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Novel Electrochemical Sensor based on ZrO_2 Nanoparticles Modified Glassy Carbon Electrode for low-trace Level Determination of Amlodipine by Differential Pulse Voltammetry

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Abstract- A fast and selective electrochemical sensor for determination of amlodipine was developed based on ZrO_2 nanoparticles modified glassy carbon electrode. Amlodipine could be determined directly by electrochemical oxidization with the modified electrode. ZrO_2 nanoparticles increased electrochemical response to amlodipine. Experimental variables, such as the deposited amount of the modifier suspension, pH of the supporting electrolyte and the potential scan rate were optimized by monitoring the electrochemical responses of amlodipine. Under the optimum conditions, the modified electrode showed a wide linear dynamic range of 10.0–200.0 μM with a detection limit of 2.0 μM for the voltammetric determination of amlodipine. The prepared modified electrode showed high sensitivity, stability and good reproducibility in response to amlodipine, confirming its usability for the accurate determination of trace amounts of amlodipine in pharmaceutical and clinical preparations.

Keywords- Amlodipine, ZrO_2 nanoparticles, Glassy carbon electrode, Voltammetry

1. INTRODUCTION

Amlodipine (AML) is chemically designated as 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylic acid, 3-ethyl, 5-methylester,

besylate (Scheme 1). Amlodipine is a dihydropyridine derivative with calcium-channel blocker (CCB) activity, widely used in the management of hypertension caused by coronary artery disease, chronic stable angina pectoris and prinzmetal's variant angina [1-4]. It inhibits selectively the arterial vascular smooth muscle cell proliferation resulting in prevention of the progressive narrowing of the arteries as well as preventing the coronary spasms resulting in increased blood flow with myocardial oxygen supply [5-7]. The control of high blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. Therefore, the development of an analytical procedure for amlodipine determinations with high sensitivity and selectivity is not only of pharmaceutical significance for point-of-care detection, but also important for industrial purposes [8,9]. Several analytical techniques including spectrophotometry, high performance liquid chromatography (HPLC), high performance thin layer chromatography (HPTLC), gas chromatography (GC), capillary electrophoresis (CE), flow injection and enzyme-linked immune-sorbent assay have been reported for amlodipine determination in pharmaceutical formulations and biological fluids [10-16]. Although these methods are sensitive for determination of amlodipine, they require expensive instruments, laborious sample pre-treatment, highly skilled technicians, long analysis time and generate large amount of wastes, which make them unsuitable in quality control laboratories. Taking the above-mentioned lacuna and the electroactivity of amlodipine into consideration, electrochemical methods have been widely explored because of their merits to provide an accurate, sensitive and yet [17-28].

Among the various electrode, the glassy carbon electrode (GCE) is the most promising carbon substrate for loading electroactive materials due to its direct role as the current collector to intimately contact with electroactive materials [29]. However, the bare electrodes very often suffer from the fouling effect, which results in rather poor sensitivity and selectivity [30-34].

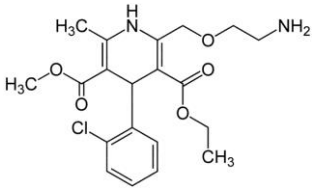
Electrode surface modification is a field of modern electrochemistry, especially chemically modified glassy carbon electrodes which have found many applications in electroanalytical methods in recent years because of ease of electrode fabrication [35-40].

In the past few decades, nanostructured materials have attracted extraordinary research interest due to their unique physical and chemical properties in comparison with those of their bulk counterparts [41-50]. Therefore, numerous research works have been carried out to decorate nanoparticles on the surface of electrode and to investigate their performance in electrochemical sensing [51-60].

Among the family of inorganic compounds, zirconium dioxide (ZrO_2) is of vital importance, due to some of its key properties such as chemical resistance, good mechanical strength, high ionic conductivity and good thermal stability [61]. Based on the above mentioned properties, ZrO_2 has found broad applications in areas such as catalysis,

restorative dentistry, high temperature ceramics, polymer nanocomposites and sensor [62, 63].

According to the previous points, it is important to create suitable conditions for analysis of amlodipine in biological fluids. In this study, ZrO_2 nanoparticles were used to improve the selectivity and sensitivity of sensors for voltammetric determination of amlodipine. The proposed sensor showed good electrocatalytic effect on amlodipine. ZrO_2/GCE shows advantages in terms of selectivity, reproducibility and sensitivity. Eventually, we evaluate the analytical performance of the suggestion sensor for amlodipine determination in real samples.



Scheme 1. Chemical structure of amlodipine

2. EXPERIMENTAL

2.1. Apparatus and chemicals

The electrochemical measurements were performed with an Autolab potentiostat/galvanostat (PGSTAT 302N, Eco Chemie, the Netherlands). The experimental conditions were controlled with General Purpose Electrochemical System (GPES) software. A conventional three electrodes cell was used at 25±1 °C. An Ag/AgCl/KCl (3.0 M) electrode, a platinum wire, and the ZrO_2/GCE were used as the reference, auxiliary and working electrodes, respectively. A Metrohm 710 pH meter was employed for pH measurements.

All solutions were freshly prepared with double distilled water. Amlodipine and all other reagents were of analytical grade and were obtained from Merck chemical company (Darmstadt, Germany). The buffer solutions were prepared from orthophosphoric acid and its salts in the pH range of 2.0-9.0. The ZrO_2 nanoparticles (surface area=65 m^2g^{-1} and particle size=21.0 nm) was purchased from Sigma Aldrich.

2.2. Preparation of modified electrode

The bare glassy carbon electrode was coated with ZrO_2 nanoparticles as follows. A stock solution of ZrO_2 in 1 mL aqueous solution was prepared by dispersing 1 mg ZrO_2 with ultrasonication for 1 h, and a 5 µl aliquot of the ZrO_2/H_2O suspension solution was casted on the glassy carbon electrodes, and waiting until the solvent was evaporated in room temperature.

3. RESULTS AND DISCUSSION

3.1. Electrocatalytic oxidation of amlodipine at a ZrO_2/GCE

The electrochemical behavior of amlodipine is dependent on the pH value of the aqueous solution. Therefore, pH optimization of the solution seems to be necessary in order to obtain the electrocatalytic oxidation of amlodipine. Thus the electrochemical behavior of amlodipine was studied in 0.1 M PBS in different pH values (2.0<pH<9.0) at the surface of ZrO_2/GCE by CV. It was found that the electrocatalytic oxidation of amlodipine at the surface of ZrO_2/GCE was more favored under neutral conditions than in acidic or basic medium. Thus, the pH 7.0 was chosen as the optimum pH for electrocatalysis of amlodipine oxidation at the surface of ZrO_2/GCE.

Fig. 1 depict the cyclic voltammetric responses for the electrochemical oxidation of 200.0 μM amlodipine at ZrO_2/GCE (curve a) and bare GCE (curve b). The anodic peak potential for the oxidation of amlodipine at ZrO_2/GCE (curve a) is about 850 mV compared with 790 mV for that on the bare GCE (curve b). Similarly, when the oxidation of amlodipine at the ZrO_2/GCE (curve a) and bare GCE (curve b) are compared, an extensive enhancement of the anodic peak current at ZrO_2/GCE relative to the value obtained at the bare GCE (curve b) is observed. In other words, the results clearly indicate that the ZrO_2 nanoparticles improve the amlodipine oxidation signal.

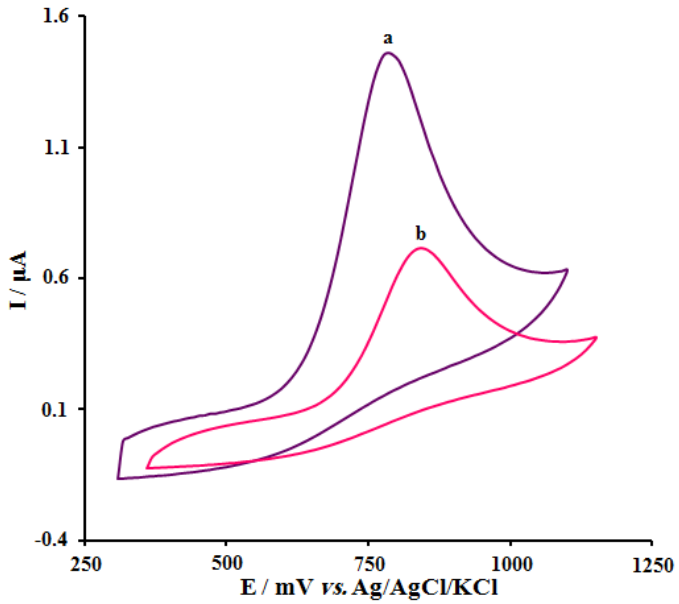


Fig. 1. Cyclic voltammograms of (a) ZrO_2/GCE and (b) bare GCE in 0.1 M PBS (pH 7.0) in the presence of 200.0 μM amlodipine at the scan rate 50 mVs^{-1}

The effect of potential scan rates on the oxidation current of amlodipine has been studied (Fig. 2). The results showed that increasing in the potential scan rate induced an increase in the peak current. In addition, the oxidation process is diffusion controlled as deduced from

the linear dependence of the anodic peak current (I_p) on the square root of the potential scan rate ($v^{1/2}$) over a wide range from 10 to 300 mV s^{-1}.

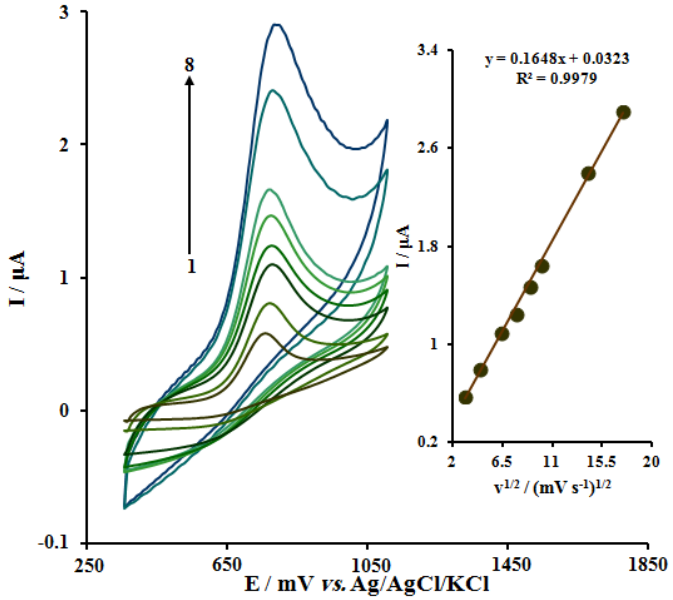


Fig. 2. Cyclic voltammograms of ZrO_2/GCE in 0.1 M PBS (pH 7.0) containing 100.0 µM amlodipine at various scan rates; numbers 1-8 correspond to 10, 20, 40, 60, 80, 100, 200, and 300 mV s^{-1}, respectively. Inset: variation of anodic peak current *vs.* $v^{1/2}$

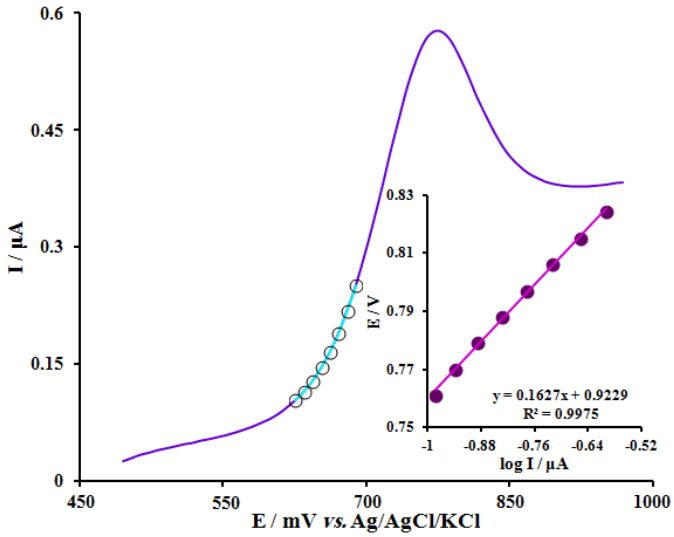


Fig. 3. LSV (at 10 mV s^{-1}) of electrode in 0.1 M PBS (pH 7.0) containing 100.0 µM amlodipine. The points are the data used in the Tafel plot. The inset shows the Tafel plot derived from the LSV

Fig. 3 show a Tafel plot that was drawn from points of the Tafel region of the LSV. The Tafel slope of 0.1627 V obtained in this case agrees well with the involvement of one

electron in the rate determining step of the electrode process, assuming a charge transfer coefficient of α=0.64 [64].

3.2. Calibration plot and limit of detection

The peak current of amlodipine oxidation at the surface of the modified electrode can be used for determination of amlodipine in solution.

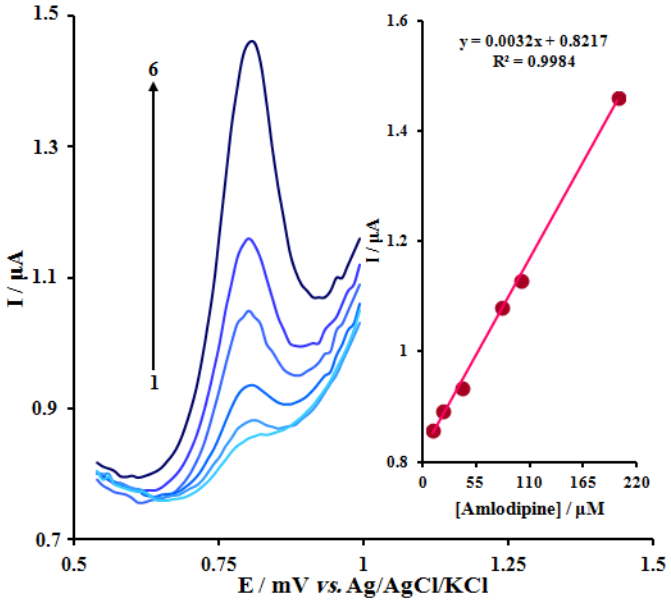


Fig. 4. DPVs of ZrO_2/GCE in 0.1 M (pH 7.0) containing different concentrations of amlodipine. Numbers 1–6 correspond to 10.0, 20.0, 40.0, 80.0, 100.0 and 200.0 µM of amlodipine. Inset: plot of the electrocatalytic peak current as a function of amlodipine concentration in the range of 10.0-200.0 µM

Table 1. Comparison of the efficiency of some modified electrodes used in the determination of amlodipine

Electrode	method	LOD (M)	LDR (M)	Ref.
Cathodically pretreated boron-doped diamond electrode	Voltammetry	6.0×10^{-9}	2.0×10^{-7}–9.09×10^{-6}	[65]
Cathodically pretreated boron-doped diamond electrode	Voltammetry	2.3×10^{-7}	4.9×10^{-7}- 7.2×10^{-6}	[66]
Carbon paste	Voltammetry	2.0×10^{-10}	9.9×10^{-9} - 1.4×10^{-7}	[67]
Glassy carbon	Voltammetry	2.0×10^{-6}	1.0×10^{-5} – 2.0×10^{-4}	This Work

Therefore, differential pulse voltammetry (DPV) experiments were done for different concentrations of amlodipine (Fig. 4). The oxidation peak currents of amlodipine at the

surface of a modified electrode were proportional to the concentration of the amlodipine within the ranges 10.0 to 200.0 μM. The detection limit (3σ) of amlodipine was found to be 2.0×10^{-6} M. These values are comparable with values reported by other research groups for determination of amlodipine at the surface of modified electrodes (see Table 1).

3.3. Real sample analysis

In order to evaluate the analytical applicability of the proposed method, also it was applied to the determination of amlodipine in amlodipine tablet and urine samples. The results for determination of amlodipine in real samples are given in Table 2. Satisfactory recovery of the experimental results was found for amlodipine. The reproducibility of the method was demonstrated by the mean relative standard deviation (R.S.D.).

Table 2. The application of ZrO_2/GCE for determination of amlodipine in amlodipine tablet and urine samples (n=5). All concentrations are in μM

Sample	**Spiked**	**Found**	**Recovery (%)**	**(%)R.S.D.**
Amlodipine tablet	Amlodipine	Amlodipine	Amlodipine	Amlodipine
	0	12.0	-	3.1
	2.5	14.4	99.3	1.8
	5.0	17.5	102.9	2.7
Urine	0	-	-	-
	10.0	10.1	101.0	1.9
	20.0	19.5	97.5	2.9

4. CONCLUSIONS

In summary, we have demonstrated the use of a simple electrochemical method for amlodipine determination in amlodipine solutions, drug tablet and urine samples. Drop casting technique was performed to create ZrO_2/GCE and used as the working electrode for the study of the redox mechanism of amlodipine. The presence of the ZrO_2 nanoparticles possesses an efficient catalytic activity in amlodipine oxidation. In addition, the main advantages for the use of ZrO_2/GCE are in term of high sensitivity, good accuracy and simple fabrication. The calibration curve was constructed in a concentration range of 10.0 to 200.0 μM. The low detection limit was 2.0 μM, which is one of the lowest provided by modified electrodes. High sensitivity and improved detection limit of the ZrO_2/GCE are promising for the determination of trace amounts of amlodipine in real samples. The proposed method is suitable for quality control laboratories as well as pharmacokinetic studies where economy and time are essential.

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