

Simple Sensor Application: Determination of Electrochemical Properties of Carvedilol in CPE Based on Zinc Oxide Nanoparticles and Development of the Method for its Determination in Pharmaceutical Samples

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ABSTRACT

In this study, the electrochemical properties of carvedilol (CAR) were investigated by cyclic voltammetry (CV) and square wave voltammetry (SWV) on carbon paste electrode modified with zinc oxide nanoparticles (ZnONP/CPE) in pH 8.0 Britton Robinson (BR) buffer. The adsorption characteristics of the molecule on the modified electrode and the electron number accompanying the electrode reaction were calculated. Furthermore, a new square wave anodic stripping voltammetry (SWAdSV) method was proposed for the determination of CAR in drug samples. The linear concentration range and detection limit of the method were found to be 0.07 μM –2.61 μM and 0.09 μM , respectively. To test the accuracy of the developed method, recovery studies of CAR in the pharmaceutical sample were carried out. With the developed method, results with high reliability, reproducibility, accuracy, and precision were obtained for the determination of CAR in pharmaceutical samples.

Keywords:

Carbon paste electrode; Carvedilol; Stripping voltammetry; Zinc oxide nanoparticles

INTRODUCTION

CAR is called 1-(9H-carbazole-4-yloxy)-3-[[2-(2-methoxy phenoxy)ethyl]amino]-2-propanol (Figure 1). It is a β -adrenoreceptor blocker used clinically in the treatment of chronic heart failure and in the treatment of left ventricular dysfunction and hypertension after myocardial infarction. Along with its traditional effects, CAR and its metabolites show various antioxidant effects, such as inhibiting lipid peroxidation in the myocardial cell membrane and neutrophil release of O_2 , serving the body's natural antioxidant systems (vitamin E and glutathione), and cleaning peroxy and hypochlorous radicals. It also has various pharmacological characteristics [1]. Determination of CAR in drug forms and biological fluids is very important because of all these important effects and its widespread use in the treatment of many diseases. Many processes have been reported in the literature for CAR analysis, including spectrophotometry [2–4], gas chromatography [5, 6], electrophoresis [7, 8], liquid chromatography [9-11], and electrochemistry [12-14].

Electrochemistry is the most appropriate technique for searching the redox characteristics of drugs. Outputs from the electrochemical methods are generally related to the molecular structure and pharmacological activities of the drug moreover, electrochemical methods have a well-defined role in the quantitative analysis of drugs. Electrochemical methods are very popular due to their fast response, high sensitivity, and stability against miniaturization. The most preferred feature of modern electroanalytical methods is that they are not influenced by interference. Thus, the sample can be easily prepared by dissolving it in a suitable solvent without the need for pre-separation processes. [15]. Electrochemical methods are important because they offer a basic and fast technique for customary analysis.

In electrochemical studies, carbon paste electrode (CPE) has an important place due to their wide anodic potential range, robustness, low residual current, surface renewability, chemical inertness, ease of production, and low cost [16-18]. Although these advantages, CPEs have several disadvantages such as low sensitivity, and

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slow electron transfer. The addition of metal oxide nanoparticles to the CP mixture is promising to overcome the existing disadvantages of CP [16-21]. Nanotechnology is an interdisciplinary field used by many scientists. Metal oxide nanoparticles used in modifications of many electrochemical sensing platforms are very popular due to their high surface area, simple fabrication methods, small size [22], chemical stability, low toxicity, good electrical conductivity, catalytic activity, and good biocompatibility [23]. Metal oxide nanoparticles used in modifications of many electrochemical sensing platforms have been widely used in electrochemistry applications such as electrochemical sensors [24], lithium-ion batteries [25], and electrochemical capacitors [23].

In this study, the electrochemical properties of CAR were investigated by CV and SWV methods on ZnONP/CPE and a new method was proposed for the analysis of pharmaceutical samples by SWAAdSV. The results obtained are given below.

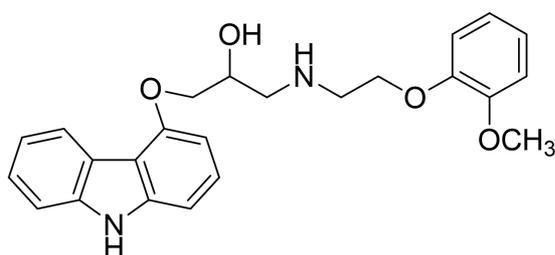


Figure 1. Molecular structure of CAR.

EXPERIMENTAL

Chemicals and Samples

CAR, graphite powder (powder > 20 μm), ZnONP (< 50 nm particle size), and paraffin oil, were obtained from Sigma-Aldrich. Acetic acid, methanol, phosphoric acid, potassium chloride, and boric acid were supplied from Merck. 0.04 M of each phosphoric acid, acetic acid, and boric acid were mixed for the preparation of BR buffer solution [26]. The stock solution of CAR (1.25×10^{-3} M) was dissolved in a Methanol-BR mixture (1:5) and diluted to the required concentration with 0.04 M BR buffer. Pharmaceutical formulations (Arlec tablets) were obtained from a local drug store. Ten Arlec tablets, each containing 12.5 mg of CAR, were weighed and crushed into powder. The weight equivalent to one tablet was transferred to a flask and made up to 50.0 mL with methanol. This mixture was sonicated for 1 hour and then centrifuged at 2000 rpm for 5 minutes and filtered through ordinary filter paper. The clear liquid was transferred to a 250 mL measuring flask and the volume was made up with BR. The required volumes of the prepared tablet stock solution

were mixed with BR buffer in the electrochemical cell.

Apparatus and measurements

Voltammetry studies were performed using a Bipotentiostat/Galvanostat Microstat 400 (Dropsens, Spain). The working electrode was ZnONP-modified CPE (2.87 mm ID, BASi MF 2010). A platinum wire (0.5 mm diameter, BASi MW 1032) and an Ag/AgCl electrode (BASi MF 2052) were used as auxiliary electrodes and reference electrodes, respectively. pH values were measured with a HANNA Instruments HI 2211 pH meter using an incorporated glass electrode (Hanna Instruments, USA). Double distilled water from a PURELAB Option QDV 25 system was used throughout the experiments. All experiments were carried out at room temperature. CV studies were performed in the potential range of 0.0 – 1.0 V at a scan rate of 100 mV s⁻¹. SWAAdSV readings were recorded on ZnONP/CPE in BR buffer at pH 8.0. In SWAAdSV experiments, specific volumes of CAR stock solution were mixed into the cell including 10.0 mL of BR buffer. The cell solution was treated with nitrogen for 5 minutes before the first measurement and 30 seconds between all measurements. The deposition step was performed at 0.3 V for 15 seconds under stirring (300 rpm). Mixing was then stopped and after a 3 seconds rest period, the CAR was stripped off using the SWV method. A pulse amplitude (ΔE_a) of 0.01 V, a frequency of 10 Hz (f), and a scan increment of 0.01 V (ΔE_i) were used in the SWV measurements. The standard deviation of the three measurements was used to plot the error bars in the figures.

Fabrication of the carbon paste electrodes

To prepare the ZnONP / CPE 12.0 mg graphite powder, 3.0 mg ZnONP, and 10 μL paraffin oil were thoroughly hand-mixed to obtain a homogeneous paste. After homogenization for 30 min, the carbon paste was filled into the bore of the electrode and flattened on a weighing paper. A similar procedure was used for the fabrication of the unmodified CPE (15 mg graphite powder and 10 μL paraffin oil).

RESULTS

Electrochemical behavior of CAR

The electrochemical properties of 1.0×10^{-4} M CAR were investigated by CV on bare CPE and ZnONP/CPE in pH 8.0 BR buffer (Figure 2). A well-defined oxidation peak was obtained in bare CPE and ZnONP/CPE at a potential of about 0.69 V. The oxidation peak current of CAR obtained at the modified electrode was higher than the peak current recorded at the bare CPE. The significant incre-

ase in peak current indicates a higher electron transfer rate for CAR on ZnONP/CPE, which can be attributed to the larger effective surface field of the modified electrode. On the other hand, no cathodic peak was obtained at the reverse scan suggesting an irreversible electrode reaction.

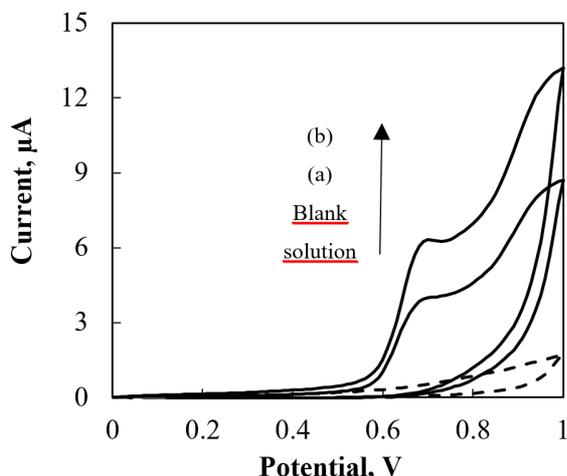


Figure 2. Cyclic voltammograms of 1.0×10^{-4} M CAR solution in pH 8.0 BR buffer on bare CPE (a) and modified CPE (b) (scan rate 100 mVs^{-1}).

To elucidate the electrochemical reaction occurring in ZnONP/CPE, the effect of scanning speed (v) on anodic peak potential (E_{pa}) and anodic peak current (i_{pa}) was investigated with CV (Figure 3). Figure 3A shows that potentials shift to positive as the scan rate increases from 0.05 to 0.50 Vs^{-1} . This result shows that the electrooxidation step is not reversible. [27].

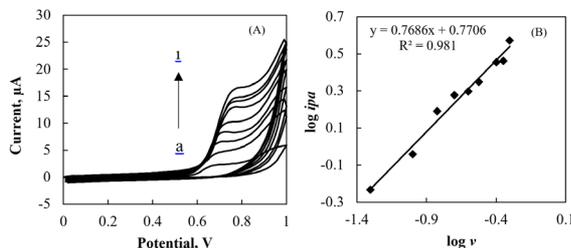


Figure 3. (A) Cyclic voltammograms of 1.0×10^{-4} M CAR at different scan rates in pH 8.0 BR buffer (scan rates: a: 0.05, b: 0.1, c: 0.15, d: 0.2, e: 0.25, f: 0.3, g: 0.4, h: 0.45, i: 0.5) (B) Plot of $\log i_{pa}$ vs. $\log v$.

CV experiments at different scanning speeds were used to determine the adsorption characteristics of CAR on ZnONP/CPE. For this purpose, the logarithm of the peak current ($\log i_{pa}$) versus the logarithm of the scan rate ($\log v$) was plotted. (Figure 3B). The obtained slope of 0.77 is close to the theoretical value of 1.0 for the adsorbed species. Therefore, the nature of the electrochemical reaction for the oxidation of CAR at ZnONP/CPE can be attributed to the adsorption-controlled electrode process [28].

In electrochemical studies, pH is the most important factor affecting the location (E_p) and intensity (i_p) of the

electrochemical signal. Therefore, the effect of pH on the oxidation reaction of CAR in ZnONP/CPE was investigated by SWV. SW voltammograms of 1.0×10^{-4} M CAR solution in BR buffer were recorded at varying pH values (Fig. A. 1) The current and potential values obtained from the measurements were plotted with pH (Figure 4). Figure 4 shows that the potentials shifted to more negative potentials as the pH increased. The pH-dependent variation of the oxidation potential indicated that the electron involved in the oxidation reaction of CAR in ZnONP/CPE is accompanied by a proton. As seen in Figure 4, pH 8 was determined as the optimum pH at which the highest peak current was observed.

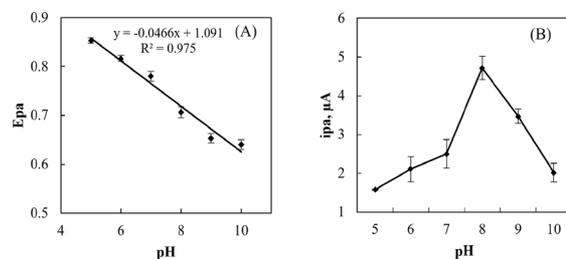


Figure 4. Variation of peak potential (A) and peak current (B) with pH (1.0×10^{-4} M CAR in BR buffer solution).

The ratio of the proton number to the electron number in the oxidation reaction of CAR in ZnONP/CPE was calculated from Equation 1 using the slope of the graph given in Figure 4A. [29].

$$E_p = E^0 + \frac{RT}{nF} \ln \left[\frac{Q}{R} \right] - \frac{\partial RT}{nF} \ln [H^+] \quad (1)$$

Equation 1, ∂ represents the proton number and n the electron number. When the values of known quantities in the equation and the slope of Figure 4A are used, the ratio of ∂/n is determined as 0.79. This result showed that each electron is accompanied by an equal number of protons in the electrode reaction of CAR. Also, the electron number transferred in the CAR reaction in ZnONP/CPE was calculated from Equation 2. In equation 2, n is the electron number, β : refers to the anodic charge transfer coefficient. For this purpose, the change of the peak potential of CAR with the logarithm of the scan rate in ZnONP/CPE was investigated. When the slope ($E_p = 0.0495 \log v + 0.752$) of the obtained graph is substituted in Equation 2, the $n\beta$ value was determined as 1.19 (Fig. A. 2).

$$E_p = k + \frac{RT}{(n\beta)F} \ln v \quad (2)$$

The β ranged from 0 to 1, and this value was 0.50 for most working electrodes, indicating that two electrons were

transferred in the electrode reaction of CAR. According to these results, the possible electrode reaction mechanism of CAR in ZnONP/CPE is given below (Figure 5) [15].

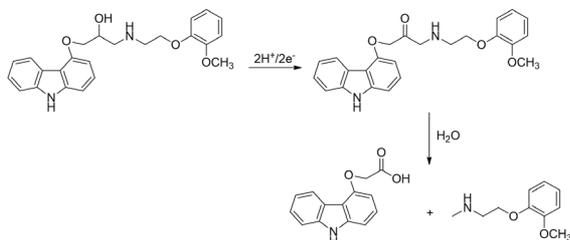


Figure 5. Electrochemical oxidation of CAR.

Analytical performance of the voltammetric method

In this practice, a new method was developed for the determination of CAR in tablets by SWAAdSV in ZnONP/CPE. For this purpose, instrument parameters and method parameters were optimized. The optimum instrument parameters were as given in the experimental part. The analytical parameters of the SWAAdSV method were determined using the optimum instrument and method parameters. Obtained results are given below.

Optimization of method parameters

In adsorptive stripping voltammetry, it is important to determine the effect of accumulation potential and accumulation time on the peak signal. For this purpose, the optimum accumulation potential and optimum accumulation time of the SWAAdSV method with 2.0×10^{-6} M CAR were investigated. In ZnONP/CPE, the effect of deposition potential on peak intensity was investigated in the range of 0.0 V - 0.5 V (Figure 6A). Peak currents increased between 0.0 and 0.3 V and then decreased. At 0.3 V, the highest peak current was observed. The influence of the accumulation time on the peak current was also researched in the 15 – 180 s range. The peak current decreased as the deposition time increased from 15 s to 180 s (Figure 6B). Thus, the optimum deposition time was chosen as 15 seconds.

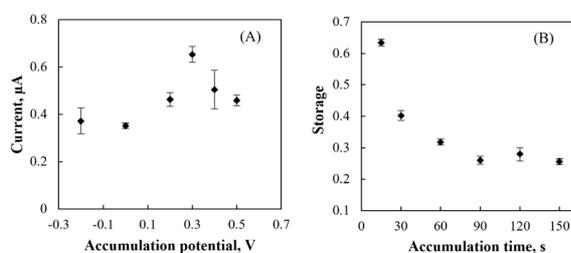


Figure 6. Influences of (A) accumulation potential and (B) accumulation time on the anodic signal of 1.0×10^{-6} M CAR on ZnONP/CPE (pH 8.0 BR buffer).

Various concentrations of CAR were used to plot calibration curves of CAR with SWAAdSV measurements under the determined optimum operating conditions (Figure 7A). The presented method showed a linear range from (0.07 μ M (0.03 mg L⁻¹) to 2.61 μ M (1.06 mg L⁻¹)) for the determination of CAR in ZnONP/CPE (Figure 7B). For linear range the regression equation was: $ip(\mu A) = 0.1921 \times C_{CAR} (\mu M) + 0.2931$ ($R^2 = 0.9833$). The detection limit (LOD) and quantification limit (LOQ) values were evaluated by the following formula: $LOD = 3s/m$ and $LOQ = 10s/m$ [30], using the standard deviation of the intercept (s) and the slope of the regression line (m). The LOD and LOQ values were calculated as 0.09 μ M (0.036 mg L⁻¹) and 0.3 μ M (0.12 mg L⁻¹), respectively.

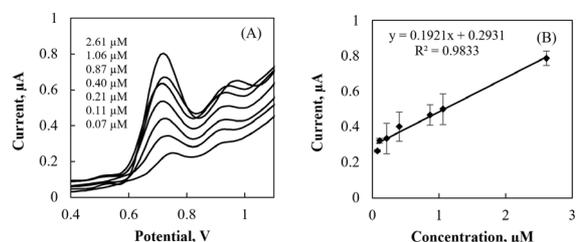


Figure 7. (A): Square wave voltammograms of CAR at ZnONP/CPE containing different concentrations of CAR ranging from 0.07 μ M to 2.61 μ M (B): the corresponding calibration curves.

Parameters such as accuracy, precision, and reproducibility of the proposed method were determined under optimum experimental conditions. For this, five ZnONP/CPEs were prepared and the response of these modified electrodes to 1.0×10^{-6} M CAR was recorded to examine the reproducibility of the presented method. The relative standard deviation (%RSD) of the current response was 4.3%. This result demonstrated the high reproducibility of the presented method. The repeatability of CAR in pH 8.0 BR buffer was examined by recording changes in the anodic signal of the 1.0×10^{-6} M standard CAR solution. The RSD of the peak currents for five replicate measurements was 4.8%. The result shows good repeatability of the sensor.

The analytic performance characteristics of the presented method for the determination of CAR are compared with previous studies (Table 1). Table 1 shows that the proposed method in this study exhibits a lower detection limit and a wider linear range than most of the before these reported studies.

Real Sample Analysis

Sample studies of the suggested SWAAdSV method for the analysis of CAR in pharmaceutical samples were performed with the direct calibration process using the equation of the obtained calibration curve. Tablet samples were prepared as in the experimental section. Voltam

Table 1. Comparison of the presented method with the previous voltammetric studies.

Method	Working electrode	Linear range, μM	LOD, μM	Recovery tablet, %	Recovery serum, %	Recovery urine, %	Ref.
DPV	GCE	0.62-25	0.25	100.8	-	-	[12]
DPV	OMC/GCE	0.1-23	0.034	97.5-102.5	96.6-103.3	98-103	[13]
DPV, SWV	GCE-MIP-MWCNT	50-325	16	90.2	-	-	[28]
LSV	Pt electrode	12-98	3.2	-	96-101.7	-	[31]
SWAAdSV	ZnONP/CPE	0.07-2.6	0.09	99.0-103.1	-	-	Present work

LSV: Linear sweep voltammetry, Pt: Platinum, OMC/GCE: Ordered mesoporous carbon / glassy carbon electrode, DPV: Differential pulse voltammetry, GCE-MIP-MWCNT: Glassy carbon electrode-molecular imprinted polymer-multiwall carbon nanotube, SWV: Square wave voltammetry

metric measurements were recorded by adding different volumes of CAR stock solution to tablet samples (Table 2). When table 2 was examined, it was seen that the recovery values obtained for the determination of CAR in drugs with ZnONP/CPE ranged from 98.99% to 103.13%. The new method developed for the analysis of CAR in tablets was found to be comparable to other processes in the literature.

Table 2. Results of ZnONP/CPE sensor performance in tablets

Nominal value, mg	Found, mg	Recovery*, %	RSD, %	t_{exp}
12.5	12.26; 13.20; 13.20	103.13 \pm 4.35	4.21	1.25
12.5	12.08; 12.38; 12.66	98.99 \pm 2.34	2.36	-0.25

Results of recovery values are given as mean \pm ts/ \sqrt{N} (at 95% confidence level)

CONCLUSION

In this research, the electrochemical behavior of CAR was suggested for the first time on the surface of ZnONP/CPE. The oxidation reaction of CAR on ZnONP/CPE was found to be irreversible and adsorption-controlled in the presence of $2e^-/2H^+$. A new process was developed for the analysis of CAR in tablet samples. The concentration range and lower detection limit of the proposed process were determined and the tablet recovery values were calculated. The results obtained suggest that the proposed modified CPE for CAR determination shows superior properties that can compete with other reported voltammetric electrodes and can make significant contributions to the literature.

CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

AUTHOR CONTRIBUTION

Emre Guven and **Funda Oztürk** conducted the investigation. In addition, **Funda Oztürk** conducted

the conceptualization, methodology, writing-original draft, writing-review & Editing stages of the study.

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