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Voltammetric and Square-Wave Anodic Stripping Determination of Amlodipine Besylate on Gold Electrode

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The oxidative behaviour of amlodipine besylate was studied. The gold electrode and Au/o-MWCNT (oxidized multi-wall carbon nanotubes) were used for determination of amlodipine besylate standard and as a content of Alopres tablet, in 0.05 M $NaHCO_3$ and in phosphate buffer (pH=11) by cyclic voltammetry and square-wave anodic stripping voltammetry. Electrode surfaces were characterized by AFM in the presence of amlodipine and the concentrations of drugs in electrolytes were simultaneously followed by HPLC. The linear dependency of the anodic currents of amlodipine besylate as standard and in Alopres tablet *vs*. concentration was observed in both electrolytes, but in phosphate buffer for the higher concentrations. The peak currents obtained in all experiments are more than fifty-fold higher comparing to all previously published results concerning the glassy carbon electrode and the carbon paste electrode. The gold electrode is better catalyst for anodic oxidation of amlodipine besylate than glassy carbone. The results obtained with Au/o-MWCNT show lower anodic activity comparing to previously published GC/o-MWCNT. GC/o-MWCNT is better catalyst than Au/o-MWCNT under similar experimental conditions.

Keywords: amlodipine; gold electrode; o-MWCNT; atomic force microscopy

1. INTRODUCTION

Amlodipine, chemically, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylic acid, 3-ethyl,5-methylester, besylate (Fig. 1), is a dihydropyridine calcium channel blocker, which acts only on the L-type channel to produce their pharmacological effect [1-3]. Like most of the second generation dihydropyridine derivatives, it has greater selectivity

for the vascular smooth muscle than myocardial tissue and therefore their main effect is vasodilatation [4]. Amlodipine is used alone or in combination with other medicines for the treatment of chronic stable angina, certain types of vasospastic angina and in the management of mild-to-moderate essential hypertension [4-8].

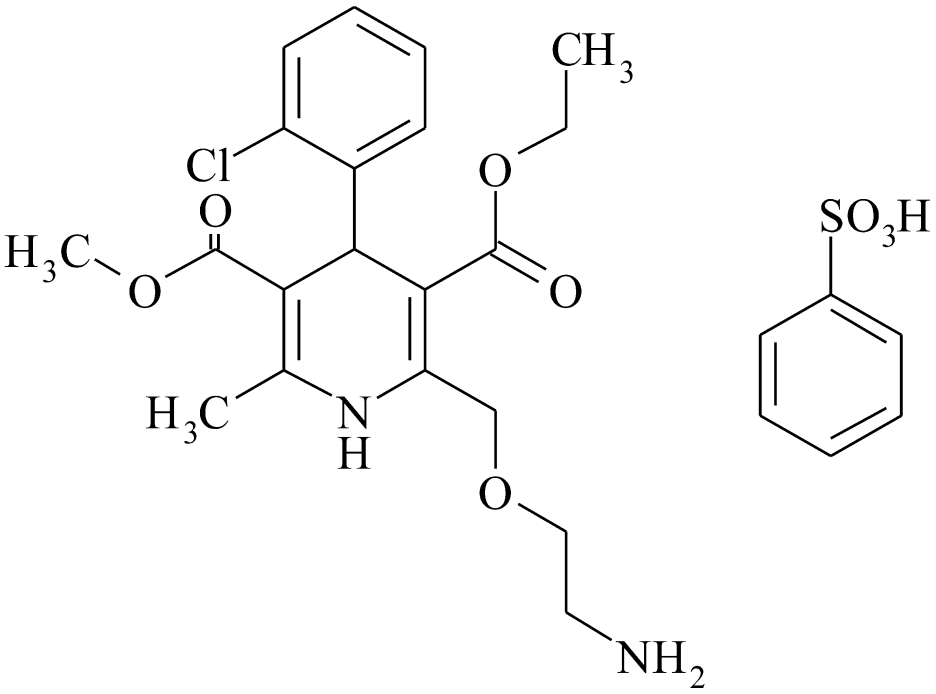


Figure 1. Structure of amlodipine besylate.

Different analytical methods have been reported for the assay of amlodipine besylate in pure form as well as in pharmaceutical formulations and biological fluids. They include high performance liquid chromatography [9-12], high performance thin layer chromatography [13-15], gas chromatography [16], liquid chromatography with mass spectrometry [17-21] and capillary electrophoresis [22]. Different spectrophotometric methods are also commonly used in industrial laboratories because of their simplicity, selectivity and sensitivity [23-25].

Voltammetric methods have been found as a highly-sensitive, convenient and effective tool for the analysis of important biomolecules including drugs in pharmaceutical formulations and human body fluids owing to their simplicity, low cost and relatively short analysis time as compared to the other routine analytical techniques. It is interesting to note that several valuable analytical electrochemical methods such as differential pulse voltammetry and adsorptive square-wave anodic stripping voltammetry for determination of amlodipine in pharmaceuticals or in biological fluids on glassy carbon, carbon paste electrodes and or modified by multi wall nanotubes, have been reported [26-29]. The use of the gold electrode has not been reported until now.

The aim of this work is to present the use of the gold and modified electrode by MWNT in determination of amlodipine besylate as standard and in Alopres, by cyclic and square-wave anodic striping voltammetry. All investigated concentrations of amlodipine besylate as standard and in

Alopres in 0.05 M $NaHCO_3$ and phosphate buffer (pH=11), were checked by HPLC. The structural characterization of a gold and modified electrode by oxidized multi-wall carbon nanotubes (o-MWNT) and covered by amlodipine besylate was performed by atomic force microscopy (AFM).

2. EXPERIMENTAL

Amlodipine besylate standard, kindly provided by Zdravlje Leskovac, Actavis Company, Leskovac, Serbia, was used as a pure substance without further purification and was dissolved in deionised water and added into the electrolytes (100 cm^3 $NaHCO_3$ or phosphate buffer) in concentrations correctly assigned in the figure captions. Potassium dihydrogen phosphate ($KH_2PO_4xH_2O$), and $NaHCO_3$ were p.a. purity, obtained from Merck. Potassium hydroxide was p.a. purity obtained from J. T. Baker. Water was purified by Milli-Q system.

2.1. Preparation of the standard solutions for the concentrations of amlodipine besylate as a content of solid dosage form

The pharmaceutical preparations analyzed were Alopres tablets (10 mg of amlodipine) produced by Zdravlje Leskovac, Actavis Company, Leskovac, Serbia, containing 13.88 mg of amlodipine besylate per tablet. In addition to the active ingredient, each tablet contained the following inactive ingredients: microcrystalline cellulose, magnesium stearate, povidone K30, colloidal anhydrous, silicium dioxide and corn starch. The pharmaceuticals were prepared by the following procedure. Ten tablets were weighed and then the average mass per tablet was determined. The tablets were carefully grounded to a fine powder and the required amount from the crushed tablets powder was dissolved in 10 mL of deionised water l by sonication for 30 min and filtered in a 100 mL measuring flask. The residue was washed three times with 0.05 M $NaHCO_3$ or with buffer (phosphate) solution and the volume was completed to the mark by the same solvent.

Buffer (phosphate) solution pH 11.0 was prepared by dissolving of 1.74 g of potassium dihydrogen phosphate in 80 mL of deionised water, adjust the pH with 1M potassium hydroxide and dilute to 100.0 ml with deionised water.

The obtained concentrations of amlodipine besylate were checked by HPLC.

2.2. Apparatus

2.2.1. Cyclic voltammetry

Standard equipment was used for the cyclic voltammetry measurements and the three electrode electrochemical cell was described in detail previously [36]. Polycrystalline gold served as the working electrode, a gold wire was used as the counter electrode and a saturated calomel electrode as the reference electrode. All the potentials are given *vs.* SCE. Prior to the addition of amlodipine besylate,

the electrolytes were deoxygenated by purging with nitrogen. All the experiments were performed at room temperature.

2.2.2 Anodic square wave stripping voltammetry

Square-wave voltammetry (SWV) measurements were conducted using a Gamry potentiostat Reference 600 controlled with software PV 220. The operating parameters were selected to be comparable to those used in earlier studies on amlodipine besylate determination in a pH 11 buffer solution [27]: step size 2 mV, pulse size 25 mV, frequency 50 Hz and scan rate 100 mV s^{-1}.

2.2.3. Equipment and chromatographic conditions

HPLC analysis was performed by using HPLC instruments Agilent 1100 series, (Agilent Binary pump G 1312A, autosampler Agilent ALS G 1313A), diode array detector (G1315B). Column: Symmetry C18, 5 μm, size: (150 mm x 4.6 mm), stationary phase: Octadecilsilyl Symmetry C18, Waters. Mobile phase: mix 15 volumes of acetonitrile, 35 volumes of methanol and 50 volumes of a solution prepared as follows: dissolve 7.0 mL of triethylamine in 1 litre of water and adjust to pH 3.0±0.1 with orto-phosphoric acid 85% (pH meter Metrohm type 27 pH Lab). Flow rate 1 mL min^{-1}, temperature 20°C, wavelength 237 nm. Samples are filtered through the filter made from cellulose 0.45 μm.

2.4. AFM measurements

The structural characterization of a gold electrode covered by amlodipine besylate and a gold electrode modified by oxidized multi-wall carbon nanotubes (o-MWCNT) covered by amlodipine besylate was performed by atomic force microscopy (AFM). NanoScope III A (Veeco, USA) microscope operated in tapping mode under ambient conditions was employed. Etched silicon probes with a spring constant of 20–80 N m^{-1} were used.

2.5. Preparation of electrode surfaces

Polycrystalline gold (surface area 0.500 cm^2), which served as the working electrode, was polished with diamond paste, cleaned with a mixture of 18 MΩ deionised water and sulfuric acid and further cleaned with 18 MΩ cm deionised water in an ultrasonic bath.

Raw-MWCNT (Sigma-Aldrich) used in the present work were prepared by a chemical vapour deposition (CVD) method and used as received without purification. The purity of raw-MWCNT was more than 95 wt% and the outer and inner diameters were 20-30 nm and 5-10 nm, respectively.

Oxidation of MWCNT was performed according to well known method [30]. An amount of 110 mg of raw-MWCNT was first treated with a (V/V 3:1) mixture of concentrated H_2SO_4 and HNO_3 acid (120 ml). This mixture was then sonicated for 3 h at 40°C in an ultrasonic bath to introduce

oxygen containing functional groups on the MWCNT surface. After cooling to the room temperature, the oxidized (o-MWCNT) was added drop wise to 300 ml of cold DI water and then vacuum-filtered through a 0.05 μm pore size polytetrafluoroethylene (PTFE) filter membrane, the filtrant was then washed with deionized water until pH was neutral. The sample was then dried in a vacuum oven at 80°C for 8 h.

The detail characterization of raw-MWCNT and o-MWCNT using FTIR, TGA, UV, XRD, TEM, elemental analysis techniques as well electrochemical characterization of thin layer o-MWCNT has been previously presented [30,31]. The acidic and basic sites concentrations (carboxyls, lactones, phenols, total acidic and basic sites) on the surfaces of raw-MWCNT and o-MWCNT were quantitatively determined by the Boehm method [31]. It has been shown that oxidation process performed by the use of strong acids significantly decreases the metal catalyst residue in o-MWCNT [32].

For electrochemical measurements o-MWCNT were applied on a gold electrode surface in the form of a thin film, as was previously described in detail [33-35]. This procedure of film preparation gave 0.10 mg of nanotubes per cm^2 of the Au surface.

3. RESULTS AND DISCUSSION

Before voltammetric experiments the electrode surfaces were characterized by AFM. AFM studies were conducted to give insight into the surface topography of the amlodipine/gold and amlodipine/o-MWCNT.

Figs. 2 and 3 show typical two-dimensional (2D) and three-dimensional (3D) AFM images of amlodipine besylate obtained by dropping the water suspension of amlodipine on the gold surface.

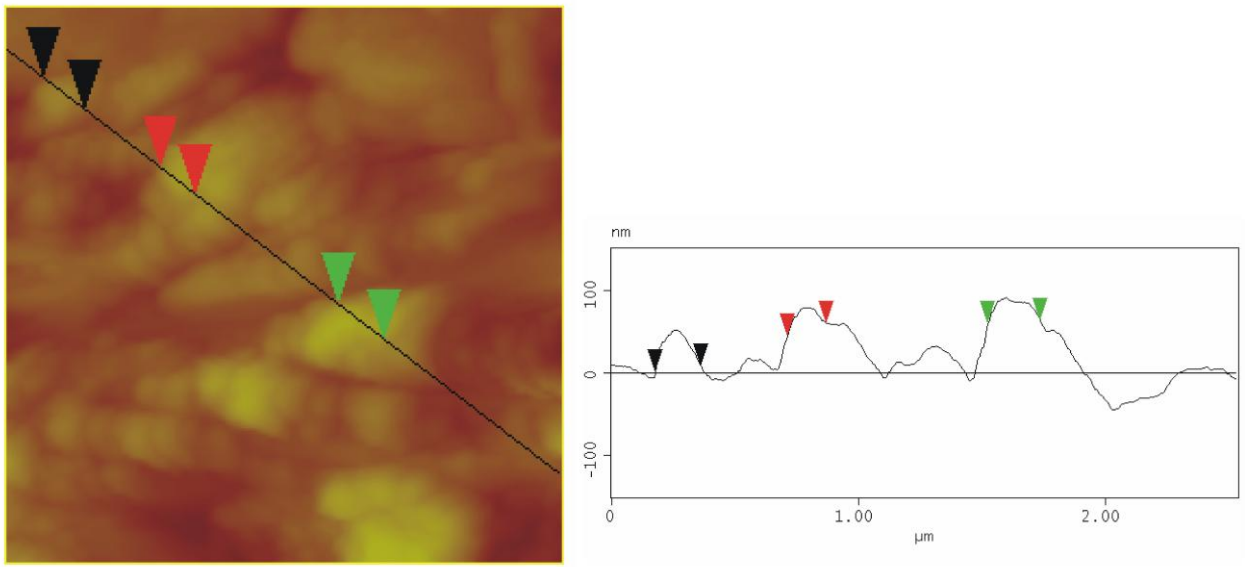


Figure 2. 2D AFM image and height profile (3 x 3 x 0.3 μm) of amlodipine besylate/Au.

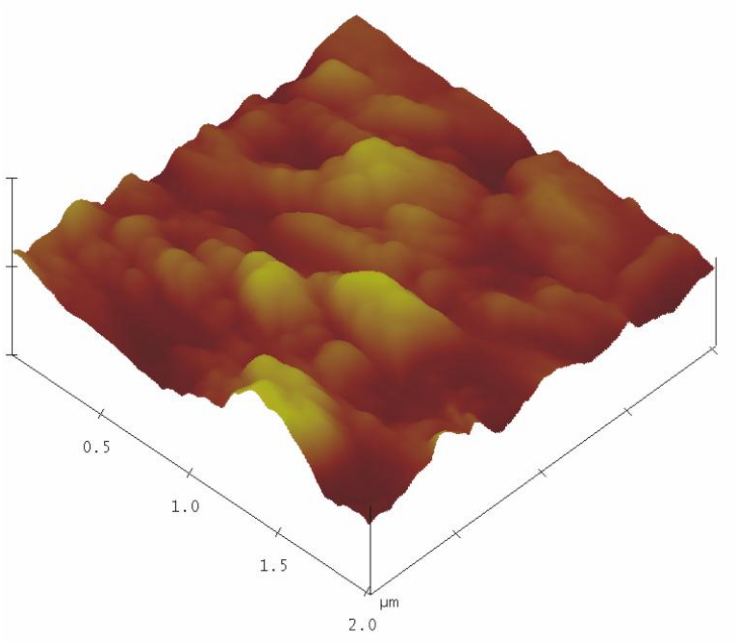
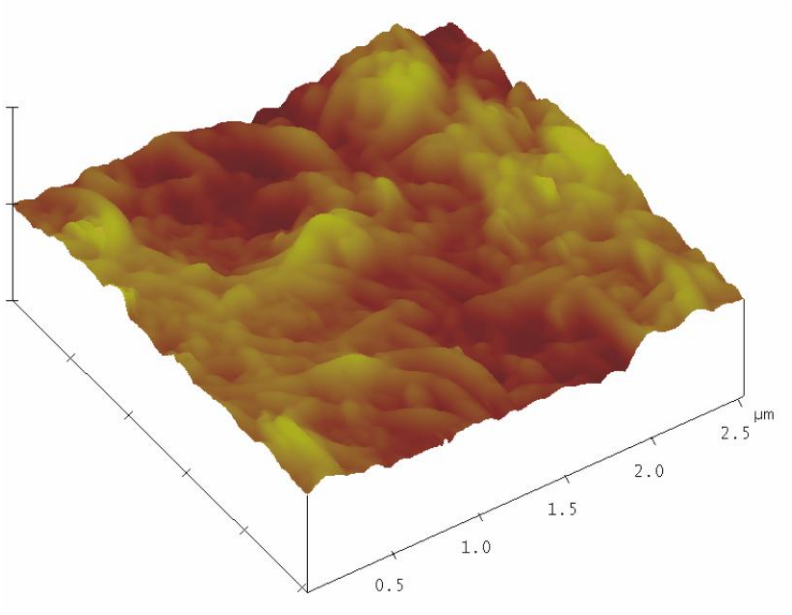


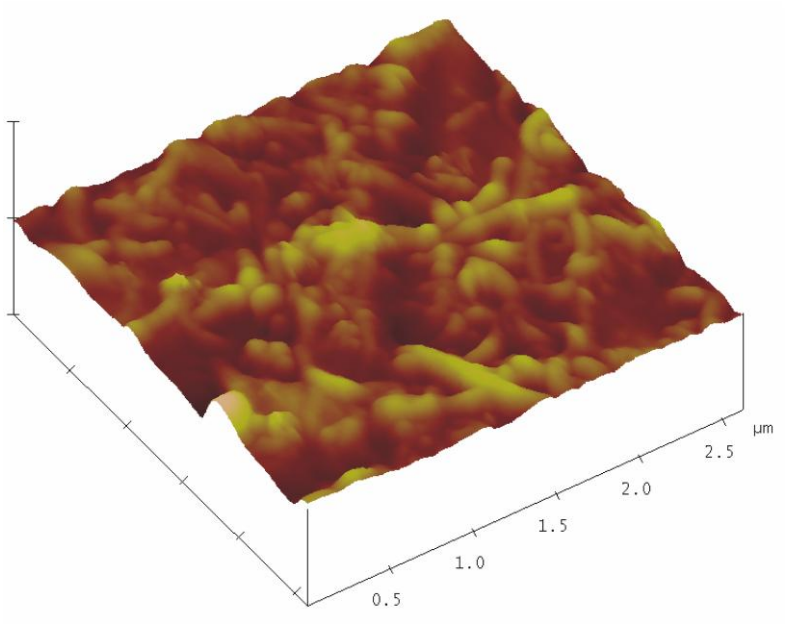
Figure 3. 3D image (2 x 2 x 0.3 μm) of amlodipine besylate/Au.

The sample of amlodipine besylate/gold is made up of small agglomerates which are compact and uniformly cover the entire substrate (Fig. 2), with average diameter of 200 nm (Fig. 3).

Gold electrode modified by oxidized multi-wall carbon nanotubes was prepared by placing a drop of the water suspension of the nanotubes on the gold surface. As shown in Fig. 4, it was clearly seen that randomly oriented MWCNT covered the entire surface of the substrate homogeneously, with average diameter of 100 nm (Fig. 5a).



A



B

Figure 4. 3D AFM images of a) o-MWCNT/Au (2.5 x 2.5 x 0.4 µm) and b) amlodipine besylate/o-MWCNT/Au (2.5 x 2.5 x 0.5 µm).

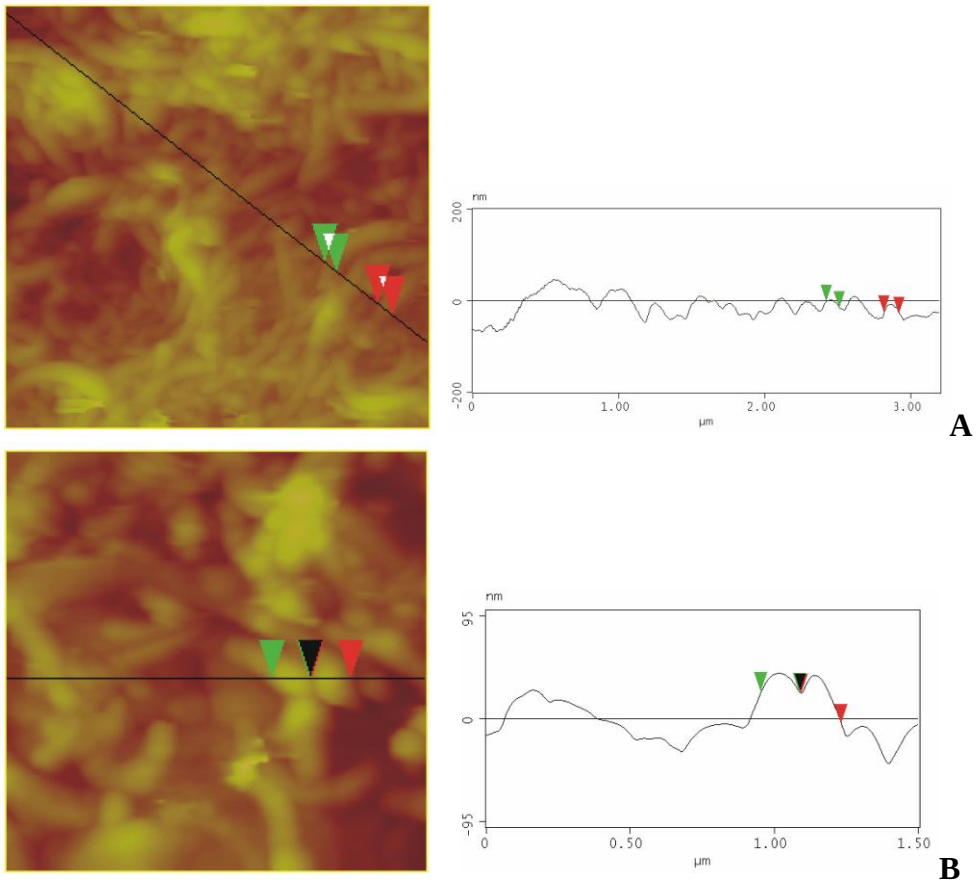


Figure 5. 2D images and height profiles of a) o-MWCNT (3 x 3 x 0.4 µm) and b) amlodipine besylate/o-MWCNT/Au (1.5 x 1.5 x 0.2 µm)

The acid treatment of raw-MWCNT, using strong oxidizing agent nitric acid, caused severe etching of the graphitic surface of the material, leading to tubes with a population of disordered sites and shortened nanotubes. Shortened o-MWCNT assembles on the gold electrode more easily because of their decreased rigidity and present oxygen functionality contribute better adherence to the gold electrode surface.

However, after adsorbing amlodipine, the diameter of o-MWCNT coated by amlodipine besylate became "wide" as compared with the o-MWCNT with average diameter of 140 nm (Fig. 5b). The sample of amlodipine/o-MWCNT was also well-dispersed, implying that the o-MWCNT would connect well the amlodipine on the surface.

Fig. 6 presents the cyclic voltammograms of amlodipine besylate standard in 0.05M $NaHCO_3$ obtained without accumulation. The small agglomerates of amlodipine besylate on gold seen by AFM (Fig. 2) cover the electrode surface and during the first cycle stay adsorbed on it causing the significantly lower currents in second and consecutive sweeps. This was confirmed by experiment presented in Fig. 7. After twenty cycles in the presence of 2.439 μg mL^{-1} of amlodipine besylate, the cyclic voltammogram was recorded (Fig. 7, line a), the electrode was washed with deionised water, dried on the air during the night and than transferred into the completely clean electrochemical cell and electrolyte. In the first sweep, cycling voltammogram shows anodic oxidation of amlodipine with lower currents than was recorded for previous 20^{th} sweep (Fig. 7, line b), indicating that amlodipine obviously stayed strongly adsorbed at the electrode surface. In Fig. 6 and following figures only the first sweep is presented and the electrode surface was prepared for the each presented concentration as is described in experimental part.

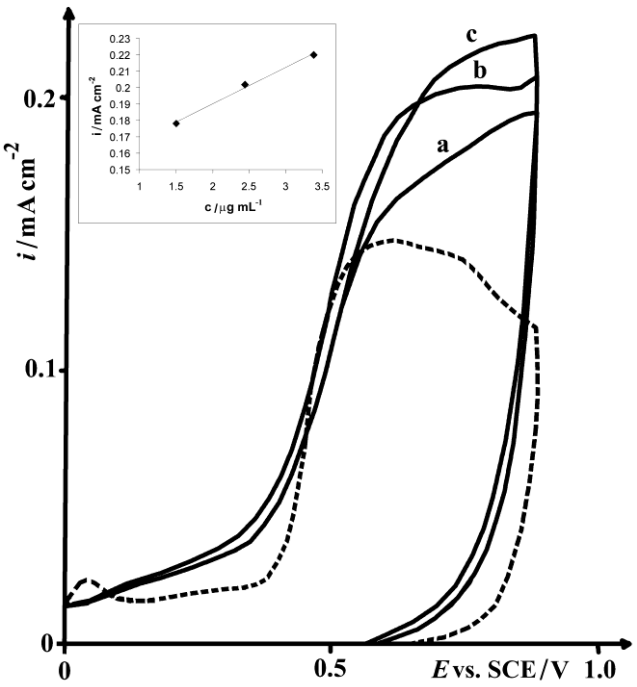


Figure 6. Cyclic voltammogram of gold electrode in 0.05M $NaHCO_3$ (dashed line) and in a presence of amlodipine besylate (full line) a) 1.5 μg mL^{-1}, b) 2.439 μg mL^{-1}, c) 3.38 μg mL^{-1}, sweep: 50mV s^{-1}.

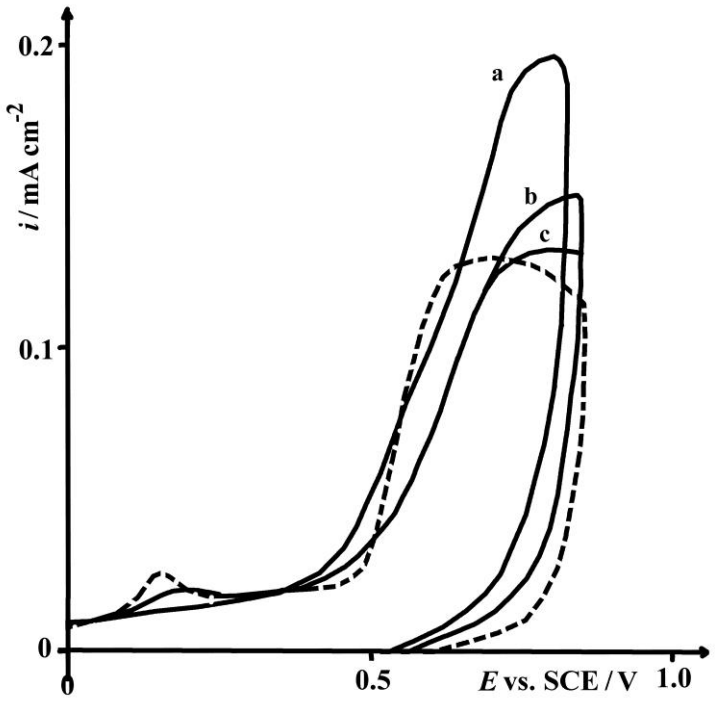


Figure 7. Cyclic voltammogram of gold electrode in 0.05M $NaHCO_3$ (dashed line) and a) after 20 cycles in the presence of 2.439 μg mL^{-1} amlodipine besylate (full line); b) the electrode was dried in the air during the night and transferred into the clean electrochemical cell and electrolyte (first sweep); c) second sweep, sweep rate: 50 mV s^{-1}.

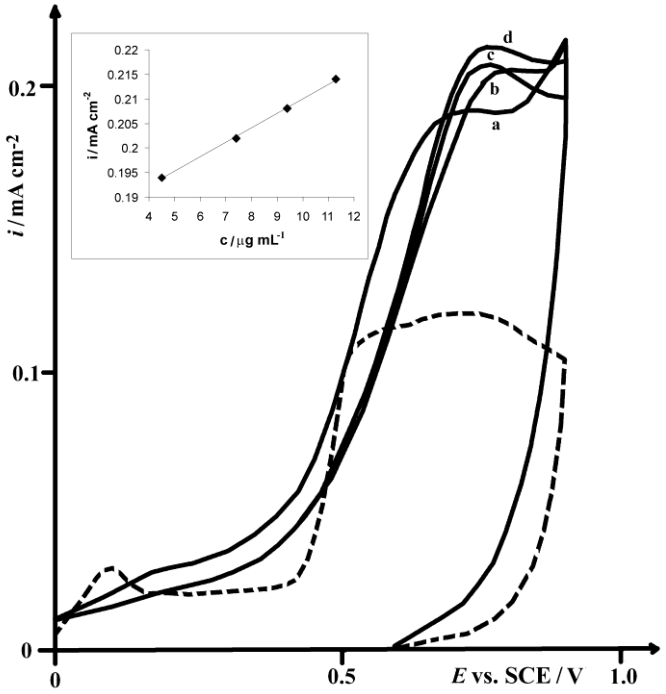


Figure 8. Cyclic voltammogram of gold electrode in 0.05M $NaHCO_3$ (dashed line) and in a presence of amlodipine in Alopres tablet (full line) a) 5 μg mL^{-1}, b) 6.5 μg mL^{-1}, c) 9 μg mL^{-1},d) 12 μg mL^{-1}sweep: 50 m V s^{-1}.

The apparent anodic reaction, with wide plateau is observed between 0.5 V and 0.85 V for all presented concentrations. In the inset of Fig. 6 is presented the linear dependency of the anodic currents versus concentration in the investigated range (1.50 - 3.38 μg mL^{-1}), obtained at 0.75 V.

Fig. 8 presents the cyclic voltammograms of Alopres in 0.05 M $NaHCO_3$ obtained without accumulation. All presented excipients, as was previously published, have no electrochemical activity under the same experimental conditions [36] and amlodipine besylate as a content of Alopres exhibits in their presence also the linear dependency of the anodic current *vs*. concentration, but for the higher values (4.0 - 11.5 μg mL^{-1}) obtained at 0.75 V (as is presented in the left corner of Fig. 8). Comparing Fig. 6 and Fig. 8 it can be supposed that excipients could cover the electrode surface and in some way prevent the formation of strongly adsorbed agglomerates of amlodipine besylate, causing its anodic reaction to occur at higher concentrations.

For higher concentrations in Fig. 8 the shape of voltammograms stabilizes, which can be attributed to the reached equilibrium concerning the competitive adsorption between amlodipine besylate and some or all present excipients.

According to [26-29], with cyclic and adsorptive square-wave anodic stripping voltammetry the determination of amlodipine in pharmaceuticals was performed in a best way using electrolytes at pH=11, mostly phosphate buffer.

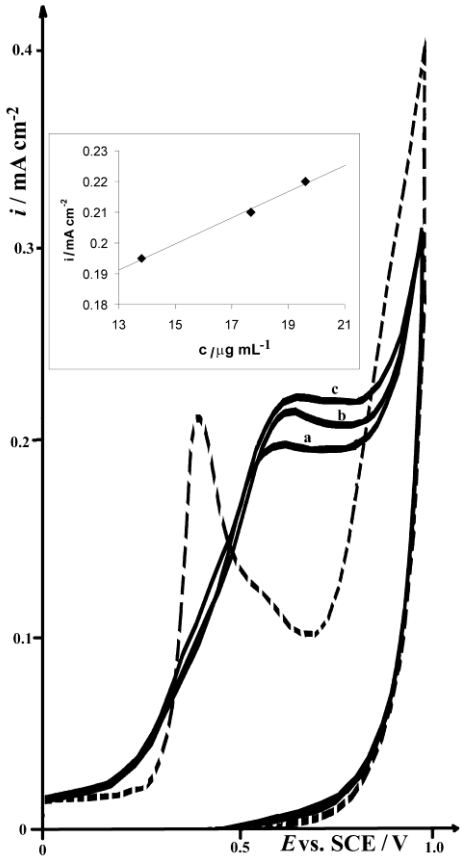


Figure 9. Cyclic voltammogram of gold electrode in phosphate buffer (pH=11) (dashed line) and in a presence of amlodipine besylate a), 13.80 μg mL^{-1}, b) 17.68 μg mL^{-1}, c) 19.61 μg mL^{-1}, sweep: 50m V s^{-1}.

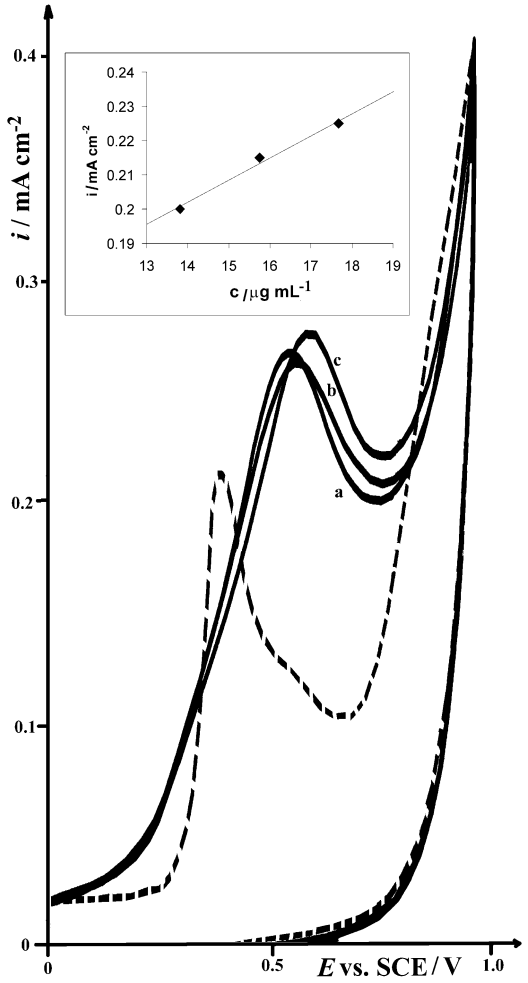


Figure 10. Cyclic voltammogram of gold electrode in phosphate buffer (pH=11) (dashed line) and in a presence of amlodipine in Alopres tablet (full line) a) 13.80 μg mL^{-1}, b) 15.75 μg mL^{-1}, c) 17.68 μg mL^{-1} sweep: 50mV s^{-1}.

In Figs. 9 and 10 are displayed the cyclic voltammograms of amlodipine besylate and Alopres in phosphate buffer, pH=11, obtained without accumulation. Comparing to Figs. 6 and 8, it is obvious that improved anodic activity with higher currents is obtained with higher concentrations of amlodipine besylate and Alopres tablet. In phosphate buffer, as can be observed from Figs. 9 and 10, the voltammograms have the same shape and one can suppose the lack of the excipients competitive adsorption influence, which is apparent in 0.05M $NaHCO_3$.

The linear dependency of anodic currents vs. concentration of amlodipine besylate in a range: 13.80 - 19.61 μg mL^{-1}, is presented in the left corner of Fig. 9, obtained at 0.75V.

The linear dependency of anodic currents vs. concentration of amlodipine in Alopres tablet in a range: 13.80 - 17.68 μg mL^{-1}, is presented in the left corner of Fig. 10, obtained at 0.75V.

Fig. 11 presents the cyclic voltammograms of amlodipine in Alopres tablet in phosphate buffer, pH=11, obtained with accumulation at 0.1 V during 220 s. After the accumulation, comparing to Fig. 10, anodic oxidation of amlodipine in Alopres tablet proceeds with higher currents and their linear

dependency *vs*. concentration is obtained at 0.15 V more negative potential. This is displayed in the left corner of Fig. 11 in a range: 7.94 - 11.86 μg mL^{-1}.

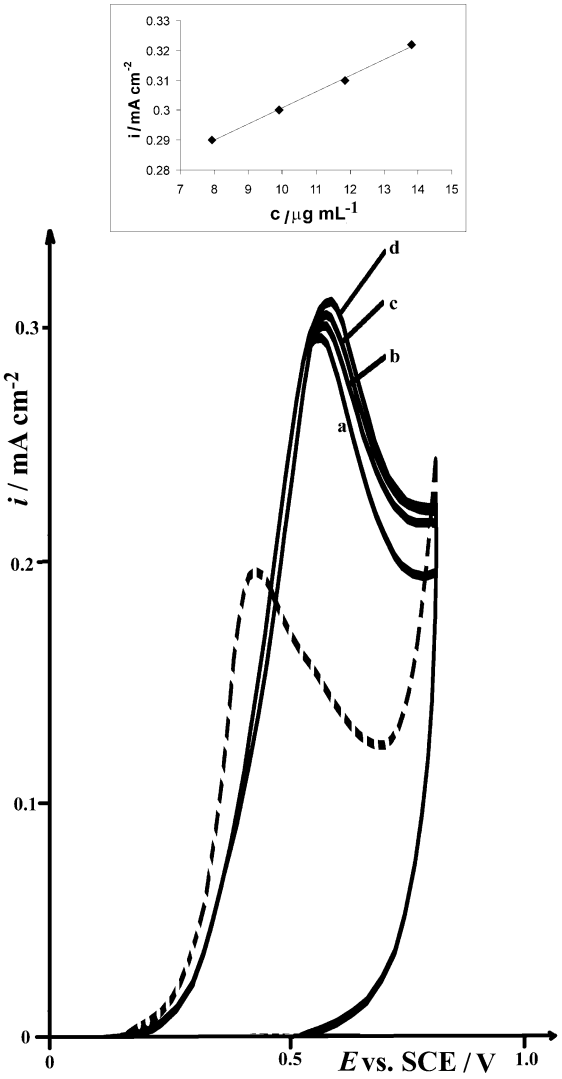


Figure 11. Cyclic voltammograms of gold electrode in phosphate buffer (pH=11) (dashed line) and in a presence of amlodipine in Alopres tablet (full line), with accumulation at 0.1 V after 220 s, a) 7.94 μg mL^{-1}, b) 9.90 μg mL^{-1}, c) 11.86 μg mL^{-1} sweep: 50 mV s^{-1}.

For a gold electrode, the best anodic activity of amlodipine besylate and Alopres tablet is obtained in phosphate buffer pH=11, as was obtained for glassy carbon electrode. Comparing to results in [27] with glassy carbon electrode, under the similar experimental conditions at pH=11, the gold electrode is a better catalyst for the anodic oxidation of amlodipine besylate and in pharmaceutical preparation, Alopres tablet, than a glassy carbon electrode, giving in all experiments at least fifty times bigger current maximum values.

Square-wave voltammetry analysis was applied in order to further examine the electrochemical determination of amlodipine in Alopres tablet on a gold electrode in a pH 11 phosphate buffer solution. Voltammograms were recorded in the range of potential between +0.1 and +0.9 V for different

concentrations of amlodipine in Alopres tablet and before each scan a pre-concentration step was performed at the potential of +0.1 V for 220 s in order to accumulate amlodipine besylate on the electrode surface.

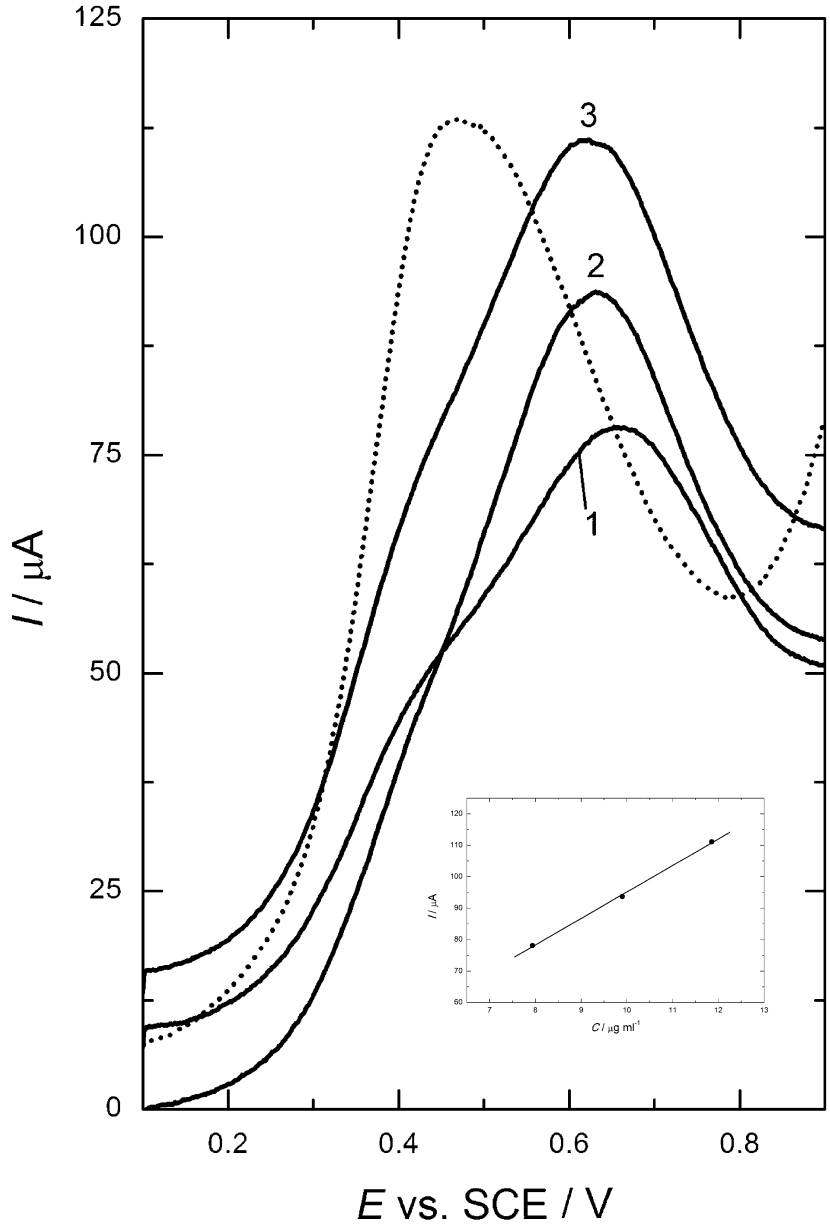


Figure 12. Square-wave anodic stripping voltammograms recorded on a polycrystalline gold electrode for (1) 7.94, (2) 9.90 and (3) 11.86 μg mL^{-1} of amlodipine in Alopres tablet in a phosphate buffer solution pH 11 (the dotted line represents a blank solution). Accumulation time: 220 s at E = +0.1 V; step size: 2 mV; pulse size: 25 mV; frequency: 50 Hz; scan rate: 100 mV s^{-1}.

Results are presented in Fig. 12. The anodic voltammogram recorded in a blank buffer solution (a dotted line) is characterized by the presence of one large peak at +0.47 V, corresponding to the

oxidation of Au. With the addition of amlodipine in Alopres tablet in the solution (solid lines), this peak practically disappeared (only a small shoulder remained), indicating an inhibition of the electron exchange process due to the adsorption of amlodipine besylate and/or present excipients on a gold electrode surface. All voltammograms obtained in the presence of Alopres tablet in the solution possess new, well-defined peak, positioned at approximately +0.63 V that may be attributed to the oxidation of adsorbed amlodipine molecules. The anodic stripping peak current, I_p, shows a linear relationship with the concentration of amlodipine in Alopres tablet from 7.94 to 11.86 μg mL^{-1} (Fig. 12), following the equation:

$$I_p\ (\mu A) = 11.000\ (\pm 2.754) + 8.415\ (\pm 0.274)\ C\ (\mu g\ mL^{-1}),\ R = 0.9995 \quad (1)$$

In Fig. 13 is presented the oxidation of amlodipine in Alopres tablet on Au/o-MWCNT in a pH 11 phosphate buffer solution (7.94 μg mL^{-1}), with accumulation at 0.1 V during 220 s. Comparing to Fig. 11 it is clear that anodic activity of amlodipine in Alopres tablet is much lower on Au/o-MWCNT than on a gold electrode.

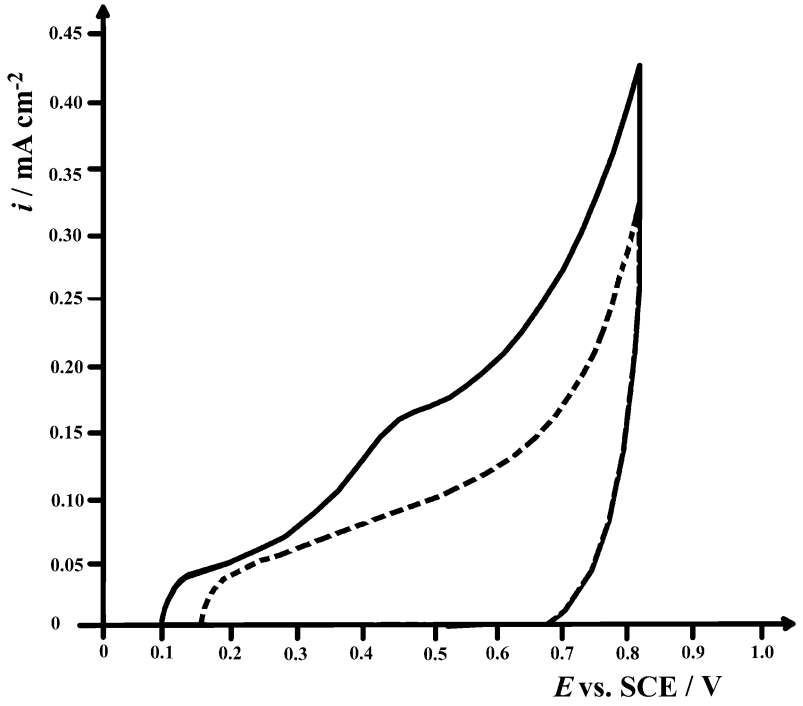


Figure 13. Cyclic voltammograms of Au/o-MWCNT in phosphate buffer (pH=11) (dashed line) and in a presence of amlodipine in Alopres tablet (full line), with accumulation at 0.1V after 220 s, 7.94 μg mL^{-1}, sweep rate; 50 mV s^{-1}.

Fig. 4 clearly shows that randomly oriented o-MWCNT covered the entire surface of the substrate homogeneously, with the average diameter of 100 nm (Fig. 5a). The sample of amlodipine besylate/o-MWCNT was also well-dispersed, implying that the o-MWCNT would connect well the

amlodipine on the surface and inhibit its oxidation. This explains the better electrocatalytic activity of the gold surface which is covered with small agglomerates. Square-wave voltammetry analysis was applied and on Au/o-MWCNT under the same experimental conditions and very low anodic activity of amlodipine in Alopres tablet is obtained, as is presented for cyclic voltammetry in Fig. 13. In [29] was published significant anodic oxidation of amlodipine besylate on a glassy carbon electrode modified by o-MWCNT in physiological solution. The results clearly show that glassy carbon electrode modified by o-MWCNT is better catalyst than gold modified by o-MWCNT for the oxidation of amlodipine besylate and in pharmaceutical preparation.

4. CONCLUSIONS

The results obtained with gold electrode shown that the small agglomerates of amlodipine besylate, seen by AFM cover the gold electrode surface. In 0.05M $NaHCO_3$, without accumulation, the linear dependency of the anodic currents versus concentration in a range (1.50 - 3.38 μg mL^{-1}) is obtained for amlodipine besylate and in a range (4.0 - 11.5 μg mL^{-1}) for Alopres tablet.

In phosphate buffer (pH 11), without the accumulation, the anodic oxidation of amlodipine besylate is improved and the linear dependency of its anodic currents *vs*. concentration in a range: 13.80 - 19.61 μg mL^{-1} is obtained as well as for Alopres tablet. After the accumulation, anodic reaction of amlodipine in Alopres tablet proceeds with higher currents.

With cyclic and square wave anodic stripping voltammetry is shown that anodic activity of amlodipine in Alopres tablet is much lower on Au/o-MWCNT than on a gold electrode. AFM analysis shows that randomly oriented o-MWCNT covered the entire surface of the substrate homogeneously with the average diameter of 100 nm.

In a phosphate buffer, the gold electrode is a better catalyst for the oxidation of amlodipine besylate as standard and in Alopres tablet than the glassy carbon electrode, giving more than fifty times bigger current maximum values. Glassy carbon electrode modified by o-MWCNT is better catalyst than gold modified by o-MWCNT in the oxidation of amlodipine besylate and in Alopres.

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