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Determination of Pravastatin Drug Formulation by Square-wave Voltammetry on Glassy Carbon Elektrode

Pravastatin'in Camımsı Karbon Elektrot Üzerinde Kare-dalga Voltametrisi ile İlaç Formülasyonunda Tayini

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Abstract

The electrochemical behavior of Pravastatin, a lipid-lowering drug, on a glassy carbon electrode was explored in Britton-Robinson buffer by using cyclic and square-wave voltammetry. Cyclic voltammetric studies indicated that the compound underwent irreversible oxidation, which was a diffusion-controlled process. Using square-wave voltammetry, Pravastatin could be determined at +1.24 V (vs. Ag/AgCl) in the concentration range 2.4×10^{-7}-2.8×10^{-6} M at pH 2.0, with a detection limit of 5.0×10^{-8} M. The suggested method was successfully applied for the assay of Pravastatin in tablets.

Keywords: *Pravastatin, Square-Wave Voltammetry, Glassy Carbon Electrode, Drug Formulation*

Öz

Lipit düşürücü ilaç olan Pravastatin'in, camımsı karbon elektrot üzerindeki elektrokimyasal davranışı, Britton-Robinson tamponu içerisinde dönüşümlü voltametri ve kare-dalga voltametrisi teknikleri kullanılarak araştırılmıştır. Dönüşümlü voltametrik çalışmalar, molekülün tersinmez olarak yürüyen yükseltgenmesinin difüzyon-kontrollü olduğunu göstermiştir. Kare-dalga voltametrisi kullanılarak, Pravastatin'in pH 2.0 değerinde +1.24 V (vs. Ag/AgCl) gerilim değerinde 2.4×10^{-7}-2.8×10^{-6} M derişim aralığında (saptama sınırı, 5.0×10^{-8} M) tayini gerçekleştirilmiştir. Önerilen yöntem, Pravastatin'in tablet ilaç şeklinden tayinine başarıyla uygulanmıştır.

Anahtar Kelimeler: *Pravastatin, Kare-dalga voltametrisi, Camımsı karbon elektrot, İlaç formülasyonu*

1. Introduction

Pravastatin (PRV) (Figure 1) is a semisynthetic agent belonging to the class of the lipid-lowering drugs called statins [1]. PRV reduces cholesterol production by acting as an inhibitor of microsomal enzyme 3-hydroxy-3-methylglutaryl-co-enzyme A (HMG-CoA) reductase. It is used in combination with diet, exercise, and weight loss for lowering cholesterol and preventing cardiovascular disease. [2-6].

Several analytical methods are available for the estimation of PRV in bulk form, pharmaceutical preparations and biological matrices, including high-performance liquid chromatography [7-10], ultraviolet-visible spectrophotometry

[11,12], liquid chromatography-mass spectrometry [13-16], and capillary electrophoresis [17,18].

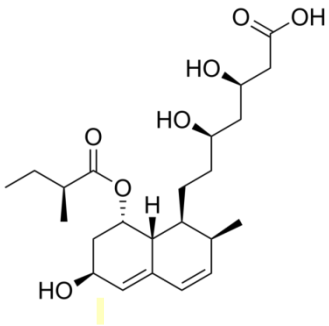

Figure 1. Molecular structure of Pravastatin

Although chromatographic methods have high selectivity, time-consuming extraction steps and instrumental limitations such as expensive reagent grades, mobile phases, and equipment, are considered to be the disadvantages of such methods. Electrochemical assays such as the voltammetric ones have been extensively used for pharmaceutical analysis [19-21] and have been proven to be fast, precise and to produce low-cost results with minimum interference from the drug excipients. However, from the electroanalytical point of view, till date there are only three reports on the determination of PRV. The first investigation was performed by Coskun et al [22], which was concerned with studying the reductive behavior and differential pulse polarographic (DPP) determination of PRV in tablets. A hanging mercury drop electrode (HMDE) was also used to determine the electrochemical reduction and adsorptive voltammetric behavior of PRV [23]. In a recent study, a glassy carbon electrode (GCE) and screen-printed carbon electrode (SPCE) were applied to the determination of PRV in weakly acidic solution (at pH 5.0) based on its electrochemical oxidation [24]. However, it should be noted at this point that anodic behavior of PRV was not sufficiently documented in that report. The more attention was given to the quantification of the compound in pharmaceutical products by using both electrode types.

Bearing in mind the very limited data on voltammetric determination of PRV, the aim of the present study was to throw a more light upon its redox behavior at the surface of GCE, and to establish a methodology for its more sensitive determination in the case of strongly acid solution.

2. Materyal ve Metot

2.1. Chemicals

PRV (as sodium salt) standard was purchased from Sigma. Tablet dosage form containing the active compound was procured from commercial local pharmacies. Other reagents used were of analytical grade (Merck or Sigma), and their stock solutions were prepared with deionized water further purified via a Milli-Q system (Millipore) (except uric acid which was prepared in 0.1 M NaOH). Standard stock solutions of PRV (1 mg mL^{-1}) were prepared daily in methanol/water mixture (1:1, v/v) and kept refrigerated when not in use. Working solutions were prepared by diluting the stock solution with a selected supporting electrolyte, and used immediately to avoid decomposition. Experiments were conducted in Britton-Robinson (BR) buffer (0.04 M in each of acetic acid, phosphoric acid, and boric acid adjusted to the desired pH between 2.0-8.0 with 3 M sodium hydroxide solution).

2.2. Apparatus

The cyclic voltammetric (CV) and square-wave voltammetric (SW) experiments at a GCE were performed using a μAutolab type III electrochemical analyzer controlled with the GPES 4.9 software (EcoChemie, The Netherlands). All SWV curves were smoothed using a Savicky and Golay algorithm and baseline-corrected by the moving average method (peak width of 0.01 V), using the GPES software. A classical three-electrode-system in a 10 mL one-compartment voltammetric cell was employed consisting a GCE (Ø: 3mm, diameter), a platinum wire auxiliary electrode, and an Ag/AgCl (3 M NaCl) reference electrode (Model RE- 1, BAS, USA) to which all electrode potentials hereinafter are referred. Before each measurement, the working electrode was polished manually with aqueous slurry of alumina powder (Ø: 0.01 μm) on a damp smooth polishing cloth (BAS velvet polishing pad) to produce a mirror-like surface, and then ultrasonically cleaned in deionized water thoroughly in order to remove any residual alumina.

The pH value of solutions was measured using digital pH-meter Model PHS-3C (Shanghai

Leici Device Works, Shanghai, China) with a combined electrode (glass-reference electrodes) which was daily calibrated with standard buffer solutions.

CV and SWV experiments were initiated in the anodic direction. The initial and final potential were variable for CV studies, depending on the pH value and the cut-off the electrolyte. Scan rate measurements in the range 50-450 mV s^{-1} were carried out. For analytical application, the following SWV parameters being employed: frequency, 75 Hz; scan increment, 10 mV; and pulse amplitude, 30 mV.

All measurements were performed in triplicate at ambient temperature of the laboratory (23-27^{0}C).

2.3. Sample preparation

Pravachol® tablets labeled as containing 20 mg PRV (as sodium salt) were used for the present analytical application. Ten tablets were weighed and the average mass per tablet was determined. The tablets were carefully grounded to a fine powder in a mortar with a pestle. An adequate amount of the resulting powder was weighed and transferred into a 25 mL calibrated dark flask, which was completed to the volume with the mixture solution of methanol/water (1:1, *v/v*). The content of the flask was sonicated for about 30 min to complete dissolution. The desired concentrations of PRV were obtained by taking suitable aliquots from the upper clear layer of the mixture and diluting with BR buffer at pH 2.0. An aliquot volume of these solutions was transferred to the voltammetric cell containing the same solution, and analyzed in the day of the preparation according to the procedure developed for the pure electrolyte using the calibration curve method from the related regression equation.

3. Results and Discussion

3.1. Investigation of the electrochemical behavior on glassy carbon electrode

Initially, CV studies were performed to explore the basic voltammetric characteristics of PRV on GCE. Figure 2A shows the three consecutive CV curves of 70 µg mL^{-1} PRV in BR buffer of pH 2.0 (optimized response) recorded within the potential window from 0.5 to +1.5 V at a scan rate of 100 mV s^{-1}. A cyclic voltammogram without PRV was also plotted in the graphs for the sake of comparison. As it can be observed from the figure, PRV was oxidized in this medium yielding one main irreversible process at +1.23 V. However, in alkaline media (pH 8.0), an additional ill-defined peak was also observed at more positive potential values (data not shown). No peaks were observed in the cathodic branch, indicating that the PRV oxidation is an irreversible process.

In order to understand the nature of the oxidation process, the influence of scan rate (between 50-450 mV s^{-1}) on electrochemical response of PRV was investigated under the above conditions. As shown in Figure 2B, the oxidation peak shifted slightly towards more positive potentials as the scan rate increased; a behavior typical of irreversible electrochemical reactions. The results show that the oxidation peak current (*ip*) of PRV increased linearly with the square root of the scan rate ($v^{1/2}$), and can be expressed as following: ip (μA) = 0.4578 $v^{1/2}$ (mV s^{-1}) – 0.1255 (r = 0.997), that the oxidation process is diffusion-controlled in the whole scan rate range studied. In addition there was a linear relation between logarithm of peak current (log *ip*) and logarithm of scan rate (log ν), corresponding to the following equation: log *ip* (µA)= 0.5002 log *v* (mV s^{-1}) – 0.3487 (r =0.996). As can be seen from the equation, the value of slope is close to the theoretically value of 0.5 for a diffusion-controlled process, indicating that the electrochemical reaction of PRV is controlled by diffusion.

In order to ascertain the electron number (n) involved in PRV oxidation process at GCE, the n value was determined by using CV curves according to the equation $Ep-Ep/2 = 47.7/\alpha n$ [25] for the irreversible electrode process, where *Ep* is peak potential, *Ep*/2 is half-wave potential, α is the charge transference coefficient (generally, assumed as 0.5 for totally irreversible electrode process) and n is the number of electrons. Using the CV curve obtained for PRV oxidation at 100 mV s^{-1}, the value of $Ep-Ep/2$ was determined as 40.0 mV, so *n* value was calculated to be 2.38 (≈2). This result indicates that the irreversible oxidation of PRV involves two electrons per molecule at GCE. Thus, the electrooxidation of hydroxyl group of pravastatin can proposed for possible reaction mechanism.

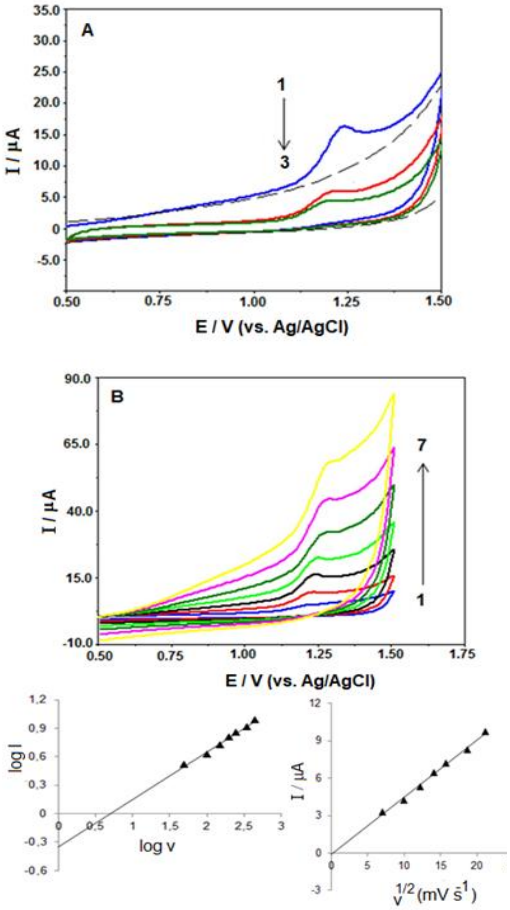

Figure 2. The repetitive cyclic voltammograms at scan rate of 100 mV s^{-1} (A), and the cyclic voltammograms at different scan rates (1-7: 50, 100, 150, 200, 250, 300, 350 and 400 mV s^{-1}) of 70 µg mL^{-1} Pravastatin in Britton-Robinson buffer, pH 2.0 obtained by means of GCE. (A): The numbers 1 through 3 shown within the graph correspond to the order of the recorded scans. Dashed lines represent background current. Insets (B): the plots of i_p / $v^{1/2}$ and log i_p / log v.

After the results given previously, the attention was then turned to the effect of the solution acidity on PRV oxidation process by application GCE. Due to the better-resolved signals obtained by SWV approach, the influence of changing the pH was studied using this voltammetric waveform. It should also be noted that, the percentage of methanol in the solutions was kept at the level of ≤ 1% (*v/v*) for all further experiments, which will be referred to as aqueous solutions. In Figure 3, pH effect was investigated in the range from pH 2.0-8.0 of BR buffer solution by performing measurements on 5 µg mL^{-1} PRV. As can be seen from the figure, the pH did not indicate a significant change in the peak potential between pH 2.0 and 4.0. Above pH 4.0, peak potential shifted slightly to less positive potential values, and then remained almost unchanged between pH 5.0 and 8.0. It seems that the electroactive grouping responsible for the oxidation process is in acid-base equilibrium with pK_a of about 4.2 for PRV [26]. On the other hand, by increasing in the solution pH, the peak height decreased with different degrees, the maximum current being obtained at pH 2.0. Therefore, this pH value was chosen as an optimal pH for the sensitive determination of this compound.

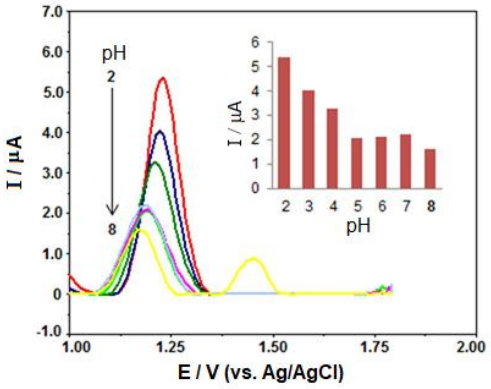

Figure 3. SWV curves of 5 µg mL^{-1} Pravastatin in Britton-Robinson buffer at pH 2.0-8.0 obtained by means of GCE. SWV parameters: frequency, 50 Hz; scan increment, 8 mV; pulse amplitude, 30 mV.

3.2. Method validation and analytical application

3.2.1. Optimization of parameters and analytical curve

In order to optimize the experimental set-up for PRV determination, the dependence of SWV responses on parameters such as square-wave frequency (*f* = 10-175 Hz), scan increment (ΔE_s = 4-16 mV) and as square-wave amplitude (ΔE_{sw} = 10-70 mV) were finally analyzed. For entire analysis the optimized values were: *f*, 75 Hz; ΔE_s, 10 mV; and ΔE_{sw}, 30 mV, taking into account repeatability, baseline stability,

accuracy, and magnitude of analytical signal at the GCE for PRV determination.

Under application of the above mentioned optimized experimental parameters, SWV curves at different concentrations of PRY were recorded in BR buffer at pH 2.0 (Figure 4). The analytical curve shown in the inset of Fig. 4, using the peak currents at a potential of +1.24 V, depicts a linear response in the range of 0.1-1.2 μg mL^{-1} (2.4×10^{-7}-2.8×10^{-6} M) [i_p (μA) = 2.47 C (μM) + 0.335 (r = 0.998)], where i_p is the oxidation peak current and C PRV concentration, and r correlation coefficient.

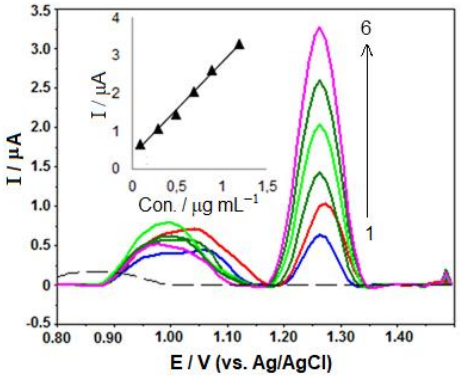

Figure 4. SWV curves for Pravastatin levels of (1) 0.1, (2) 0.3, (3) 0.5, (4) 0.7, (5) 0.9, and (6) 1.2 μg mL^{-1} in Britton-Robinson buffer (pH 2.0) obtained by means of GCE. Inset depicts a corresponding calibration plot for the quantitation of Pravastatin. SWV parameters: frequency, 75 Hz; scan increment, 10 mV; pulse amplitude, 30 mV.

The limit of detection (LOD) and limit of quantification (LOQ) were found to be as 5.0×10^{-8} M and 1.5×10^{-7} M, respectively. The LOD and LOQ values were calculated by using the following equations: LOD = $3.3s/m$; LOQ = $10s/m$, where s is the standard deviation of oxidation peak current (three replicative measurements) of the lowest level concentration of the calibration curve and m the slope of the related corresponding calibration equation.

The comparison between the analytical performance of the GCE obtained with mercury and carbon-based electrodes in previous published papers for the voltammetric determination of PRV is given in Table 1.

Table 1. Comparison of the proposed method with some previously reported electrochemical methods for determination of Pravastatin.

Electrode	Method	Linearity range (μM)	LOD (μM)	Ref.
DME	DPP	80-240	n.p.	22
HMDE	SWV	1-10	0.13	23
	SW-AdSV	0.08-0.5	0.036	
GCE	SWV	60-920	11	24
SPCE	SWV	50-1000	30	
GCE	SWV	0.24-2.8	0.05	This work

Electrode: DME, dropping mercury electrode; HMDE, hanging mercury drop electrode; GCE, glassy carbon electrode; SPCE, screen-printed carbon electrode. **Method:** DPP, differential pulse polarography; SWV, square-wave voltammetry; SW-AdSV, square-wave adsorptive stripping voltammetry. **Other:** LOD, limit of detection; Ref., reference; n.p., not provided.

From these data, it can be seen that significantly improved LOD value has been found using GCE in strongly acidic solution than those reported for dropping mercury electrode (DME) and SPCE. Despite the slightly higher sensitivity of HMDE, the toxicity of the mercury was the greatest defect in the application area of these electrodes and not environmentally friendly.

The intra-day repeatability of the magnitude of oxidation peak current was determined at PRV concentration level of 0.3 μg mL^{-1}. The results of six replicate measurements showed a relative standard deviation (RSD) of 2.25%, indicating a good method precision.

3.2.2. Interference studies

The possible interferences of some compounds commonly found in pharmaceutical samples were evaluated on the electrochemical oxidation of 0.3 μg mL^{-1} PRV in BR buffer solution (pH 2.0). It was found that 10-fold excess of inorganic ions such as K^+, Na^+, Ca^{2+}, Cl^-, I^-, and sugars such as glucose and fructose did not significantly influence on the current response of PRV (data not shown).

The effects of commonly identified biomolecules in urine, such as uric acid, ascorbic acid and dopamine, were also tested. The respective SWV curves are depicted in Figure 5. According to the results, the oxidation

peaks of mixture solutions of 0.1 µM dopamine, 0.1 µM ascorbic acid and 0.1 µM uric acid appeared at about +0.23, 0.35 and +0.68 V respectively, thus insignificantly affecting 0.3 µM PRV signal at +1.24 V. As a result, the direct application of the developed method for the determination of PRV could also be possible in the analysis of urine samples.

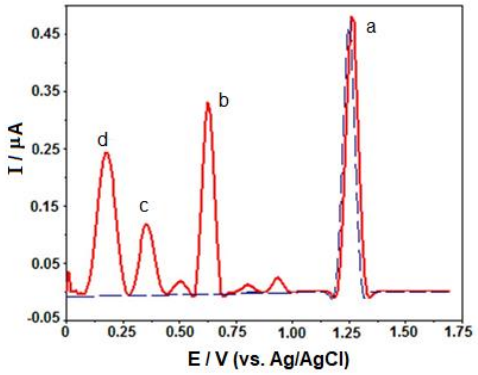

Figure 5. SWV curves demonstrating the effect of the presence of various interfering agents on 0.3 µM Pravastatin (a) in Britton-Robinson buffer (pH 2.0) obtained by means of GCE. The studied interfering agents were: 0.1 µM uric acid (b), 0.1 µM ascorbic acid (c), and 0.1 µM dopamine (d). Dashed lines: 0.3 µM Pravastatin solution without interfering agents. Other operating conditions as indicated in Figure 4.

3.2.3. Determination in pharmaceutical formulation

In order to investigate the validity of the proposed methodology, commercially available tablet samples (Pravachol® tablets) were analyzed using the calibration method. The preparation of the sample is described in the experimental section, without any sample extraction, evaporation or filtration, and after adequate dilutions.

For the tested formulation, the assay results with recoveries are summarized in Table 2. These results of the analysis of pharmaceutical products indicate the fact that the proposed protocol did not suffer from any considerable matrix effect.

Table 2. The analysis of the Pravachol® tablets containing Pravastatin (as sodium salt) using the proposed voltammetric method.

Labelled claim/mg	**20.00**
Amount found[a]/mg	21.19±0.69
RSD %	3.27
Average recovery[a] %	102.95±3.88
RSD of recovery %	3.77

[a]Mean of five experiments

4. CONCLUSION

In keeping with limited data available, a rapid, simple, selective and sensitive an electrochemical methodology for the determination of PRV in strongly acidic media at GCE was established in this study, which provides an alternative choice to other instrumental methods for its simplicity, rapidity, considerably high sensitivity and satisfactory selectivity. It might be preferred for the routine quality control of pharmaceutical formulation after dissolution of the samples, dispensing any use of organic reagents or expensive apparatus.

In addition, the proposed method has the potential to determine PRV selectively in the urine samples.

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