Voltammetric Detection of Levodopa and Benserazide at Polypyrrole and Single Walled Carbon Nanotube Based Electrode

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Abstract

In this study, it was aimed to use pyrrole monomer and single-walled carbon nanotube (SWCNT) in the production of modified electrodes, and to examine the electrochemical properties of these electrodes. Bulk electrolysis technique was used for growing polypyrrole. The applicability of the polypyrrole and SWCNT-based electrodes was tested by electrochemically detecting active substances such as levodopa (LD) and benserazide (BS) used in the treatment of Parkinson’s disease. During the design and analysis phase of the modified electrode, many electroanalytical optimization and validation parameters were examined. The developed modified electrode gave linear responses with DPV technique in concentration ranges of 10-50 µM for LD and 10-50 µM for BS. In addition, limits of detection in these wide linear ranges were obtained as very low. Limits of detection were calculated as 2.4 µM and 1.2 µM for LD and BS, respectively. In addition, the applicability of the designed electrode and method was tested in urine and drug samples. The selectivity of this electrode was carried out in placebo solutions containing the interfering species. It is advantageous that the drug active ingredients are easily, selectively and quickly determined at this modified electrode in the presence of components that affect the analysis. Eventually, very satisfactory results in terms of analytical performance and applicability have been achieved with the designed electrode.

Keywords: Electropolymerization, Parkinson's disease, polypyrrole, single-walled carbon nanotube, voltammetry

INTRODUCTION

There is a certain balance between acetylcholine, which increases the excitability of nerve cells in the brain, and dopamine, which does the opposite. In Parkinson's disease, this balance is disrupted in favor of acetylcholine, and dopamine deficit should be replaced in treatment. Synthetic dopamine cannot...
cross the barrier between blood and brain. This problem was solved by the discovery of Levodopa, which turns into dopamine after the blood-brain barrier has passed (Aviles-olmos et al., 2010; Fabbrini et al., 2007; Kobayashi 2001; Lechin et al., 2005; Sarabi et al. 2001; Shahrokhi and Asadian, 2009; Viskin and Belhassen, 1998; Wolf et al., 2006). Levodopa (L-Dopa, LD) is an aromatic amine that is metabolized to dopamine. LD has been the gold standard treatment for PD since the 1960s. Administering adequate amounts of LD, which acts as a precursor to dopamine, can preserve motor functions for a long time, resulting in improved quality of life and prolonged survival of patients. LD is normally administered in combination with a dopamine decarboxylase inhibitor such as benserazide (BS) or carbidopa to prevent the conversion of LD to dopamine in the bloodstream. BS is used to inhibit the decarboxylation of dopamine and to minimize the occurrence of extra-cerebral side effects of dopamine. Usually, these substances are oxidized in aqueous solution to form quinone compounds (Shimozawa et al., 2019; Chen et al., 1994; Oyama and Anson, 1980; Savan and Erdoğan, 2017).

Techniques such as chromatography (Adamiak-Giera and Gawronska-Szklarz, 2018; Loutelier-Bourhis et al., 2004; Martins et al., 2013), spectrophotometry (Uslu and Özkân, 2002), chemiluminescence (He et al., 2006) and voltammetry (Miraki et al., 2019; Ensafi et al., 2010) have also been used in the analysis of benserazide and levodopa binary drug mixture. The common feature of these substances is that they have a monoamine neurotransmitter substance structure that does not contain chromophore groups. Therefore, their determination by spectrophotometric methods is limited. Although the chromatographic method is more popular than other methods, the presence of interferants is a major disadvantage for this method. Furthermore, the determination of these substances by chromatographic method is also possible with the use of an electrochemical detector. Alternatively, the electrochemical method has recently gained more attention due to its advantages such as more selective, more sensitive, less solvent usage, cheaper and less time to prepare compared to other methods. It is possible to analyze drug active substances from pharmaceutical preparations and biological fluids in a fast, precise and economical way without the need for any separation method with voltammetric techniques (Kuyumcu Savan and Erdoğan, 2017, 2019, 2020; Tanrıkkut et al., 2020). One of the advantages of voltammetry is that it is used to explain the pharmacological action mechanisms of many physiologically important compounds by clarifying the redox reactions of drug active ingredients.

When bare electrodes are used as working electrodes in electroanalytical applications, electroactive interferences such as uric acid and ascorbic acid show electroactivity on the electrode surface. Thus, signal acquisition affects the amperometric response of the desired species and significantly changes the characteristic peak of the species concerned. As a result, satisfactory potential differences in peak separation of analytes cannot be reached (Jalalvand, 2020; Mazloum-Ardakani et al., 2018; Wang et al., 2006; Zhang et al., 2018). This disadvantage of the bare electrode has made the use of modified electrodes mandatory. In addition, electrode modification offers many more advantages such as lowering the over-potential, increasing the reaction rate and improving the sensitivity (Lou et al., 2020; Özdonur, 2020; Saleh et al., 2016).

Carbon nanotubes are frequently used in biosensor design, electrode modification in electroanalytical chemistry, due to their unique structure, mechanical strength and electronic properties (Aslan et al., 2016; Ince et al., 2017; Palomar et al., 2020). In this way, the studied potential decreases and the reaction rate of many electroactive substances increases. Thus, carbon nanotube modified electrodes show better electrochemical performance than other conventional carbon electrodes (Kuyumcu Savan, 2019a, 2019b; Palisoc et al., 2019). The electrochemical properties of both carbon nanotube and conductive polymers provide the modified electrode to have new and unique properties.

Polypyrrole (PPR) is a conductive polymer that can be easily oxidized from its neutral pH aqueous solution containing pyrrole monomer. The properties of this polymer such as electrochemical polymerization conditions and charge / discharge processes, strong absorptivity properties, catalytic activity, redox activity due to corrosion protection properties, ability to form nanocaps with 10^7 - 10^8 S cm⁻¹ conductivity at room temperature, ion exchange and ion separation capacities, electrochromic effect
are superior in sensor designs (Ramanavičius et al., 2006).

In this study, it was aimed to use pyrrole (PR) monomer and single-walled carbon nanotube (SWCNT) in the production of modified electrodes, to examine the electrochemical properties of these electrodes and to determine the drug active ingredients LD and BS. With this modified electrode, the components affecting the analysis were also added to the medium and identified together with the drug active ingredients easily. In addition, selective detection of such substances and species overlapping them has been successfully performed in biological fluids such as drug samples and urine.

MATERIAL AND METHODS

The chemicals used in this study; levodopa standard (Alfa Aesar (A Johnon Matthey Company)), benzerazide standard (Sigma), SWCNT (Graphene Inc.), pyrrole, tetrabutylammonium tetrafluoroborate and L- (+) - ascorbic acid (AA, Merck) were of analytical grade. In the preparation of the buffer solutions, chemicals of analytical purity such as Na2HPO4 (Merck), KH2PO4 (Carlo Erba), KCl (Merck), NaCl (Mercck), H3PO4 (Merck), H3BO3 (Merck) and CH3COOH (Merck) were used. Ultra-pure water used in electroanalytical studies was obtained with high purity from Milli-Q system (Millipore, Milford, USA).

In addition, stock solutions of LD and BS, which are used as active ingredients in electrochemical measurements, were prepared freshly with ultra-pure water at concentrations of 10-2 M. Phosphate buffer solution (PBS) consisting of KH2PO4, Na2HPO4, NaCl and KCl, and Britton-Robinson (BR) buffer solution consisting of H3BO3, H3PO4 and CH3COOH were used as buffer solutions. Acetate buffer (AT) solution was prepared by adjusting the pH of 0.1 M CH3COOH with 5.0 M NaOH and concentrated CH3COOH.

All electrochemical processes were performed by BAS (Bioanalytical Systems, Inc.) 100W electrochemical analyzer in a triple-electrode cell. As the electrochemical cell, C2 Faraday cell cage of the same company was used. Platinum electrode prepared in spiral disc form as auxiliary electrode, Ag / AgCl electrode (CHI111) as reference electrode for aqueous environments, Ag / Ag+ reference electrode (CHI112) for non-aqueous environments and glassy carbon electrode (CHI104) as working electrode were used. Glassy carbon electrodes (GCE) were cleaned on cleaning pads with alumina powder and distilled water dripped velvet disc (BAS, MF-1040) prior to experimental studies. Then, GCE was activated by applying the cyclic voltammetry (CV) technique with 20 cycles in the range of −0.5 to 2.0 V in 0.1 M H2SO4 solution at a scan rate of 100 mV s⁻¹. All experiments were carried out under nitrogen atmosphere.

Coating of Glassy Carbon Electrodes with SWCNT and Pyrrole

The surface of the bare GCE was coated with the electro polymerization of the pyrrole by applying the bulk electrolysis (BE) method at 1200 mV for 10 seconds. BE method was used for electro polymerization by means of depositing monomer on the electrode surface for 10 s at constant potential. The polymer film grown on the GCE surface was bright blue in color.

SWCNT solutions were prepared at concentrations of 0.2%, 0.5%, 1.0% (mg μL⁻¹). They were sonicated for 4 hours until a homogeneous mixture was obtained in N, N-dimethylformamide (DMF). Modified electrodes were modified in two different applications. In the first modification procedure, 10 μL and 20 μL of SWCNT-DMF dispersions were dropped on PPR. In the second modification procedure, first, 10 μL and 20 μL of SWCNT-DMF dispersions were drop-poured onto the GCE with a micropipette under the PPR. Eventually, eleven different electrodes were created. The modified electrodes were then washed with deionized water. These formed electrodes were used as working electrodes. DPV responses at these modified electrodes for LD and BS were examined. The preparation procedure of the electrode with the best response can be seen in Scheme 1.
Sample Application

As the drug sample, Madopar® dosage form was used, one tablet containing 100 mg of LD and 50 mg of BS. 10 tablets of this drug form were accurately weighed and ground into fine powder. The tablet sample containing the amount of active ingredient falling within the measuring range was weighed, and its solution was prepared with ultrapure water. Subsequently, ultrasonication was performed for one hour to allow the active ingredients to pass into the aqueous environment. The aqueous portion was filtered through a 0.45 µm filter to remove particles. Finally, the calculated amount was taken from this solution, made up to 10 mL with PBS, and five replicate samples were prepared.

Recovery studies were carried out to determine whether the additives in the tablets used in the study interfered. For this purpose, differential pulse voltammetry (DPV) technique was applied to tablet solutions prepared in certain quantities. The amount of substance in it was calculated using the appropriate calibration chart and recovery values were found. In addition, the desired amounts of pure active ingredients were added to these tablet samples and urine samples, and the recoverability of the added amounts was investigated. While preparing urine samples in triplicate, 1.0 mL of urine was taken and diluted to 10 mL with 0.1 M PBS at pH 7.0. Triple DPV measurements were taken for each sample solution and the recovery values were calculated by taking the average of these repeats.

RESULTS AND DISCUSSION

Film Thickness and pH Effect

Pyrrole monomer was grown on the GCE surface by the CV method, but no answers were obtained for the active ingredients on these film surfaces. Therefore, the BE method was tried to form a polymer film on the electrode surface. In order to obtain the PPR polymer electrodes used in the study electchemically, a 50 mM pyrrole solution in 0.1 M KCl was prepared. CV technique was applied at (-200) and (+1800) mV at 50 mV s⁻¹ scanning speed at GCE to determine the oxidation potential of the pyrrole. The first oxidation peak for pyrrole was obtained at 1178 mV. The best response for the active ingredients was obtained with the film magnified at 1200 mV.

In order to determine the thickness of PPR films grown at 1200 mV potential by the bulk electrolysis method, films of 10, 15, 20, 25, 30 seconds were formed. Oxidation peaks for 1.0 mM BS and 1.0 mM LD at these film electrodes were obtained at a potential of approximately 80 and 184 mV, respectively. As the film thickness increased, the peak currents specific to the active ingredients increased. The highest peak currents were obtained with film electrodes grown in 10 seconds.
The most suitable supporting electrolyte solution medium that can increase the response of the active ingredients at the PPR modified electrode was investigated. For this purpose, phosphate, Britton-Robinson and acetate buffer solutions were used with pH ranging from 2.0 to 11.0. The best response for the active ingredients was obtained in PBS at pH 7.0 medium.

Applications of Modified Electrodes

In order to investigate the applicability of the modified electrodes, DPV responses of LD and BS active substances in 1.0 mM solutions prepared in PBS (pH 7.0) were investigated. As a result of comparing the DPV responses of the binary mixture in the PPR and SWCNT modified electrodes, the voltammograms in Figure 1 were obtained. When the DPVs were examined, the best separation was achieved at the modified electrode (SWCNT / PPR / GCE) obtained by dropping 20 μL of 1.0% SWCNT (f voltammogram in Figure 1) after coating PPR on the GCE. The current values obtained with this modified electrode have also enhanced. In addition, the modified SWCNT / PPR / GCE responded better than the polymer electrode obtained by coating the GCE with PPR. The peak currents of LD and BS increased approximately 4-fold and 8-fold, respectively. This proved that the SWCNT modification further improved the responses. In line with these results, the modified electrode that obtained by dropping 20 μL of 1.0% SWCNT after coating PPR on the GCE (SWCNT / PPR / GCE) was used in the limit of detection, recovery and interference effect studies.

![Figure 1. DPV responses of the modified electrodes for a mixture of 1.0 mM LD and 1.0 mM BS in PBS at pH 7.0. Modified electrodes prepared by a) coating with polypyrrole, b) dropping 20 μL of 0.2% SWCNT after coating polypyrrole, c) dropping 10 μL of 0.5% SWCNT after coating polypyrrole, d) dropping 20 μL from 0.5% SWCNT after coating polypyrrole, e) dropping 10 μL of 1.0% SWCNT after coating polypyrrole, f) dropping 20 μL from 1.0% SWCNT after coating polypyrrole, g) dropping 20 μL from 0.2% SWCNT onto GCE before coating polypyrrole, h) dropping 10 μL of 0.5% SWCNT onto GCE before coating polypyrrole, i) dropping 20 μL from 0.5% SWCNT onto GCE before coating polypyrrole, j) dropping 10 μL from 1.0% SWCNT onto GCE before coating polypyrrole, k) dropping 20 μL from 1.0% SWCNT onto GCE before coating polypyrrole]

\[\text{Potential (mV)} \] \[\text{Current (A)} \]
Quantitative Determination of LD and BS with Modified Electrode

Within the scope of method validation, regression equations were obtained from the calibration graphs drawn against the concentrations of the peak currents of LD and BS and the limits of determination were found. Recovery studies have been conducted in tablet dosage forms and urine samples. The linear correlation of the calibration curve is related to the anodic oxidation peak currents and concentration. Calibration equation was calculated as \( I_{\text{pa}} (\mu A) = XC (\mu M) + Y \). Regression analysis was performed by the least square’s method. The limit of detection (LOD) was calculated from \( 3 \times s / m \) and the limit of quantification (LOQ) from \( 10 \times s / m \). In these formulas, "s" is the standard deviation of the peak currents (with 10 repetitions) repeated at a certain concentration within the calibration range, and "m" is the slope value of the relevant calibration curve. The precision of the method was calculated from ten independent replicates of 1.0 mM BS and 1.0 mM LD solutions on the same day (intra-day reproducibility) and measurements over five consecutive days (inter-day repeatability). In the measurements between days, three repetitions were made and the average was taken into account.

The DPVs and calibration graph of BS at different concentrations (10.00, 19.98, 29.70, 39.41, 49.03 \( \mu M \)) prepared in 0.1 M PBS (pH 7.0) at modified SWCNT / PPR / GCE, and the calibration graph were shown in Figure 2. DPVs at modified SWCNT / PPR / GCE for increasing concentrations of LD in 0.1 M PBS at pH 7.0 (10.00, 19.98, 29.70, 39.41, 49.03 \( \mu M \)), and the calibration plot for levodopa was shown in Figure 3. The linear equation for BS in the concentration range of 10.0 – 49.0 \( \mu M \) was obtained as \( I_{\text{pa}} (\mu A) = 11.019C (\mu M) - 53.187 \). The linear equation for LD in the concentration range of 10.0 – 49.0 \( \mu M \) was obtained as \( I_{\text{pa}} (\mu A) = 0.6818C (\mu M) - 2.2133 \). LODs were calculated as 2.41 \( \mu M \) for LD and 1.19 \( \mu M \) for BS. All the obtained validation parameters for the modified SWCNT/PPR/GCE and the method were summarized in Table 1.

![Figure 2](image-url)
Figure 3. DPV responses in PBS at pH 7.0 at modified electrode dropped 20 μL from 1.0% SWCNT after coating polypyrrole for LD in the range of 10.00 – 95.77 μM. Inset: calibration graph for LD in the concentration range 10.00 – 49.12 μM

Table 1. Validation data obtained with modified SWCNT / PPR / GCE in quantitative determination of BS and LD

|                         | Benzerazide | Levodopa |
|-------------------------|-------------|----------|
| Equation of the calibration curve | $I(\mu A) = 11.019C(\mu M) - 53.187$ | $I(\mu A) = 0.682C(\mu M) - 2.213$ |
| Potential measured (mV) | 128         | 312      |
| Linearity range (μM)    | 10 - 50     | 10 - 50  |
| Slope (μA μM⁻¹)         | 11.020      | 0.682    |
| Intercept (μA)           | -53.187     | -2.213   |
| Correlation coefficient  | 0.993       | 0.992    |
| Standard deviation of slope | 0.526    | 0.035    |
| Standard deviation of the intercept | 17.172 | 1.143 |
| LOD (μM)                | 1.189       | 2.410    |
| LOQ (μM)                | 3.962       | 8.040    |
| Repeatability of potential (RSD%) | 0.870 | 1.490 |
| Reproducibility of potential (RSD%) | 2.550 | 0.570 |
| Repeatability of current (RSD%) | 1.010 | 0.430 |
| Reproducibility of current (RSD%) | 4.710 | 2.970 |

Interference Effect of Ascorbic Acid

The interaction effect of AA, a type that can interfere with LD and BS, in the PBS electrolyte medium was investigated. AA and BS were added to the PBS solution at a constant concentration. Then, LD was added to increase in concentration each time and the measurement was taken. When Figure 4A is examined, it can be seen that while the AA and BS peaks remain the same, the LD peaks increase linearly. In addition, the concentration of the LD and BS binary mixture was kept constant and the AA concentration was increased (Figure 4B). While the peak current heights remained constant for LD and BS, the peak current heights increased as the
concentration of AA increased. Ten consecutive measurements were taken at five-second intervals in the solution containing all three components to see the stability of the measurement. The voltammograms obtained are shown in Figure 4C. While no shift was observed in the peak potentials of all analytes, the peak current heights remained constant. The very good resolution and stability of these peaks representing all three components proved the applicability of this modified electrode.

To see how the produced modified electrode would behave against the matrix effect in real samples, these three substances were also added to the urine sample. First, constant concentrations of LD and BS were added to the urine sample, followed by increasing concentrations of ascorbic acid. In addition, ten consecutive measurements were made at five seconds intervals in the urine sample containing ascorbic acid, LD and BS to see the stability of the modified electrode. Interference effect studies in urine samples have proven that these three species can be selectively distinguished and identified also in real samples.
Figure 4. DPV responses for A) LD (1.0, 2.0, 3.0, 4.0 mM) in the presence of 5 mM AA and 0.1mM BS, B) 0.1mM LD, 0.1mM BS and AA (5.0, 6.0, 7.0, 8.0, 9.0 mM), C) 7.0 mM AA, 0.1mM BS and 1.0 mM LD in PBS (pH 7.0) at modified electrode dropped 20 μL from 1.0% SWCNT after coating polypyrrole

Recovery Studies on Drug Sample

The drug sample (Madopar) in tablet form containing LD and BS was weighed to contain the active ingredient at the appropriate concentration, and solutions were prepared. Five repeat samples were prepared by taking 1.0 mL of this solution and filling it to 10 mL with PBS electrolyte. Analysis of these samples was carried out using the DPV technique at modified SWCNT / PPR / GCE. The corresponding amount of active ingredient in the mixture was found from the appropriate calibration graphs and the recovery values were calculated. In addition, the same procedures were applied to the solutions prepared by adding standard substances to urine samples.

The recovery studies of Madopar® (100 mg LD / 50 mg BS) tablet sample at modified SWCNT / PPR / GCE were shown in Table 2. In addition, standard chemicals were spiked into urine and drug samples, with the modified SWCNT / PPR / GCE very high recovery values could be obtained (Table 3). The data obtained from these analytical studies showed positive results that the applied method and modified SWCNT / PPR / GCE can be used to determine binary mixtures.

Table 2. Analysis results of Madopar tablet sample

| Sample | Amount in the tablet (mg) | Measured quantity (mg) | Recovery, % |
|--------|--------------------------|------------------------|-------------|
|        | LD  | BS  | LD  | BS  | LD  | BS  |
| 1      | 1.972 | 0.986 | 1.9303 | 0.9952 | 97.89 | 100.94 |
| 2      | 1.972 | 0.986 | 1.9893 | 0.9878 | 100.88 | 100.18 |
| 3      | 1.972 | 0.986 | 1.967 | 0.9752 | 99.75 | 98.91 |
| 4      | 1.972 | 0.986 | 1.9502 | 0.952 | 98.90 | 96.56 |
| 5      | 1.972 | 0.986 | 1.9482 | 0.9688 | 98.80 | 98.26 |
|        |      |      |      |      | X  | 99.24  | 98.97  |
|        |      |      |      |      | SD | 1.009 | 1.53 |
|        |      |      |      |      | RSD % | 1.02 | 1.54 |
|        |      |      |      |      | RE % | 0.76 | 1.03 |

* X: average of the results found, b SD: standard deviation, c RSD%: coefficient of variation, d RE%: percent relative error
Table 3. Results measured by spiking standard active ingredients into Madopar tablet sample and urine sample

| Sample | Measured quantity (mg) | Recovery, % | Spiked (mg) | Tablet LD | Tablet BS | Urine LD | Urine BS | Tablet LD | Tablet BS | Urine LD | Urine BS | Table 3 X | SD 0.313 | RSD % 0.313 | RE % 0.083 |
|--------|------------------------|-------------|-------------|-----------|-----------|---------|---------|-----------|-----------|---------|---------|-----------|---------|-----------|-----------|
| 1      |                        |             |             | 0.197     | 0.294     | 0.1961  | 0.2896  | 0.2896    | 0.1892    | 0.2783  | 99.43   | 98.60   | 95.95     | 94.76   | 99.92     | 96.61     | 92.70     | 92.48     |
| 2      |                        |             |             | 0.197     | 0.294     | 0.1971  | 0.2914  | 0.2914    | 0.1848    | 0.2876  | 0.1896  | 0.2716  | 99.96   | 98.32   | 93.72     | 92.48     |
| 3      |                        |             |             | 0.197     | 0.294     | 0.1980  | 0.2884  | 0.2884    | 0.1821    | 0.2732  | 100.4   | 98.20   | 92.35     | 93.02   |
| 4      |                        |             |             | 0.197     | 0.294     | 0.1970  | 0.2700  | 0.2700    | 0.1793    | 0.2693  | 0.1921  | 0.2693  | 99.91   | 99.14   | 90.93     | 91.69     |
| 5      |                        |             |             | 0.197     | 0.294     | 0.1969  | 0.2793  | 0.2793    | 0.1786    | 0.2657  | 99.87   | 95.10   | 90.57     | 90.47   | 99.92     | 96.61     | 92.70     | 92.48     |
|        |                        |             |             |           |           |         |         |           |           |         |         | X        |         | SD 0.313  | RSD % 0.313 | RE % 0.083 |

CONCLUSION

Within the scope of this study, applications of electrodes designed with single-walled carbon nanotubes and electropolymerized of pyrrole were investigated. The best stability, resolution and highest peak currents were achieved with the modified electrode obtained by coating polypyrrole on GCE and dropping 20 μL 1.0% SWCNT on it. High recoveries were obtained in urine and drug samples. In the presence of interfering AA, the active ingredients were determined simultaneously, selectively and sensitively. According to these studies, it can be suggested that the experiments can be recovered without being affected by the tablet matrix.

As a result of all electroanalytical studies, quantitative determinations with modified SWCNT / PPR / GCE were performed without any separation process. Based on this, it can be suggested that this electrode can be used for quantitative analysis in many fields.

ACKNOWLEDGMENT

This study was derived from the doctoral thesis with the project number 2013-54 supported by Inonu University Scientific Research Projects Unit.

CONFLICT OF INTEREST

The authors report no conflict of interest relevant to this article.

RESEARCH AND PUBLICATION ETHICS STATEMENT

The authors declare that this study complies with research and publication ethics.

REFERENCES

Adamiak-Giera, U. and Gawronska-Szklarz, B. (2018). Simultaneous Determination of Levodopa and 3-O-Methylidopa in Patients with Parkinson’s Disease by High-Performance Liquid Chromatography with Electrochemical Detection. Journal of Liquid Chromatography and Related Technologies, 41 (19–20), 1047–1051.

Aslan, N., Başman, N. and Uzun, O. (2016). Formik Asit Kullanılarak Elektrokimyasal Yolla Sentezlenen Elmas Benzeri Karbon Filmlerinin Optik, Yüzey ve Mekanik Özelliklerinin İncelenmesi. International Journal of Pure and Applied Sciences, 2 (2), 57 – 63.

Aviles-Olmos, I., Martinez-Fernandez, R. and Foltynie, T. (2010). L-dopa-Induced Dyskinesias in Parkinson’s Disease. European Neurological Journal, 2, 2.

Chen, C., Hutchison, J.E., Postlethwaite, T.A., Richardson, J.N. and Murray, R.W. (1994). Chemically Modified Electrodes by Nucleophilic Substitution of Chlorosilylated Platinum Oxide Surfaces. Langmuir, 10 (9), 3332–3337.

Ensafi, A.A., Arabzadeh, A. and Karimi-Maleh H. (2010). Sequential Determination of Benserazide and Levodopa by Voltammetric Method using Chloranil as a Mediator. Journal of Brazilian Chemical Society, 21 (8), 1572-1580.

Fabbri, F., Brothie, J.M., Grandas, F., Nomoto, M. and Goetz, C.G. (2007). Levodopa-Induced Dyskinesias. Movement Disorders, 22 (10), 1379–1389.
He, W.W., Zhou, X.W. and Lu, J.Q. (2006). Simultaneous Determination of Benserazide and Levodopa by Capillary Electrophoresis-Chemiluminescence Using an Improved Interface. Journal of Chromatography A, 1131 (1–2), 289–292.

Ince, M. and Ince, O. K. (2017). Su/Atıksuda Ağır Metal Giderimi için Adsorpion Teknigiı Genel Bir Bakış: Önemli Bir İnceleme. International Journal of Pure and Applied Sciences, 3 (2), 10 – 19.

Jalalvand, A.R. (2020). Four-Dimensional Voltammetry: An Efficient Strategy for Simultaneous Determination of Ascorbic Acid and Uric Acid in the Presence of Dopamine as Uncalibrated Interference. Sensing and Bio-Sensing Research, 28, 100330.

Kobayashi, K. (2001). Role of Catecholamine Signaling in Brain and Nervous System Functions: New Insights from Mouse Molecular Genetic Study. Journal of Investigative Dermatology Symposium Proceedings, 6 (1), 115–121.

Kuyumcu Savan, E. (2019a). Square Wave Voltammetric Determination of Quercetin in Tea Samples at a Single-Walled Carbon Nanotube (SWCNT) Modified Glassy Carbon Electrode (GCE). Analytical Letters, 0 (0), 1–15.

Kuyumcu Savan, E. and Erdogdu, G. (2020). Pirol ve Çok Duvarlı Karbon Nanotüp Modifiye Sensör ile Levodopa ve Benserazidin Elektrokimyasal Olarak Eşzamanlı Tayini. İnönü Üniversitesi Sağlık Hizmetleri Meslek Yüksek Okulu Dergisi, 8 (2), 336–355.

Lechin, F., Van Der Dijs, B. and Lechin, A.E. (2005). Circulating Serotonin, Catecholamines, and Central Nervous System Circuitry Related to Some Cardiorespiratory, Vascular, and Hematological Disorders. Journal of Applied Research, 5 (4), 605–621.

Lou, B.S., Rajaji, U., Chen, S.M. and Chen, T.W. (2020). A Simple Sonochemical Assisted Synthesis of NiMoO4/Chitosan Nanocomposite for Electrochemical Sensing of Amlodipine in Pharmaceutical and Serum Samples. Ultrasonics Sonochemistry, 64, 104827.

Loutelier-Bourhis, C., Legros, H., Bonnet, J.J., Costentin, J. and Lange, C.M. (2004). Gas Chromatography/Mass Spectrometric Identification of Dopaminergic Metabolites in Striata of Rats Treated with L-DOPA. Rapid Communications in Mass Spectrometry, 18 (5), 571–576.

Martins, H.F., Pinto, D.P., De A. Nascimento, V., Marques, M.A.S. and Amendoeira, F. (2013). Determination of Levodopa in Human Plasma by High Performance Liquid Chromatography-Tandem Mass Spectrometry (HPLC-MS/MS): Application to a Bioequivalence Study. Quimica Nova, 36 (1), 171–176.

Mazloum-Ardakani, M., Abolhasani-Soorki, M., Khooshroo, A., Sabaghian, F. and Mirjalili, B.F. (2018). Simultaneous Determination of Ascorbic Acid, Uric Acid and Tryptophan by Novel Carbon Nanotube Paste Electrode. Iranian Journal of Pharmaceutical Research, 17 (3), 851–863.

Mikra, M., Karimi-Maleh, H., Taher, M.A., Cheraghi, S., Karimi, F., Agarwal, S. and Gupta, V.K. (2019) Voltammetric amplified platform based on ionic liquid/NiO nanocomposite for determination of benserazide and levodopa. Journal of Molecular Liquids, 278, 672–676.

Oyama, N. and Anson, F.C. (1980). Catalysis of Electrode Processes by Multiply-Charged Metal Complexes Electrostatically Rotating to Polyelectrolyte Coatings on Graphite Electrodes, and the Use of Polymer-Coated Disk Electrodes in Diagnosing Kinetic and Conduction Mechanisms. Analytical Chemistry, 52 (8), 1192–1198.

Özdokur, K.V. (2020). Voltammetric Determination of Isoniazid Drug in Various Matrix by Using CuOx Decorated MW-CNT Modified Glassy Carbon Electrode Electroanalysis, 32 (3), 489–495.

Palisoc, S., De Leon, P.G., Alzona, A., Racines, L. and Natividad, M. (2019). Highly Sensitive Determination of Tetracycline in Chicken Meat and Eggs Using AuNP/ MWCNT-Modified Glassy Carbon Electrodes. Heliyon, 5 (7), e02147.

Palomar, Q., Xu, X.X., Gondran, C., Holzinger, M., Cosnier, S. and Zhang, Z. (2020). Voltammetric Sensing of Recombinant Viral Dengue Virus 2 NS1 Based on Au Nanoparticle–Decorated Mult walled Carbon Nanotube Composites. Microchimica Acta, 187 (6), 1–10.

Ramanavičius, A., Ramanavičienė, A., Malinauskas, A. (2006). Electrochemical sensors based on conducting polymer-polymerro. Electrochimica Acta, 51, 6025–6037.

Saleh, G.A., Askal, H.F., Refaat, I.H., Naggar, A.H. and Abdel-aal, F.A.M. (2016). Adsorptive Square Wave Voltammetric Determination of the Antiviral Drug Valacyclovir on a Novel Sensor of Copper Microparticles-Modified Pencil Graphite Electrode. Arabian Journal of Chemistry, 9 (1), 143–151.

Sarabi, A., Hoffer, B.J., Olson, L. and Morales, M. (2001). Catecholamine-Containing Cells in the Central Nervous System and Periphery of Aplysia Californica. Journal of Comparative Neurology, 441 (2), 91–105.

Kuyumcu Savan, E. and Erdogdu, G. (2017). Simultaneous Determination of Levodopa and Benserazide Using Poly(3-Methylthiophene) and a Multi-Walled Carbon
Nanotube Sensor. Journal of Solid State Electrochemistry, 21 (8), 2209–2217.
Kuyumcu Savan, E. and Erdoğan, G. (2019). Poly(3-Methylthiophene) Modified Gold Sensor for Determination of 3,4-Dihydroxyphenylacetic Acid, Ascorbic Acid and Uric Acid in Biological Fluids Using Voltammetric Techniques. Marmara Pharmaceutical Journal, 23 (1), 25–33.
Shahrokhian, S. and Asadian, E. (2009). Electrochemical Determination of L-Dopa in the Presence of Ascorbic Acid on the Surface of the Glassy Carbon Electrode Modified by a Bilayer of Multi-Walled Carbon Nanotube and Poly-Pyrrole Doped with Tiron. Journal of Electroanalytical Chemistry, 636 (1–2), 40–46.
Shimozawa, A., Fujita, Y., Kondo, H., Takimoto, Y., Terada, M., Sanagi, M., Hisanaga, S. and Hasegawa, M. (2019). Effect of L-DOPA/Benserazide on Propagation of Pathological α-Synuclein. Frontiers in Neuroscience, 13 (595), 1–8.
Tanrıkut, E., Özcan, İ., Sel, E., Köytepe, S. and Kuyumcu Savan, E. (2020). Simultaneous Electrochemical Detection of Estradiol and Testosterone Using Nickel Ferrite Oxide Doped Mesoporous Carbon Nanocomposite Modified Sensor. Journal of The Electrochemical Society, 167 (8), 087509.
Uslu, B. and Özkan, S.A. (2002). Determination of Binary Mixtures of Levodopa and Benserazide in Pharmaceuticals by Ratio-Spectra Derivative Spectrophotometry. Analytical Letters, 35 (2), 303–314.
Viskin, S. and Belhassen, B. (1998). Polymorphic Ventricular Tachyarrhythmias in the Absence of Organic Heart Disease: Classification, Differential Diagnosis, and Implications for Therapy. Progress in Cardiovascular Diseases, 41 (1), 17–34.
Wang, L., Huang, P., Bai, J., Wang, H., Wu, X. and Zhao, Y. (2006). Voltammetric Sensing of Uric Acid and Ascorbic Acid with Poly (p-Toluene Sulfonic Acid) Modified Electrode. International Journal of Electrochemical Science, 1 (6), 334–342.
Wolf, J.P., Bouhaddi, M., Louisy, F., Mikehev, A., Mourot, L., Cappelle, S., Vuillier, F., Andre, P., Rumbach, L. and Regnard, J. (2006). Side-Effects of L-Dopa on Venous Tone in Parkinson’s Disease: A Leg-Weighing Assessment. Clinical Science, 110 (3), 369–377.
Zhang, K., Zhang, N., Zhang, L., Wang, H., Shi, H. and Liu, Q. (2018). Simultaneous Voltammetric Detection of Dopamine, Ascorbic Acid and Uric Acid Using a Poly[2-(N-Morpholine)Ethane Sulfonic Acid]/RGO Modified Electrode. RSC Advances, 8 (10), 5280–5285.