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Determination of Enalapril in Pharmaceuticals using Electrochemical Sensing with Amperometric Detection

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Abstract- In this work a new electrochemical method will be presented for the determination of enalapril in pharmaceutical tablets using unmodified screen printed electrode (SPE). The studies were done using amperommetric detection. Enalapril provides well defined, oval-shape oxidation peak at +1.05 V (*vs.* Ag/AgCl, 3.0 M KCl) in Britton-Robinson buffer solution (BRBS) at pH 5.0. After optimization of the experimental conditions, the influence of most common interferent compounds was tested. Under optimized experimental conditions, the signals were linearly proportional to the concentration of enalapril in the range from 2.5 to 90 µM with a detection limit of 0.9 µM. Repeatability of ten replicate measurements of 5 µM enalapril was estimated to be 1.5%. Proposed method was successfully applied for the determination of the total amount of enalapril content in pharmaceutical preparations. Nevertheless, proposed method could be beneficial for the quick quantifications of enalapril in drugs using unmodified SPE electrode without any further treatment.

Keywords- Enalapril, Pharmaceutical tablets, Screen printed electrode, Amperometry

1. INTRODUCTION

Enalapril (ENP) is widely used as an antihypertensive drug. Metabolites of enalapril are active inhibitors of angiotensin-I converting enzyme (ACE). Enalapril maleate (EM) {1-[*N*-[(*S*)-1-carboxy-3-phenylpropyl]-L-anayl]-L-proline 1-ethyl ester, maleate (1:1)} is an official drug in B.P. [1]. EM is used for the treatment of rennin-dependent hypertension [2] arterial hypertension [3,4], and congestive cardiac insufficiency [3], alone or in a combination with other drugs [5]. It is also a prodrug (an ethylester) which is hydrolyzed to an active compound, enalaprilat [6,7]. It is a very powerful drug with minimal side effects [4] at low therapeutic doses [8]. Lately, it was found that the use of enalapril decreases the mortality and diminishes the frequency of patient hospitalizations. Due to this fact, the development of a low-cost, sensitive, selective and simple analytical procedure for quantification of enalapril is of dominant importance especially for quality control of drug. Recently, there are some techniques that have been used for enalapril determination in biological samples and pharmaceutical formulations based on potentiometry [9], spectrophotometry [10-15], high performance liquid chromatography (HPLC) [7, 16-19] and colorimetry [20]. HPLC methods are widely used due to their selectivity and sensitivity. These techniques suffer from a time-consuming sample preparation and analysis and high cost of the instrumentation. Electroanalytical methods offer high selectivity and sensitivity, simplicity in sample preparation and low-cost instrumentations. Therefore, based on these facts they are widely used in analysis of biologically active compounds [21-23]. Due to the enalapril's complex structure, the best of our knowledge there is only a few published research artticles dealing with electrochemical determination of enalapril based on modified paste electrode [24] and mercury electrodes [25,26].

The aim of this work was to develop simple, sensitive and selective electroanalytical procedure for determination of total enalapril content in pharmaceutical preparation using unmodified screen printed electrode with amperometric detection. Influence of most common interferent compounds of enalapril were tested and proposed method was successfully applied for the enalapril quantification in pharmaceutical formulation.

2. EXPERIMENTAL

2.1. Apparatus, solvents and reagents

Water was purified with a cartridge purification system (Milli-Q) with a resistivity of 18 MΩ cm and was used for preparation of all the solutions used for this work. Enalapril, ascorbic acid, uric acid, dopamine, boric acid, sodium hydroxide, acetic acid, maleic acid, magnesium stearat, sodium lauryl sulphate and phosphoric acid were purchased from Sigma-Aldrich (Vienna, Austria) and used as received without any further purification. Calibration standard solutions were prepared from the stock solutions to appropriate dilution with

supporting electrolyte. Britton-Robinson buffer solution (BRBS) was prepared by mixing of phosphoric acid, acetic acid and boric acid (all at 40 mM) adjusting the pH with sodium hydroxide (0.2 M) to the desired value.

Cyclic voltammetric (CV) and amperometric measurements were performed using an electrochemical analyzer (PalmSens BV, The Netherlands) controlled by a personal computer with the necessary software (PS Trace, version 1.2).

The electrochemical cell (20 mL) contained a three-electrode system with a screen printed working electrode, an Ag/AgCl (3.0 M KCl) reference electrode and a Pt as a counter electrode. All working potential values in this work are reported versus Ag/AgCl reference electrode at room temperature.

For the CV measurements, the potential was swept over the range from 0 to +1.4 V (*vs.* Ag/AgCl) at the different scan rates, and for amperometric measurements potential was kept constant at +1.05 V (*vs.* Ag/AgCl).

2.2. Sample preparation

Tablets containing ENP were weighed and a suitable amount of the powder was transferred to 10.0 mL calibrated volumetric flasks containing ethanol. Next, 100 µL of this solution was transferred to electrochemical cell with BRBS (pH 5.0). The ENP concentrations in each sample were determined using the regression equation of previously plotted analytical curves obtained with standard solutions of each analyte. These results were finally compared with those proposed by supplier.

3. RESULTS AND DISCUSSIONS

3.1. Electrochemical behavior of enalapril, effect of pH and scan rate

Electrochemical behavior of enalapril was studied using cyclic voltammetry and the influence on peak current and peak potential was investigated at different pH values of Britton-Robinson buffer solution. In acidic media, enalapril provided well-defined irreversible oxidation peak at around +1.05 V. Increasing of pH of the supporting electrolyte solution effects in a loss of the peak. When increasing the pH value of supporting electrolyte from 2.0 to 6.0 the peak potentials shifts to less positive potential and peak current increases to the pH value of 5.0. From Figure 1A and 1B can be concluded that most suitable pH of supporting electrolyte for oxidation of enalapril is at pH 5.0. Dependence of the peak potential from pH (Figure 1C) gives the conclusion that there is no proton participation in the electrode reaction that occurs at SPE electrode. Proposed electrode mechanism is given in Scheme 1.

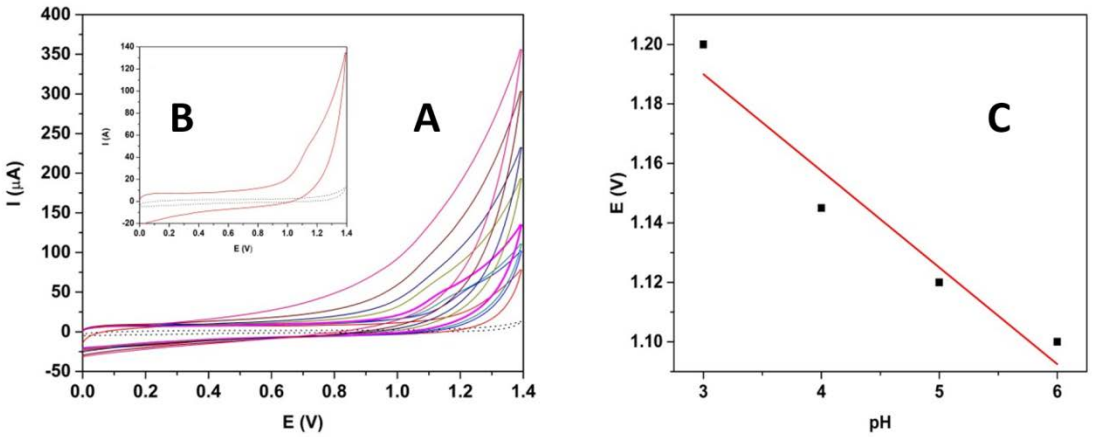
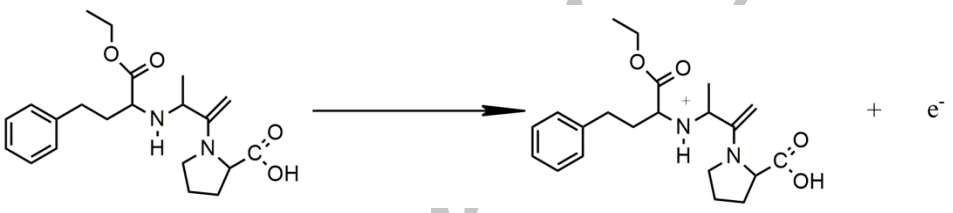


Fig. 1. A) CV voltammograms of enalapril at SPE in BRBS at different pH (2.0-9.0), scan rate 100 mV/s. B) CV voltammogram of enalapril at SPE in BRBS at pH 5.0, scan rate of 100 mV/s. C) dependence of peak potential and peak current from pH of supporting electrolyte



Scheme 1. Proposed mechanism for electrochemical oxidation of enalapril at SPE in BRBS at pH 5.0

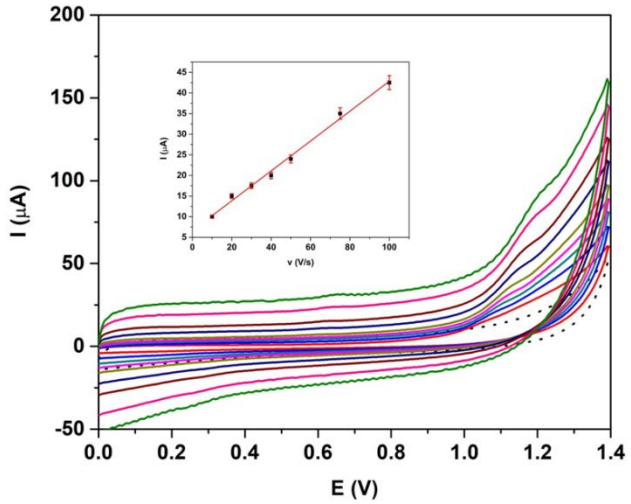


Fig. 2. CV voltammograms obtained for 0.1 mM of enalapril solution at SPE, at pH 5.0 of BRBS at different scan rates (10-100 mV/s). Inset figure present dependence of peak current from scan rate

3.2. Enalapril detection and performance of screen printed electrode

Amperometric determination of enalapril has been performed over a wide analyte concentration range of 2.5-90 µM at previously optimized experimental conditions, detection potential and pH of supporting electrolyte solution. Limit of detection and response time were estimated from the amperometric response of analyte. Calibration curve was constructed by plotting current values and different concentrations of enalapril. Under optimized experimental conditions, the signals were linearly proportional to the concentration of enalapril in the range from 2.5 to 90 µM (Figure 3A) with a detection limit of 0.9 µM.

Corresponding regression equation (Figure 3B) was calculated to be *I(µA)=(0.0146±0.0008) c (µM)+(1.6317±0.0003)* with correlation coefficient of 0.9977. Proposed method has wide linear range and obtained detection limit is comparable or better than those reported in literature using chemically modified electrodes [24-26]. Valezi et al. proposed similar detection limit of 0.81 µM but lower linear range from 2 to 57 µM [24], Gusakova and Ivanovskaya proposed wider linear range with similar LOD using mercury film electrode [25], while Elmali et al. proposed higher LOD and lower linear range from 40-100 µM using differential pulse polarography at static mercury dropping electrode [26]. However, mercury itself has been recently considered as poisonous and toxic substance and due to that our developed method can be satisfactory procedure for fast, environmentally friendly and reliable detection of ENP.

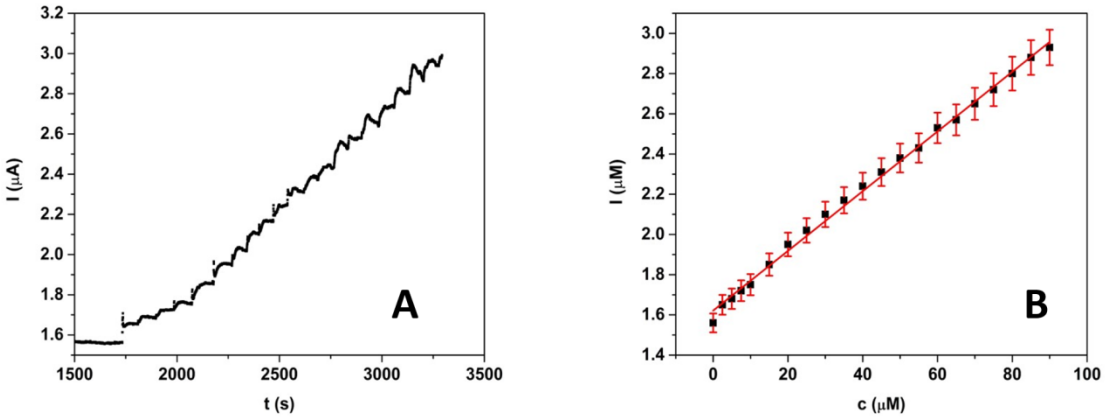


Fig. 3. A) Amperometric response obtained by proposed sensor under optimized experimental conditions, at potential of +1.05 V. B) Calibration curve for amperometric response of proposed electrode

3.3. Influence of most common interferences

Perhaps most important advantages of one analytical methodology are based on the selectivity. Influence of most common interferents of enalapril in pharmaceutical formulations was studied under optimized experimental parameters. Amperomeric response

of SPE for determination of analyte was analyzed or tested in presence of magnesium stearate (MS), sodium lauryl sulphate (SLS) and maleic acid (MA). It was found that tested compounds do not have significant influence on obtained current responses for enalapril in 10-fold excess (Figure 4A). In presence of ascorbic acid (AA), uric acid (UA) and dopamine (DOP) there are significantly changes in current by adding same amount of tested compound which indicated that proposed analytical procedure is not suitable for determination of enalapril in human samples (Figure 4B).

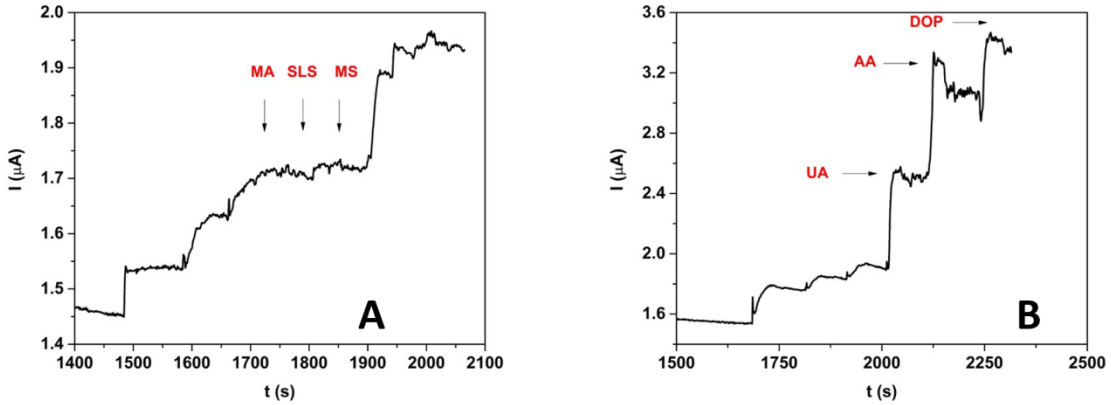


Fig. 4. A) Amperometric response of proposed electrode for determination of enalapril in presence of MA, SLS and MS as an interferent compounds. B) Amperometric response of SCE for enalapril in presence of AA, DOP and UA. All measurements were carried out under optimized parameters at potential of +1.05 V

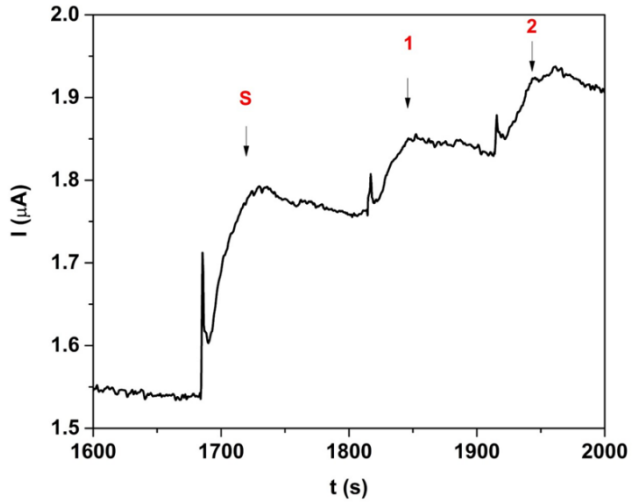


Fig. 5. Amperometric response obtained for the determination of enalapril in tablets under optimized parameters at potential of + 1.05 V

3.4. Analytical application

In order to investigate applicability of the proposed analytical methodology and accuracy of recovery measurements, SPE was applied for the determination of total enalapril content in pharmaceutical tablets using amperometric detection. Tablets are prepared as previously described. Figure 5 shows the current peaks recorded by addition of the solution of enalapril obtained from the pharmaceutical tablets and duplicate additions of the enalapril standard solution. Results are obtained from calibration curve (Table 1) and compared with those proposed by supplier. It can be concluded that these obtained results for quantification of enalapril are in a good agreement with those proposed by supplier and recovery was in the range of 98-104 % which indicates the efficacy of the proposed sensor for practical analysis.

Table 1. Results obtained for the determination of enalapril and recovery experiments

Sample	Found mg/tablet	Proposed by supplier mg/tablet	Added µM	Found µM	Recovery %
Tablet 1	10.01	10.00	5.00/5.00	14.71/20.41	98/102
Tablet 2	10.15	10.00	5.00/5.00	15.31/20.96	101/104

4. CONCLUSION

In this work we have demonstrated the use of unmodified screen printed electrode as an electrochemical sensor for the quick quantification of enalapril in pharmaceuticals using amperometric detection. The proposed sensor does not require any complex procedure for the construction. The enalapril content was detected with a low detection limit and wide linear range. Effect of most common interferent compounds was also investigated and proposed method was successfully applied for the determination of enalapril content in pharmaceutical tablets with satisfactory recovery. This method offers alternative procedure for the determination of enalapril with a high selectivity and sensitivity, low cost instrumentation setup and could be replacement for separation methods.

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