.091
Intercept,	6.444	0.228
Number of measurements	5	5
R^2	0.981	0.985
LOD (µM)	0.006	0.012
LOQ(µM)	0.020	0.040
%RSD	0.286	0.735

3.4. Determination of the Amount of Methyldopa in Commercial Drug Forms and Validity of Applied Voltammetric Method

To determine the amount of methyldopa in ALFAMET tablets by voltammetric method, 5 tablets of alfamet tablets are weighed and powdered and its solution containing 0.1 µM methyldopa prepared. Voltammogram of this solution was measured and the current value to concentration graph was drawn. The amount of methyldopa in 1 tablet was 245.25 mg for the modified-GCE and it was 243.75 mg for PGE. This value was specified on the tablet as 250 mg compared with Table 2.

The method was developed to check the validity (accuracy and precision) of results. Determination of the amount of methyldopa in alfamet tablet forms and recovery studies. The results was shown in Table 2.

Table 2. Determination of the amount of methyldopa from its Alfamet tablets and Recovery % (average of 5 experiments)

PARAMETERS	MODIFIED-GCE	PGE
Labeled methyldopa, mg	250.00	250.00
Amount found, mg	245.25	243.75
Relative Standard deviation (RSD / %)	0.286	0.735
Added methyldopa, mg	10.00	10.00
Found methyldopa, mg	9.87	9.75
Recovery percentage (%)	98.75%	97.50%

A recovery study was performed to check the accuracy and precision of the two different voltammetric methods applied. For this purpose, the peak current of 0.1 µM methyldopa was measured. The current value was placed in the equality of the calibration graph and the amount of methyldopa as an active ingredient in the alfamet tablet was calculated. Then, 10 mg of

methyldopa was added to the same solution. The recovery of methyldopa was calculated 98.70% in modified-GCE and 97.50% in PGE in Table 2. by comparing the amount of methyldopa that was added and the amount of methyldopa that was found. Since the recoveries of both different electrodes were 98.70% and 97.50%, it was concluded that the accuracy of the two voltammetric methods applied and the drug additives did not affect our analysis method.

4. CONCLUSIONS

Neurological diseases are related to the amount of dopamine in the body. Since dopamine is a molecule secreted by brain cells, the reduction of dopamine secretion as a result of damage to these cells causes neurological disease such as Schizophrenia and Parkinson's (Mo and Ogorevc, 2005).

The most common method used for dopamine determination is electrochemical methods. Although dopamine sensors based on electrochemical responses are constantly being developed, studies on the development of more reliable and effective sensors based on low detection range analysis of dopamine are still interesting topics. Therefore, the selection of the material to be used in electrode modification is very imporant in the design of sensors with excellent performance.

In this study, the electrochemical oxidation of methyldopa at 4-(ABSA)-modified-GCE by differential pulse and cyclic voltammetry techniques. In the voltamograms were taken at pH 7.40 in PBS, an oxidation peak was obtained between 0-0.45 V. 4-ABSA modified- GC electrode was prepared by coating the GCE surface with electropolymerization technique. It was observed that the modified electrode was conductive and enabled to oxidize of the methyldopa. It was determined that the oxidation current peak of methyldopa prepared in this modified electrode and gave much higher signals compared to the pencil tip electrode. For same concentration (0.1µM), a current of 1.35µA was obtained at the PGE electrode, while a current of 7.60 µA was obtained modified-GCE. When the two electrodes are compared, current was observed more 5 times high at modified-GCE than at PGE.

Electron transfer is facilitated as a result of the electroanalytic effect of the GCE surface covered by polymeric film. This shows that the modified electrode is more sensitive. It has been concluded that the applied voltammetric methods are more preferable than HPLC and UV spectroscopy due to their advantages as fast, economical and sensitive, working with small amount of samples and being able to analyze without need for time-consuming processes as separation. For the validity of the voltammetric method, recovery studies indicated that the drug additives did not affect the determination of methyldopa.

Acknowledgements

We thank The Scientific Research Commision of Canakkale Onsekiz Mart University (Project: FBA-2018-2454) for financial support

REFERENCES

AZARI, S., and ZOU, L. 2012, Using zwitter ionic amino acid l-DOPA tomodify the surface of thin film composite polyamide reverse osmosis membranes to increase their fouling resistance. *J. Memb. Sci.*, 401–402, 68–75.

BASTIDE, M.F., MEıSSNER, W.G., PıCCONı, B., FASANO, S., FERNAGUT, P.-O., FEYDER, M., FRANCARDO, V., ALCACER, C., DıNG, Y., BRAMBILLA, R., FISONE, G., JON S.A., BOURDENX, M., ENGELN, M., NAVAILLES, S., DE DEURWAERDÈRE, P., KO, W.K.D., SIMOLA, N., MORELLI, M., GROC, L., RODRIGUEZ, M.-C., GUREVICH, E. V., QUIK, M., MORARI, M., MELLONE, M., GARDONI, F., TRONCI, E., GUEHL, D., TISON, F., CROSSMAN, A.R., KANG, U.J., STEECE-COLLIER, K., FOX, S., CARTA, M., ANGELA CENCI, M., AND BÉZARD, E., 2015, Pathophysiology of L-dopa-induced motor and non-motor complications in Parkinson'sdisease. *Prog. Neurobiol.*, 132, 96–168.

BENZA K.R., GASH B., KLEBOVICH I, 1996, Determination of Methyldopa in Human Plasma by Validated HPLC with fluorescence detection, *Journal of Chromatography*, 730, 125-131.

DE D, P., DI GIOVANNI, G., and Millan, M.J., 2017, Expanding the repertoire of L-DOPA'sactions: A comprehensive review of its functional neurochemistry. *Prog. Neurobiol.*, 151, 57–100.

DI GIOVANNI, G., CHAGRAOUI, A., PUGINIER, E., GALATI, S., and DE DEURWAERDÈRE, P., 2019, Reciprocal interaction between monoaminergic systems and the pedunculopontine nucleus: Implication in the mechanism of L-DOPA. *Neurobiol. Dis.*, 128, 9–18.

FOULADGAR, M., KARIMI, M.H., 2013, Ionic Liquid/Multiwall Carbon Nanotubes Paste Electrode for Square WaweVoltammetic Determination of Methyldopa, 19, 1163-70.

GHOLIVAND M.B., AMIRI, M., 2009, Preparation of Polypyrrole/Nuclear Fast Red Films on Gold Electrode and Its Application on the Electrocatalytic Determination of Methyldopa and Ascorbic Acid, *Electroanalysis*, 21,22, 2461-67.

HAUSER, R.A. 2009, Levodopa: Past, Present, and Future. *Eur. Neurol.*, 62 (1), 1–8.

HUANG F., JIN G., LIU Y., KONG J., 2008, Sensitive Determination of Phenylephrine and Chlorprothixene at Poly (4-aminobenzene sulfonic acid)-Modified Glassy Carbon Electrode, Talanta, 1435-41.

JIN G., ZHANG Y., CHENG W., 2005, Poly (p-aminobenzene sulfonic acid)-Modified Glassy Carbon Electrode for Simultaneous of Dopamine and Ascorbic Acid, Sensors and Actuators B, 107, 52834.

MERCURI, N., and BERNARDI, G. (2005) The 'magic' of -dopa: why is it the gold standard Parkinson's disease therapy? *Trends Pharmacol. Sci.*, **26** (7), 341–344.

MO, J.W., OGOREVC, B., 2005, Simultaneous Measurement of Dopamine and Ascorbate at Their Physiological Levels Using Voltammetric Microprobe Based on Over oxidized Poly (1,2-Phenylenediamine)-Coated Carbon Fiber. Analytical Chemistry, 73, 1196-1202.

MU, K., ZHANG, D., SHAO, Z., QıN, D., WANG, Y., WANG, S. 2017 Enhanced permeability and anti fouling performance of cellulose acetate ultra filtration membrane assisted by l-DOPA functionalized halloysite nanotubes. *Carbohydr. Polym.*, 174, 688–696.

MURRAY R.W., EWING A.G., DURST A.R., 1987, ChemicallyModifiedElectrodes Molecular Design for Electroanalysis, *AnalyticalChemistr*y, 59 (5), 379A-390A

NOROUZI, P., GANJALI, M.R., SHAHTAHERİ S.J., DINARVAND, R., HAMZEHPOOR, 2009, A., Monitoring of Methyldopa by Fast Fourier Transform Continuous Cyclic Voltammetry at Gold Microelectrode, *Chinese Journal of Chemistry*, 27, 732-38.

ÖZDEMİR, N, 2006 Karbon ve Metal Elektrotların Bazı Aromatik Aminlerle Elektrokimyasal Modifikasyonu ve Karakterizasyonu, (Yüksek Lisans Tezi), Ankara Üniversitesi.

REDDAIAH, K., REDDY, T.M., RAGHU, P., 2012, Electrochemical investigation of L-dopa and simultaneous resolution in the presence of uric acid and ascorbic acid at a poly (methylorange) film coated electrode: A voltammetric study, *Journal of Electroanalytical Chemistry*, 682, 164-171.

REZAEI, B., ASKARPOUR, N., ENSAFI, A.A., 2013, Adsorptive Stripping Voltammetry Determination of Methyldopa on the Surface of a Carboxylated Multiwall Carbon Nanotubes Modified Glassy Carbon Electrode in Biological and Pharmaceutical Samples, *Colloids and Surfaces B: Biointerfaces*, 109, 253-58.

SAĞLIKOĞLU, G., 2011, Nitroimidazol Türevi Antibakteriyel Etkili İlaç Aktif Maddelerinin Dozaj Formlarından Modifiye ve Modifiye Edilmemiş Elektrotlarda Voltametrik Teknikler ile Kantitatif Analizi, (Doktora Tezi), Çanakkale Onsekiz Mart Üniversitesi Fen Edebiyat Fakültesi.

SHAHROKHIAN S., RASTGAR S., 2011, Electrodeposition of Pt-Runanoparticles on Multi-walled Carbon Nanotubes: Application in Sensitive Voltammetric Determination of Methyldopa, Electrochimica Acta, 58, 125-33.

SKRZYPEK S., CIESIELSKI W., SOKOŁOWSKI A., YILMAZ S., KAZMIERCZAK D., 2005 ElectrochemicalStudy of Famotidine-Analytical Application toUrine, *Talanta*, 66, 1146-1151,

STRADIOTTO, N.R., YAMANAKA, H., AND ZANONI, M.V.B., 2003, Electrochemical sensors: a powerful tool in analytical chemistry. *J. Braz. Chem. Soc.*, 14 (2), 159–173.

SUBAK, H., OZKAN, A.D, 2018, Label-free electrochemical biosensor for the detection of Influenza genes and the solution of guanine-based displaying problem of DNA hybridization, *Sensors and Actuators B: Chemical*, 263, 196-207.

YANG Z., HU G., LIU Y., ZHAO J., ZHAO G., 2006, Poly(p-aminobenzene sulfonic acid)-Modified Glassy Carbon Electrode for Selective Determination of Hydroquinone in the Presence of Catechol and Resorcinol, *Canadian Journal of Analytical Sciences and Spectroscopy*, 52, 1, 11-17.