Research Article

Nevila Broli*, Majlinda Vasjari, Loreta Vallja, Sonila Duka, Alma Shehu, Sadik Cenolli

Electrochemical determination of atenolol and propranolol using a carbon paste sensor modified with natural ilmenite

<https://doi.org/10.1515/chem-2021-0071>

received April 9, 2021; accepted June 30, 2021

Abstract: In this study, a simple voltammetric method was reported for independent determination of propranolol (PROP) and atenolol (ATN) in pharmaceutical tablets using carbon paste electrode modified with natural ilmenite (CPE-I). The analytical performance of the modified sensor was evaluated using the square wave voltammetry and cyclic voltammetry for determination of both β (beta) blockers in 0.1 mol L^{-1} of sulfuric acid solution (H_2SO_4). The signal obtained with modified carbon paste electrode in 0.1 mol L^{-1} of H_2SO_4 showed a good electrocatalytic activity toward the oxidations of PROP and ATN compared with the bare one. The enhanced oxidation peak current response can be attributed to the catalytic effect of the ilmenite nanomaterial incorporated into the carbon paste electrode. Under optimal condition, good linear calibration curves were obtained ranging from 0.20 to 8.9 mmol L^{-1} for PROP and 2.0 to $9.9 \mu\text{mol L}^{-1}$ for ATN, with detection limits of 80 and $0.31 \mu\text{mol L}^{-1}$, respectively. The CPE-I sensor had good repeatability and reproducibility ($\text{RSD} \leq 3.2\%$) and high sensitivity for the detection of both ATN and PROP. The proposed sensor was applied for detection of these drugs in pharmaceutical tablets. The obtained results indicate that the voltammetric CPE-I sensor could be an alternative method for the routine quality control of the β blockers in complex matrices.

Keywords: β blockers, square wave voltammetry, ilmenite nanomaterial, cyclic voltammetry, pharmaceutical tablets

1 Introduction

The use of nanomaterials for the determination of variety of compounds is attracting attention in recent electro-analytical research [1]. In order to modify and improve the sensitivity and selectivity of working electrode, nanomaterials have been shown as suitable materials [2,3]. The presence of nanomaterials on the surface of the working electrode can improve the sensitivity and the rate of electron transfer to the surface electrode, according to some previous results. The development and application of modified carbon paste electrodes (CPE) have received considerable attention due to its low residual current, easy preparation, renewable surfaces, and low cost. Behpour et al. (2010) [8] have prepared a gold nanoparticle-modified carbon paste electrode (GN-CPE) for simultaneous determination of Acetaminophen (ACEP) and ATN. The results obtained demonstrated the potentiality of the GN-CPE for simultaneous determination of ACEP and ATN with high selectivity, good sensitivity, and low detection limits with the low cost of the sensor. Other authors like Ghapanvari et al. (2020) [9] have successfully modified the CPE with Fe_3O_4 at multi-walled carbon nanotubes at polyacrylonitrile for the detection of imatinib (IMA). Ilmenite ($\text{FeO}\cdot\text{TiO}_2$) has been widely known as an excellent catalyst in antimicrobial activity, chemical oxygen demand sensing, photocatalysis, and photoelectrocatalysis. In recent studies, the catalytic effect of ilmenite and rutile on composite CPE was reported, where these modified sensors have shown an excellent performance for detection of phenol, pesticides, and drugs [4–7]. The modified process could improve the sensitivity, electrocatalytic behavior, and surface area. Several related studies reported that CPE modification is one of the most effective methods to improve electrode performance especially in electrode sensitivity for the determination of important compounds such as Epinephrine and Tyrosine, Amiodarone, Bisphenol A, and Losartan Potassium in trace level concentrations [3,4,10,11]. In clinical chemistry, doping and pharmaceutical investigations

* Corresponding author: Nevila Broli, Department of Chemistry, Faculty of Natural Sciences, University of Tirana, Tirana, Albania, e-mail: nevila.broli@fshn.edu.al

Majlinda Vasjari, Loreta Vallja, Sonila Duka, Alma Shehu, Sadik Cenolli: Department of Chemistry, Faculty of Natural Sciences, University of Tirana, Tirana, Albania

the quantification and determination of drugs in pharmaceutical samples and biological fluids are essential [12]. ATN (4-(2-hydroxy-3-isopropylaminopropoxy)phenylacetamide) and PROP (1-(isopropylamino)-3-(1-naphthyloxy)-2-propranolol) are cardioselective-adrenergic receptor blocking agents. These blocker agents are widely used in the treatment of cardiovascular diseases, arterial hypertension, cardiac arrhythmias, angina pectoris cardiac arrhythmias, and myocardial infarction [13]. Therefore, the simpler and faster methods for analyses of different receptor blocking agents are interesting in the quality of pharmaceutical formulations that contain them and also for therapeutic drug monitoring purposes. Despite their high use and application, little work has been reported on the determination of cardiovascular drugs by the electrochemical and related sensing devices [14]. The determination of a wide range of drug compounds was conducted using electrochemical techniques. The redox properties of drugs can provide insight into their metabolic fate, their *in vivo* redox processes, and their pharmacological activities [15–17]. For that reason, it is important to develop more sensitive sensors for detection of these drugs.

In this work a simple, selective, and highly sensitive electrochemical sensor modified with ilmenite nanostructure CPE-I is being reported for the determination of ATN and PROP. The CPE-I is an effective sensor for determination of β (beta) blockers (ATN and PROP) because this natural material (containing TiO_2 and FeO) has the ability for fast electron transfer, a good biocompatibility, etc., [5,6,18,19]. The proposed method was also applied to the investigation of these analytes in pharmaceutical formulation.

2 Materials and methods

2.1 Experimental

2.1.1 Reagents and chemicals

A pure standard form of Propranolol hydrochloride (W00336) and ATN (series 00336) in powdered form was purchased from TCI Chemicals Pvt. Ltd., India. Chemicals and reagents used for all the experiments were of analytical grade (Sigma and Merck). All solutions were prepared using double distilled water. The H_2SO_4 used to prepare the supporting electrolyte was purchased from Merck. Acetic acid, dipotassium phosphate, and dihydrogen phosphate were purchased from

Merck (99% Merck). The paraffin oil (Olio di Vaseline) used was from Zeta farmaceutici company and the graphite powder synthetic with particles size 90–71 μm was from Alfa Aesar (99.9% Alfa Aesar). Ilmenite natural nanomaterial was granulated with particle size of 90–70 μm and activated with 10% of H_2SO_4 . Commercial pharmaceutical tablets including PROP 83 (40 mg) and ATN (Profarma Sh.a) (100 mg) were purchased from a local pharmacy. A stock solution of 100 mmol L^{-1} of PROP and 10 mmol L^{-1} of ATN was prepared in 0.1 mol L^{-1} of H_2SO_4 solution and kept at 4°C in a refrigerator. These solutions were diluted to the desired concentration with 0.1 mol L^{-1} of H_2SO_4 .

2.2 Apparatus

All the electrochemical measurements were carried out using PalmSens4 (potentiostat–galvanostat) connected via Bluetooth with a personal computer and three-electrode system software. The working electrodes were a CPE-I sensor studied in this work, a platinum wire as counter electrode, silver-silver chloride Ag/AgCl/KCl (3M), and a reference electrode. The electrochemical determination of PROP and ATN was performed using cyclic voltammetry (CV) and square wave voltammetry (SWV). SW voltammograms were recorded at a potential from 0.6 to 1.5 V for PROP and 1.0 to 1.6 V (vs SCE) for ATN, with scan rate of 100 mV s^{-1} , amplitude of 0.03 V, and frequency of 25 Hz. All voltammetric measurements were done at $26 \pm 0.5^\circ\text{C}$ in an unstirred electrochemical cell containing 15 mL of 0.1 mol L^{-1} of H_2SO_4 as supporting electrolyte. Scheme of the experiment and possible oxidation mechanism is shown in Figure 1.

2.3 Preparation of modified sensor CPE-I

The CPE-I was prepared by mixing 70% of graphite, 10% of ilmenite, and 20% of mineral oil for 30 min to give a homogeneous paste. Initially, the graphite powder (with particle size 90–72 μm) and paraffin were mixed together and after that, the inorganic modifier (ilmenite natural material with the same size activated with 10% of H_2SO_4) was added and mixed with a mortar and pestle until a uniform paste was obtained. The prepared composite material was kept in a refrigerator at 4°C for 24 h before measurement. The obtained paste was packed into the plastic syringe with internal diameter 8 mm and outer diameter of

Figure 1: Schematic of experimental mechanisms of electrooxidation of ATN and PROP at surface of CPE-I electrode.

9.5 mm containing a copper wire as the external electric contact. The unmodified CPE was also prepared in the same way by mixing 70% of graphite and 30% of mineral oil for 30 min, except that no modifier (ilmenite) was added. The electrode surface was smoothed on a glass surface before the measurements. The surface of the electrode was renewed by removing a part of the paste and polishing it again on the glass surface.

2.4 Samples preparation (pharmaceutical tablets of ATN and PROP)

The PROP and ATN are taken from casual drugstore in tablet form. First, the tablets were accurately weighed (each tablet weighs; PROP 0.1708 g contains 40 mg and ATN 0.4196 g contains 100 mg). Five tablets of each were finely ground in the mortar pestle and a portion of respective powdered tablet (equivalent to the average weight of one tablet) was transferred into 50.0 mL volumetric flask using 50.0 mL of 0.1 mol L⁻¹ of H₂SO₄. From the prepared solution, 1 mL sample of PROP and 0.25 mL of ATN were

taken and were analyzed by SWV technique in 15 mL of 0.1 mol L⁻¹ of H₂SO₄. The PROP and ATN contents were determined using the standard addition method.

Ethical approval: The conducted research is not related to either human or animal use.

3 Results and discussion

3.1 Electrochemical behavior of PROP and ATN at modified CPE-I sensor

The effect of nano-ilmenite material incorporated on CPE sensor was tested by comparing the voltammograms obtained with modified and unmodified sensor toward ATN and PROP. Figure 2a and b shows the typical SWV voltammograms of 9.9 μmol L⁻¹ of ATN and 3.6 mmol L⁻¹ of PROP in 0.1 mol L⁻¹ of H₂SO₄ solution recorded with two different working electrodes (bare CPE and CPE-I).

Figure 2: Square wave voltammograms of (a) $9.9 \mu\text{mol L}^{-1}$ of ATN and (b) 3.6 mmol L^{-1} of PROP at bare CPE and CPE-I in 0.1 mol L^{-1} of H_2SO_4 solution (pH 2) with pulse amplitude of 30 mV and frequency of 25 Hz.

As seen in Figure 2a and b, the SW voltammograms of ATN and PROP at CPE-I electrode appears with enhancement in response to peak current in both the cases compared with the bare one. The modified sensor showed a good improvement in oxidation peak currents for these β blockers. The results indicate that this behavior can be attributed to the catalytic nature [6] of modified CPE-I for ATN and PROP oxidation. The possible oxidation mechanisms [20] for ATN and PROP [21–25] at the surface of the modified electrode were considered as shown in Figure 1.

Regarding the role of $\text{Fe(II)}/\text{Fe(III)}$ species in the oxidation of organic substances, there are many evidences in the literature. [26–28]. It has been reported that these species that are generated at positive potentials have the role of a redox mediator in the oxidation of some compounds at Fe related electrodes. The electrode reaction may take place with a mechanism involving a rate limiting step where an intermediate reaction is formed upon a chemical reaction with Fe(II) and Fe(III) species. [4,28]. Our results showed that the ilmenite natural material showed good improvement in oxidation peak currents for ATN and PROP. Therefore, it is suggested that the application of ilmenite leads to provide a current sensitivity in detection of these drugs

3.2 Optimization of experimental parameters

The electrochemical performance of modified CPE-I sensor towards PROP and ATN was tested in optimal experimental condition. Different parameters were optimizing such as: (a) electrochemical technique, (b) scan rate, and (c) supporting electrolyte and pH. First, in order to choose the more selective and sensitive technique, the electrochemical behavior of ATN at the surface of the modified electrode using differential pulse voltammetry (DPV), SWV, and CV was investigated. Figure 3 shows the DPV, SWV, and CV voltammograms registered with CPE-I, at $320 \mu\text{mol L}^{-1}$ of ATN, in 0.1 mol L^{-1} of H_2SO_4 .

As can be seen from the graph in Figure 3, SWV is more sensitive method for detection of ATN because the signal appears with a higher oxidation peak compared with the other two techniques. Regarding this aspect, in further experiments, SWV technique was used for determination of both the β blockers in lower concentration.

The effect of scan rate on peak current response was studied at a concentration of $340 \mu\text{mol L}^{-1}$ of ATN in 0.1 mol L^{-1} of H_2SO_4 . The cyclic voltammograms obtained with CPE-I sensor at different scan rates from 20 to

Figure 3: Voltammograms of $320 \mu\text{mol L}^{-1}$ of ATN in 0.1 mol L^{-1} of H_2SO_4 at CPE-I composite electrode using the CV, SWV, and DPV techniques. Conditions: CV, scan rate = 100 mV s^{-1} ; DPV, scan rate = 20 mV s^{-1} and pulse amplitude = 30 mV ; SWV, pulse amplitude = 30 mV , frequency = 25 Hz , and step potential = 5 mV .

Figure 4: Cyclic voltammograms for $340 \mu\text{mol L}^{-1}$ of ATN in 0.1 mol L^{-1} of H_2SO_4 solution obtained using CPE-I at different scan rates from 20 to 200 mV s^{-1} . Insert: linear dependence of the peak current with $v^{1/2}$.

200 mV s^{-1} are shown in Figure 4, and no oxidation peaks were observed. This indicates an irreversible heterogeneous

charge transfer, which is reported in the previous studies [29–31]. Cathodic peak current was proportional to the square root of the scan rate according to the previous study [32] indicating that electrooxidation is diffusion-controlled process. A linear relationship was observed between I_p and v (Figure 4 insert) and $R^2 = 0.9928$. Plots of the logarithm of the peak current versus the logarithm of the scan rate for ATN is linear with slopes of 0.62 , which are close to the theoretical expected value of 0.50 for an ideal reaction of species in solution [33].

In order to choose the best supporting electrolyte and pH for further electroanalytical measurements, the SW voltammograms were registered in 3.3 mmol L^{-1} for PROP and $3.3 \mu\text{mol L}^{-1}$ for ATN using different supporting electrolytes with pH from 2.0 to 7.0 . The best well-defined oxidation peak for both analytes was obtained in H_2SO_4 solution with adjusted pH of 2.0 at potential of 1.2 V (PROP) and 1.5 V (ATN) as shown in Figure 5.

It is clearly seen that the potential for PROP and ATN oxidation depends on the type of the supporting electrolyte and pH, so in acetate buffer solution, the intensity of oxidation current for PROP is lower and potential peak shifted to the positive value. Regarding the voltammograms obtained in phosphate buffer solution, no well-defined peak was observed. The same situation is observed with ATN in phosphate buffer solution, while in NaNO_3 solution, no oxidation peak appeared. Therefore, the solution of 0.1 mol L^{-1} of H_2SO_4 ($\text{pH} = 2$) was selected as a suitable supporting electrolyte for further experiments.

3.3 Analytical curves and validation parameters of the methods proposed for PROP and ATN determination

Analytical curves for ATN and PROP using modified CPE-I sensor were obtained using experimental parameters optimized previously. The analytical parameters obtained for ATN and PROP with two applied voltammetric techniques CV and SWV are shown in Table 1. The best analytical parameters like precision, sensitivity, and low detection limits were obtained by SWV, so this method was chosen for the determination of PROP and ATN in pharmaceutical tablets.

The SW voltammograms registered in 0.1 mol L^{-1} of H_2SO_4 for different concentrations of each β blocker using CPE-I sensor are shown in Figure 6 for concentration ranges: 0.20 – 8.9 mmol L^{-1} of PROP (Figure 6a) and 2.0 – $9.9 \mu\text{mol L}^{-1}$ of ATN (Figure 6b).

Figure 5: Square wave voltammograms obtained using CPE-I electrode for (a) of 3.3 mmol L⁻¹ of PROP in (1) acetate buffer (pH 4), (2) in 0.1 mol L⁻¹ of H₂SO₄ (pH 2), and (3) in phosphate buffer solution (pH 7), and (b) for 3.3 μmol L⁻¹ of ATN in (1) NaNO₃ (pH 4), (2) in phosphate buffer solution (pH 7), and (3) in 0.1 mol L⁻¹ of H₂SO₄ (pH 2), at scan rate of 100 mV s⁻¹ and pulse amplitude of 30 mV.

Table 1: Quantitative analytical results of the investigated β blockers by SWV and CV techniques

	Propranolol (in 0.1 mol L ⁻¹ of H ₂ SO ₄)		Atenolol (in 0.1 mol L ⁻¹ of H ₂ SO ₄)	
	Cyclic voltammetry	Square wave voltammetry	Square wave voltammetry	Cyclic voltammetry
Linear range (μmol L ⁻¹)	500–6600	200–8900	2.0–9.9	33–566
Correlation coefficient	0.9920	0.9969	0.9979	0.9943
Slope $\mu\text{A} (\mu\text{mol L}^{-1})^{-1}$	43	50	19.5	3.2
RSD (%)	4.1	3.2	2.5	3.9
Detection limit (μmol L ⁻¹)	100	80	0.31	1.9
Peak potential (V)	1.2	1.2	1.5	1.6

The respective analytical curves obtained for PROP ($R^2 = 0.9969$) and ATN ($R^2 = 0.9979$) with corresponding regression equations $I_{\text{ap}} (\mu\text{A}) = 0.0084 + 0.05019 [c (\text{mmol L}^{-1})]$ and $I_{\text{ap}} (\mu\text{A}) = 0.0039 + 0.0195 [c (\mu\text{mol L}^{-1})]$ are shown in the insert of Figure 6a and b (where I_{ap} is the anodic peak current and c is the concentration of respective analyte). The detection limit (3σ) values calculated are 80 μmol L⁻¹ for PROP and 0.31 μmol L⁻¹ for ATN. The repeatabilities of sensor determined by successive measurements at modified CPE-I electrode using 3.7 mmol L⁻¹ of PROP and 3.3 μmol L⁻¹ of ATN ($n = 5$), resulted with relative standard deviation (RSD) of 3.2 and 2.5%, respectively. The reproducibility of modified sensor estimated using the working electrodes CPE-I prepared ($n = 3$ electrodes) independently for

the same concentration of PROP and ATN were obtained with RSDs of 0.57 and 1.2%, respectively.

3.4 Analytical determination of PROP and ATN in pharmaceutical formulation

The development method was applied for determination of both β blockers in pharmaceutical tablets using SWV, since SWV possesses high sensitivity and good resolution. To determine the content of these drugs in real samples, the standard addition method was used. Solutions obtained by dissolving ATN and PROP tablets in 0.1 mol L⁻¹ of

Figure 6: Square wave voltammograms obtained using a nano-ilmenite modified CPE as working electrode for: (a) (1) 0; (2) 0.20 mmol L⁻¹; (3) 0.5 mmol L⁻¹; (4) 1.2 mmol L⁻¹; (5) 1.8 mmol L⁻¹; (6) 2.4 mmol L⁻¹; (7) 3.1 mmol L⁻¹; (8) 3.7 mmol L⁻¹; (9) 4.3 mmol L⁻¹; (10) 4.9 mmol L⁻¹; (11) 5.5 mmol L⁻¹; (12) 6.1 mmol L⁻¹; (13) 6.7 mmol L⁻¹; (14) 7.8 mmol L⁻¹; (15) 8.9 mmol L⁻¹ of PROP in 0.1 mol L⁻¹ of H₂SO₄ and (b) (1) 2.0 μmol L⁻¹; (2) 3.3 μmol L⁻¹; (3) 6.6 μmol L⁻¹; (4) 9.9 μmol L⁻¹ of ATN in 0.1 mol L⁻¹ of H₂SO₄ (pH 2.0). Inserts: Respective analytical curves for the oxidation processes of PROP (a) and ATN (b).

Table 2: Determination of ATN and PROP in real samples with CPE-I using square wave voltammetry ($n = 3$)^a

Analyte/Sample	Method	Spiked ^b	Found ^c	Recovery ^e
Propranolol (mg/tablet)	CPE-I	0	^d 36.5 ± 1.4	
		1.8	1.82 ± 0.2	101
		3.6	3.54 ± 0.4	98.0
Label value 40 mg				
Atenolol (mg/tablet)	CPE-I	0	^d 98.0 ± 5.2	
		6.6	6.45 ± 0.15	97.7
		13	12.88 ± 0.25	99.0
Label value 100 mg				

^a Mean value ± SD. ^b The unit of spiked concentration for PROP is mmol L⁻¹ and for ATN is μmol L⁻¹. ^c The measured unit is mmol L⁻¹ for PROP and μmol L⁻¹ for ATN. ^d The measured unit is mg/tablet.

^e The measured unit is %.

H₂SO₄ were subsequently diluted, in order that ATN and PROP concentrations fall in the range of the calibration plot. The SW voltammograms were obtained at CPE-I by spiking appropriate samples in H₂SO₄ solution, at optimum conditions for ATN and PROP (as described in Section 2.4). Table 2 shows the amount ATN and PROP determined with CPE-I sensor using SWV technique. It was found that ATN and PROP content determined in pharmaceutical tablets using this method are in good agreement with the reported label value.

Recovery test of PROP and ATN was carried out by spiking each analyte in highly diluted tablet samples and results obtained are also shown in Table 2. The tablet samples were spiked with two different amounts of ATN and PROP. The recoveries were found to be in the range of 97.7–101%

with a relative SD of 5.2%. These results demonstrated that the proposed methods could be used for the determination of these drugs in pharmaceutical preparations.

4 Conclusion

This work describes the preparation of CPE electrode modified with natural nano-ilmenite for the independent voltammetric determination of ATN and PROP using adequate supporting electrolyte solution of 0.1 mol L^{-1} of H_2SO_4 . The presence of modifier ilmenite could improve and facilitate the electron transfer in the electrooxidation of both β blockers through the diffusion mechanism process. The modified CPE-I sensor resulted in a higher analytical performance toward PROP and ATN compared with the bare CPE. The proposed method can be used to determine both β blockers ATN and PROP in real sample (commercial drugs) with good reproducibility and with reliable accuracy.

Acknowledgements: The authors would like to thank all the members of staff in the University of Tirana who had assisted during the experimental study.

Funding information: The authors did not receive support from any organization for the submitted work.

Author contributions: N.B. – writing – original draft, investigation, data curation; M.V. – supervision, visualization, methodology; L.V. – data curation, validation; S.D. – formal analysis; A.S. – conceptualization; S.C. – software.

Conflict of interest: The authors have no conflicts of interest to declare that are relevant to the content of this article.

Data availability statement: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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