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Differential pulse voltammetric assay of atorvastatin in tablets using an unmodified glassy carbon electrode

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Abstract: A differential pulse voltammetric (DPV) procedure was evaluated for the determination of atorvastatin (ATOR) in tablet formulations using an unmodified glassy carbon electrode (GCE). The electrochemical behavior of ATOR was examined by cyclic voltammetry in Britton–Robinson buffer, and pH 4 was selected for further measurements because it provided a well-defined irreversible oxidation signal at approximately +1.05 V vs. Ag/AgCl/3 M KCl. The scan-rate study supported a predominantly diffusion-controlled oxidation process. Under optimized DPV conditions, the anodic peak current was linear in the ATOR concentration range from 0.05 to 0.84 µM. The limit of detection was 13 nM, and the repeatability was 6.4 % for twelve consecutive measurements of 0.11 µM ATOR. The method was applied to commercial *Torvacard Novum* tablets using the standard addition method, with recoveries from 101.2 to 103.5 %. The procedure is intended as a simple low-concentration assay for tablet extracts after appropriate dilution, without electrode modification, preconcentration or complex sample preparation.

Keywords: electroanalysis; pharmaceutical quality control; standard addition; statins; surface renewal.

INTRODUCTION

Atorvastatin calcium is a synthetic lipid-lowering drug belonging to the statin class. Statins are among the most widely used pharmacological agents for the management of dyslipidemia and the reduction of cardiovascular risk.[1] The pharmacological action of atorvastatin is based on the reversible inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase, the rate-limiting enzyme in cholesterol biosynthesis. By decreasing hepatic cholesterol synthesis and increasing low-density lipoprotein receptor expression, atorvastatin effectively lowers plasma low-density lipoprotein cholesterol and triglyceride levels.[1,2] Therefore, it is widely used in the primary and secondary prevention of

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cardiovascular diseases, including coronary artery disease, myocardial infarction, and stroke. Owing to its extensive clinical use and frequent occurrence in single- and multi-component tablet formulations, reliable analytical methods are required for the routine quality control of atorvastatin-containing dosage forms.

Atorvastatin is commonly administered as the calcium salt of the active hydroxy acid form. Its physicochemical properties, including limited aqueous solubility, acid-base behavior, and possible interconversion between the hydroxy acid and lactone forms, may influence both sample preparation and analytical determination.[2–4] Recent work on statin stability in aqueous cyclodextrin-containing systems confirmed that the lactone–hydroxy acid equilibrium of statins, including atorvastatin, is strongly affected by formulation conditions and pH.[4] In pharmaceutical analysis, atorvastatin has most frequently been determined using chromatographic methods, especially reversed-phase high-performance liquid chromatography and liquid chromatography coupled with mass spectrometric detection.[5–7] These methods provide high selectivity, accuracy, and sensitivity and are suitable for the determination of atorvastatin in tablet formulations as well as in biological samples and pharmacokinetic studies. However, chromatographic methods usually require relatively expensive instrumentation, organic mobile phases, longer analysis time, and more elaborate sample preparation. Spectral methods have also been reported for atorvastatin determination in tablets.[8,9] Although these approaches are simpler and less expensive, their selectivity may be limited in the presence of excipients, degradation products, or other active pharmaceutical ingredients.

Electroanalytical methods represent a useful alternative or complementary approach for the determination of electroactive pharmaceutical compounds. Voltammetric techniques are attractive because of their instrumental simplicity, low reagent consumption, short analysis time, and suitability for miniaturization. According to a review focused on statin determination, voltammetry and polarography have been among the most frequently used electrochemical techniques for this drug class, with applications in pharmaceutical preparations and biological samples.[10] More recently, nanomaterial-based electrodes have also been summarized as important tools for the electrochemical determination of statins, including atorvastatin.[11] Atorvastatin has been studied using different working electrodes, including mercury electrodes, carbon paste electrodes, glassy carbon electrodes, boron-doped diamond electrodes, screen-printed carbon electrodes, and chemically or nanomaterial-modified electrode surfaces.[12–17]

The electrochemical behavior of atorvastatin at glassy carbon and boron-doped diamond electrodes was investigated by Doğan-Topal *et al*., who described its oxidation as an irreversible process and proposed voltammetric methods for its determination in tablet dosage forms and biological fluids.[12] Yilmaz and Kaban later reported the electrochemical behavior of atorvastatin at a glassy carbon

electrode and its direct determination in tablet preparations using square-wave and DPV.[18] Other approaches have included adsorptive stripping voltammetry, surfactant-assisted voltammetry at carbon paste electrodes, polypyrrole- and carbon nanotube-based electrodes, vertically aligned carbon nanotube/graphene oxide electrodes, and nanomaterial-based screen-printed sensors.[13–17] These methods often provide low limits of detection (LOD) and broad linear concentration ranges. Nevertheless, many of them require electrode surface modification, accumulation steps, or specialized electrode preparation, which may increase the complexity of the analytical procedure and affect reproducibility in routine use.

Glassy carbon is one of the most widely used carbon-based electrode materials in pharmaceutical electroanalysis. Its favorable properties include a wide anodic potential window, relatively low background current, chemical inertness, mechanical stability, and the possibility of rapid surface renewal by mechanical polishing.[19] These characteristics make the glassy carbon electrode suitable for studying the oxidation behavior of organic pharmaceutical compounds and for developing simple voltammetric assays. Although atorvastatin has already been determined at glassy carbon electrodes[12,18], there remains practical interest in analytical procedures based on an unmodified and easily renewable electrode surface, especially when the target application is the assay of commercial tablets rather than trace analysis in complex biological or environmental matrices. In such cases, the practical robustness of the electrode, simple sample preparation, and sufficient tolerance toward common tablet excipients may be more relevant than the use of highly modified electrode platforms.

DPV is particularly suitable for the determination of low concentrations of electroactive compounds because it offers improved discrimination against the capacitive background current and better peak resolution compared with conventional voltammetric techniques.[20] For pharmaceutical quality control, a DPV method using an unmodified glassy carbon electrode may therefore provide a simple and low-cost procedure, provided that sufficient sensitivity, precision, and accuracy are achieved. The use of an unmodified electrode also avoids additional preparation steps associated with electrode modifiers and may improve the practical reproducibility of the analytical procedure when the electrode surface is mechanically renewed between measurements.

The present work describes a simple DPV method for the determination of atorvastatin in tablet formulations using an unmodified glassy carbon electrode. The electrochemical behavior of atorvastatin was examined in Britton–Robinson buffer, and the effects of pH and scan rate were evaluated to characterize the oxidation process. The DPV parameters were optimized to obtain a well-defined analytical signal with low background current. The analytical performance of the method was evaluated in terms of linear concentration range, LOD, repeatability,

and recovery in tablet samples. Particular attention was paid to the analysis of commercial atorvastatin tablets by the standard addition method and to the influence of common tablet excipients. The method is positioned as a practical assay for atorvastatin-containing tablets, not as a universal sensor for complex biological or environmental samples.

EXPERIMENTAL

Chemicals

Atorvastatin calcium trihydrate was obtained from Sigma-Aldrich (Germany) and used without further purification. Methanol, boric acid, phosphoric acid, acetic acid, sodium hydroxide, and aluminum oxide slurry used for mechanical polishing of the glassy carbon electrode were of analytical grade. Deionized water was used throughout the experiments. Britton–Robinson (BR) buffer solution was prepared by mixing boric acid, phosphoric acid, and acetic acid, each at a concentration of 0.04 M. The pH of the buffer was adjusted to the required value in the range from 2 to 12 using 0.2 M sodium hydroxide solution. A stock standard solution of atorvastatin calcium trihydrate (ATOR) with a concentration of 10 mM was prepared by dissolving 604.8 mg of the reference material in 50 mL of methanol. This solution was used for cyclic voltammetric studies and for the optimization of experimental conditions. Working solutions of lower ATOR concentrations were freshly prepared by appropriate dilution with methanol before use. The influence of common tablet excipients was evaluated using glucose, sucrose, lactose, microcrystalline cellulose, starch, and magnesium stearate. Stock solutions or suspensions of the tested excipients were prepared at appropriate concentrations using deionized water or methanol, depending on their solubility.

Apparatus

Voltammetric measurements were carried out using an AUTOLAB PGSTAT M204 potentiostat/galvanostat (Metrohm, Switzerland) controlled by NOVA electrochemical software, version 1.11. A conventional three-electrode system was employed, consisting of a disk glassy carbon electrode (GCE, Metrohm, Slovakia) as the working electrode, an Ag/AgCl/3 M KCl reference electrode, and a platinum auxiliary electrode. The GCE embedded in a polyether ether ketone (PEEK) body had a disk diameter of 3 mm. Prior to each measurement, the GCE was not electrochemically activated or conditioned. The electrode surface was mechanically polished with 0.3 μm alumina slurry on a microcloth polishing pad for approximately 1 min, rinsed with deionized water, and gently dried with filter paper. This surface renewal step was applied to improve the reproducibility of the electrode response and to remove possible products of ATOR oxidation adsorbed on the electrode surface. The pH of buffer solutions was measured using a pHenomenal pH 1100L pH meter (VWR, USA).

Voltammetric procedures

Cyclic voltammetry was used for the preliminary investigation of the electrochemical behavior of ATOR at the GCE. The effect of pH was studied in BR buffer solutions over the pH range 2–12 using 1 mM ATOR. The influence of scan rate was examined in BR buffer at pH 4 within the range from 10 to 500 mV s^{-1}. DPV was used for the quantitative determination of ATOR. Unless stated otherwise, DPV measurements were performed in BR buffer at pH 4 in the potential range from 0.0 to +1.5 V. The optimized DPV parameters were as follows: modulation amplitude of 100 mV, modulation time of 10 ms and step potential of 5 mV. Calibration curves were constructed by successive addition of appropriate aliquots of the 10 μM

ATOR working solution into the electrochemical cell containing 10 mL of BR buffer at pH 4. After each addition, the solution was homogenized and the voltammogram was recorded. Each concentration was measured in triplicate. The linear concentration range, slope (sensitivity), intercept, coefficient of determination, and limit of detection were evaluated from the corresponding calibration data. The LOD was calculated as three times the standard deviation of the intercept divided by the slope of the calibration curve. The GCE was mechanically polished between individual measurements. During the optimization of DPV parameters, calibration experiments, and sample analysis, the recorded DPV signals of ATOR were baseline-corrected in NOVA 1.11 software using the moving-average tool with a window size of 2. Because the analytical signal corresponded to anodic oxidation of ATOR, the solutions were analyzed without prior deaeration.

Tablet formulations

The developed method was applied to the determination of ATOR in commercial tablet formulations. *Torvacard Novum* tablets containing 10, 20, and 40 mg of ATOR per tablet, declared as atorvastatin calcium trihydrate, were obtained from a local pharmacy. For each dosage strength, ten tablets were finely powdered and homogenized in a mortar. An accurately weighed portion of the homogeneous powder corresponding to 40 mg of ATOR was transferred into a 50 mL volumetric flask and dissolved in methanol. The suspension was sonicated for approximately 10 min to facilitate the extraction of ATOR and then diluted to volume with methanol. A working sample solution was prepared by transferring 500 µL of the tablet stock solution into a 50 mL volumetric flask and diluting to volume with methanol. For voltammetric analysis, 100 µL of this solution was added to an electrochemical cell containing 10 mL of BR buffer at pH 4. The solution was homogenized and analyzed by DPV under optimized conditions. The content of ATOR in tablets was determined by the multiple standard addition method. Three consecutive additions of 200 µL of 10 µM ATOR standard solution were made directly into the electrochemical cell. After each addition, the solution was mixed and the corresponding DPV curve was recorded. The amount of ATOR in each tablet formulation was calculated from the standard addition plot and compared with the declared content. Each tablet sample was analyzed in triplicate, and the results were expressed as mean value with the standard deviation.

RESULTS AND DISCUSSION

Electrochemical behavior of ATOR at the GCE and effect of pH

The electrochemical behavior of 1 mM ATOR at the unmodified GCE was first investigated by cyclic voltammetry in BR buffer solutions over the pH range from 2 to 12. ATOR exhibited an anodic signal in the positive potential region, while no corresponding cathodic peak was observed in the reverse scan, indicating that its oxidation at the GCE surface is irreversible. The position, intensity, and shape of the oxidation signal were substantially affected by the pH of the supporting electrolyte. The corresponding cyclic voltammograms and the dependences of peak current and peak potential on pH are shown in Fig. 1. With increasing pH of the BR buffer, the oxidation peak potential shifted progressively toward less positive values. A linear dependence between E_p and pH was obtained over the whole pH range, although the voltammograms recorded at higher pH values were increasingly affected by background current (Eq. 1):

$$E_p\ (V) = (1.153 \pm 0.029) - (0.025 \pm 0.004) \times pH,\ R^2 = 0.996 \quad (1)$$

This negative shift of E_p with increasing pH indicates that protons are involved in the electrode reaction of ATOR. For a reversible proton-coupled electrode reaction, the Nernst equation predicts a slope of approximately −0.059 m/n V per pH unit at 25 °C, where m and n correspond to the numbers of protons and electrons involved in the electrode process, respectively. Thus, a slope close to −59 mV per pH unit is expected when equal numbers of protons and electrons participate in the reaction, whereas a slope close to −30 mV per pH unit is commonly associated with an electrode process involving one proton and two electrons for a reversible system.[20,21] The experimentally obtained slope of (−25 ± 4) mV pH^{-1} is therefore substantially lower than the value expected for a 1:1 proton-to-electron process and is closer to the value expected for a process with an unequal proton-to-electron ratio.

A comparable E_p–pH dependence was previously reported for ATOR by Kamalzadeh and Shahrokhian.[15] They obtained a slope of approximately −28 mV pH^{-1} and related the oxidation process to the participation of one proton and two electrons. In their mechanistic interpretation, ATOR initially undergoes electron transfer to form a radical cation, followed by proton and electron transfer steps and subsequent hydrolysis of the oxidation product. The present results are consistent with this general interpretation, since the observed E_p–pH slope indicates proton involvement and is comparable to the value reported for ATOR oxidation at a nano-scaled polypyrrole film-modified electrode. However, because the oxidation of ATOR at the unmodified GCE is irreversible and no additional mechanistic experiments with product identification were performed in this work, the exact oxidation pathway is not assigned here. The E_p–pH relationship is therefore used mainly as evidence of proton participation and as an indication compatible with the previously suggested one-proton/two-electron character of the ATOR oxidation process rather than as definitive mechanistic proof.

The pH dependence of the voltammetric response can also be discussed in relation to the acid–base properties of ATOR. The reported pK_a value of ATOR is approximately 4.46 for its terminal carboxyl group[22], meaning that the pH region around 4–5 corresponds to the transition between the protonated carboxylic acid form and the deprotonated carboxylate form of the molecule. At pH 4, which is close to this pK_a value, both acid–base forms may contribute to the voltammetric response, while the protonated carboxylic acid form is still expected to predominate. At pH values above the pK_a, the anionic carboxylate form becomes increasingly dominant. This change in ionization state can influence the interaction of ATOR with the GCE surface, its diffusion behavior, and the kinetics of the oxidation process. Moreover, the acid–lactone equilibrium of statins is pH-dependent, and recent stability data have shown that the relative abundance of hydroxy acid and lactone forms is strongly affected by the pH of the medium.[4] The

selection of BR buffer at pH 4 is therefore reasonable not only from the viewpoint of peak current, but also because this pH provides a favorable compromise between peak definition, background current, and the acid–base state of ATOR.

The pH also had a pronounced influence on the peak current (I_p) and peak shape. After background correction, the highest anodic peak current was obtained at pH 4. In strongly acidic medium at pH 2, the oxidation signal was weaker, whereas at pH 4 a well-defined anodic peak with a favorable signal-to-background ratio was obtained. At higher pH values, the signal became broader and progressively less suitable for analytical purposes. Although the raw voltammograms recorded in alkaline media showed increasing background currents, the baseline-corrected peak current did not increase; instead, the analytical peak became less clearly resolved from the background. This behavior may be associated with changes in the ionization state of ATOR, increased contribution of background oxidation processes, and altered interfacial interactions at the GCE surface. BR buffer at pH 4, close to the reported pK_a of ATOR, provided the best compromise between peak definition and background contribution and was therefore selected for further measurements. Under these conditions, ATOR provided a well-resolved oxidation signal at approximately +1.05 V vs. Ag/AgCl/3 M KCl.

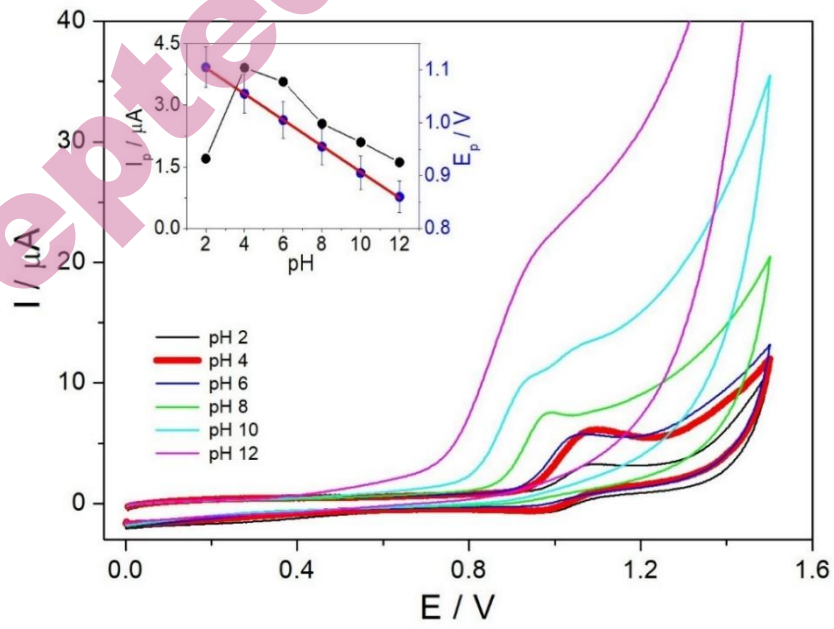

Fig. 1. Cyclic voltammograms of 1 mM ATOR at the unmodified GCE in BR buffer solutions with selected pH values in the range from 2 to 12 at a scan rate of 100 mV s^{-1}. The inset shows the dependence of the anodic peak current (I_p) and peak potential (E_p) on pH.

Effect of scan rate

The effect of scan rate (v) on the electrochemical response of ATOR was investigated by cyclic voltammetry in BR buffer at pH 4. The measurements were performed for 1 mM ATOR at scan rates ranging from 10 to 500 mV s^{-1}. With increasing scan rate, the anodic peak current increased progressively, while the peak potential shifted toward more positive values. The cyclic voltammograms recorded at different scan rates, together with the corresponding I_p vs. $v^{1/2}$ and log I_p vs. log v dependences, are presented in Fig. 2. Such a positive shift of E_p with increasing scan rate is characteristic of an irreversible electrode process, in which the peak potential depends on the kinetics of heterogeneous electron transfer and the applied time scale of the voltammetric experiment.[20] To obtain information about the mass-transfer character of the electrode process, the dependence of the anodic peak current (I_p) on the square root of the scan rate ($v^{1/2}$) was evaluated. A linear relationship was obtained over the investigated scan-rate range (Eq. 2):

$$I_p\ (\mu A) = (0.28 \pm 0.01) \times v^{1/2} + (0.76 \pm 0.08),\ R^2 = 0.995 \quad (2)$$

where v is expressed in mV s^{-1}. The proportionality between I_p and $v^{1/2}$ indicates that the oxidation of ATOR at the GCE is predominantly controlled by diffusion of the analyte from the bulk solution to the electrode surface. This conclusion was further supported by the logarithmic dependence between peak current and scan rate (Eq. 3):

$$\log I_p = (0.44 \pm 0.01) \times \log v - (5.99 \pm 0.03),\ R^2 = 0.990 \quad (3)$$

In Eq. 3, I_p is expressed in A and v in mV s^{-1}. The slope of the log I_p vs. log v plot was 0.44, which is close to the theoretical value of 0.50 expected for a diffusion-controlled voltammetric process.[20] In contrast, a slope approaching 1.0 would be expected for a process controlled mainly by adsorption of the electroactive species on the electrode surface. The slightly lower value compared with the ideal diffusion-controlled slope may reflect the irreversible nature of ATOR oxidation, minor adsorption or interfacial effects, and the increasing peak broadening observed at higher scan rates. Overall, the scan rate study confirms that the electrochemical oxidation of ATOR at the unmodified GCE in BR buffer at pH 4 proceeds predominantly as a diffusion-controlled and irreversible process.

Optimization of DPV parameters

After selecting BR buffer at pH 4 as the most suitable supporting electrolyte, DPV was employed for the quantitative determination of ATOR at the unmodified GCE. The effects of modulation amplitude and modulation time on the DPV response of ATOR were examined separately, while the remaining instrumental parameters were kept constant at the values specified below. Since the analytical signal in DPV is strongly affected by the applied pulse parameters, the modulation amplitude and modulation time (at fixed step potential of 5 mV) were optimized to obtain the highest and best-defined oxidation peak of ATOR with an acceptable

background current and peak shape. The influence of modulation amplitude was investigated in the range from 10 to 200 mV using 1 mM ATOR in BR buffer at pH 4. The modulation time was kept constant at 50 ms. The effect of modulation amplitude on the DPV response of ATOR is shown in Fig. 3. With increasing modulation amplitude from 10 to 100 mV, the oxidation peak current of ATOR progressively increased. The highest and most analytically useful response was obtained at a modulation amplitude of 100 mV. At higher amplitudes, namely 150 and 200 mV, the peak current did not further improve and the voltammetric signal became less favorable for quantitative evaluation. In addition, higher amplitudes caused peak broadening and a shift of the oxidation signal toward less positive potentials. Although high modulation amplitudes can enhance the faradaic response, they may also increase peak width and distort the peak profile, which reduces the precision of peak current evaluation. Therefore, a modulation amplitude of 100 mV was selected for further measurements.

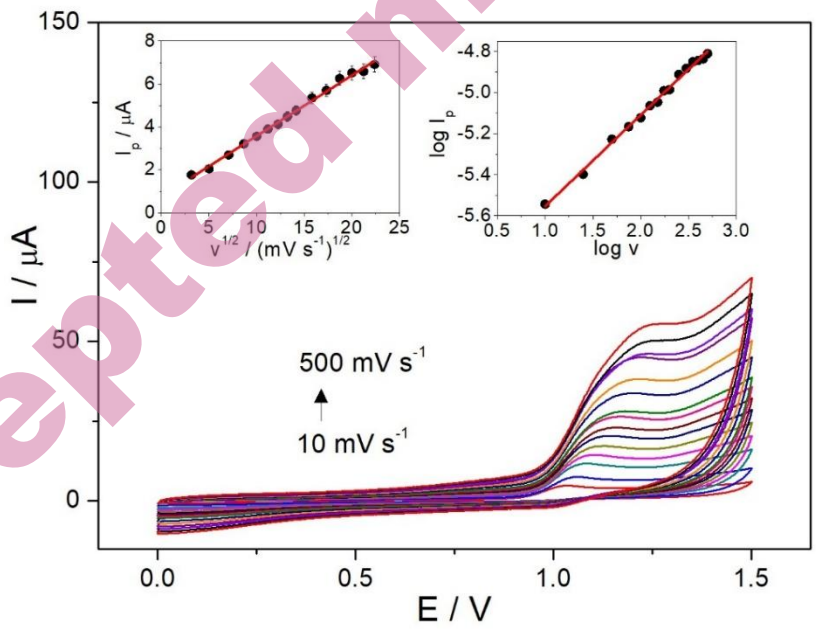

Fig. 2. Cyclic voltammograms of 1 mM ATOR at the unmodified GCE in BR buffer at pH 4 at scan rates from 10 to 500 mV s^{-1}. Insets show the dependence of the anodic peak current (I_p) on the square root of scan rate ($v^{1/2}$) and the logarithmic dependence of peak current on scan rate (log I_p vs. log v).

The effect of modulation time was examined in the range from 10 to 100 ms at fixed step potential of 5 mV. In this optimization step, the modulation amplitude was kept constant at 25 mV. The corresponding DPV curves and the dependence of peak current on modulation time are presented in Fig. 4. The highest peak

current of ATOR was obtained at a modulation time of 10 ms. Further increase in modulation time resulted in a gradual decrease in the oxidation signal. This decrease may reflect less favorable current sampling and partial depletion of ATOR near the electrode surface at longer modulation times. Based on these results, a modulation time of 10 ms was chosen as the optimal value.

Considering both optimization steps, the following DPV parameters were selected for the determination of ATOR: modulation amplitude of 100 mV, modulation time of 10 ms and step potential of 5 mV. The selected parameters represent a compromise between signal intensity, peak definition, and reproducibility of the DPV response. These optimized conditions were subsequently used for calibration measurements, repeatability testing, interference studies, and the analysis of tablet formulations.

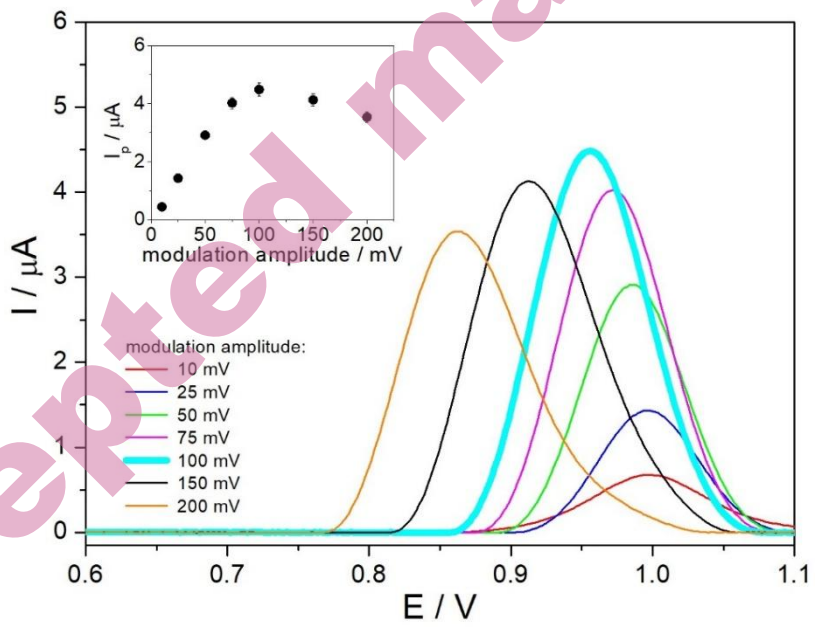

Fig. 3. DPV records of 1 mM ATOR at the unmodified GCE in BR buffer at pH 4 using different modulation amplitudes from 10 to 200 mV. The modulation time was kept constant at 50 ms. The inset shows the dependence of the anodic peak current (I_p) on modulation amplitude.

Analytical performance of the DPV method

Under the optimized experimental conditions, the analytical performance of the proposed DPV method was evaluated by constructing a concentration dependence for ATOR in BR buffer at pH 4. The measurements were carried out by successive additions of ATOR standard solution into the electrochemical cell, and the peak current of the anodic signal at approximately +1.05 V vs. Ag/AgCl/3

M KCl was used for quantitative evaluation. With increasing ATOR concentration, a proportional increase in the oxidation peak current was observed, while the peak potential changed only slightly, indicating a reproducible electrochemical response of ATOR at the mechanically renewed GCE surface. Representative DPV curves recorded for increasing ATOR concentrations and the corresponding concentration dependence are shown in Fig. 5.

The main analytical parameters of the developed DPV method are summarized in Table I. A linear response was obtained in the concentration range from 0.05 to 0.84 μM, with a coefficient of determination of 0.990. This concentration interval is relatively narrow and should not be interpreted as a broad working range for direct tablet assay. At higher ATOR concentrations, the DPV response departed from linearity under the selected experimental conditions; therefore, only the experimentally verified linear interval was used for quantitative evaluation. For tablet analysis, the sample extracts were diluted so that the ATOR concentration in the electrochemical cell was within this experimentally established range. The LOD value was found to be 13 nM. The low background current observed in BR buffer at pH 4 and the well-defined oxidation signal of ATOR contributed to the detection capability of the method.

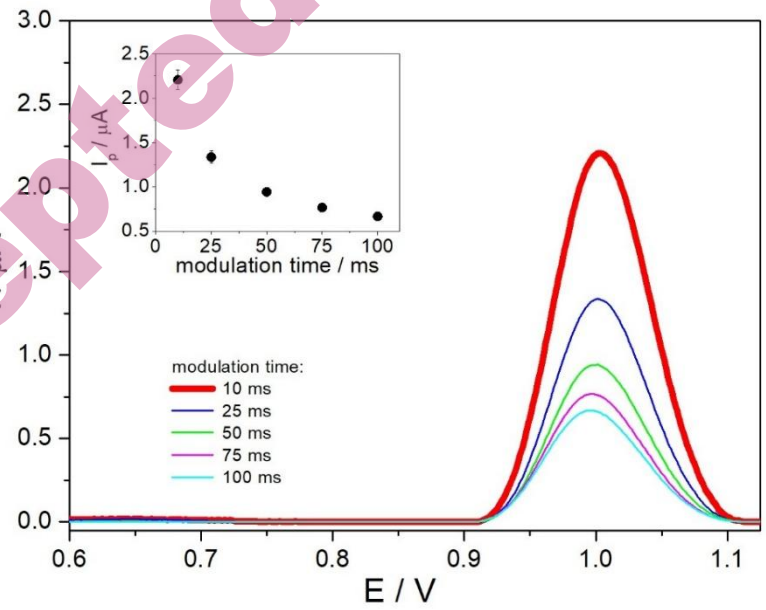

Fig. 4. DPV records of 1 mM ATOR at the unmodified GCE in BR buffer at pH 4 using different modulation times from 10 to 100 ms. The modulation amplitude and step potential were kept constant at 25 mV and 5 mV, respectively. The inset shows the dependence of the anodic peak current (I_p) on modulation time.

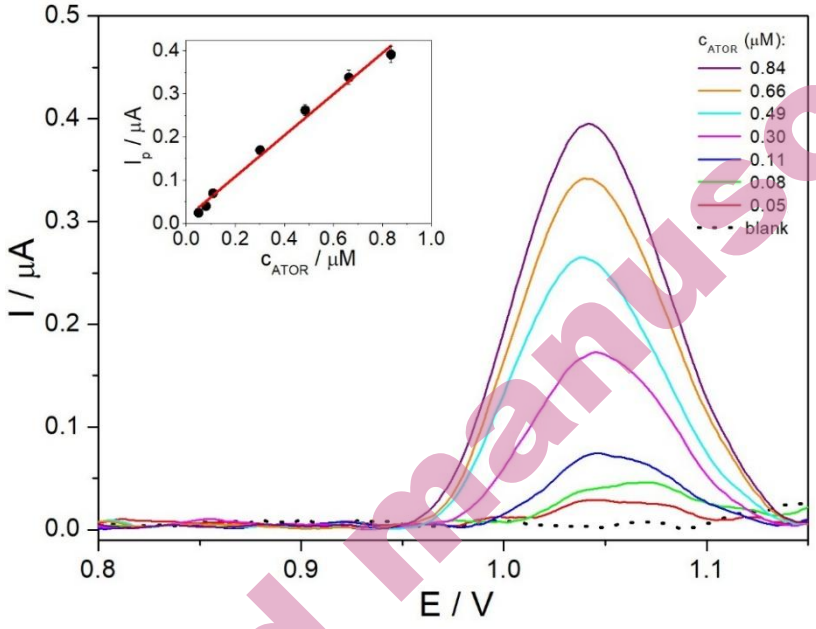

Fig. 5. DPV records for increasing concentrations of ATOR at the unmodified GCE in BR buffer at pH 4 under optimized DPV conditions. The inset shows the corresponding dependence of anodic peak current (I_p) versus ATOR concentration (c_{ATOR}). DPV parameters: modulation amplitude of 100 mV; modulation time of 10 ms; step potential of 5 mV.

TABLE I. Analytical performance for the quantification of ATOR by DPV in BR buffer solution at pH 4 using an unmodified GCE (n = 3)

Analytical parameter	Value
E_p / V vs. Ag/AgCl/3 M KCl	+1.05
Slope, µA µM^{-1}	0.474
Standard deviation of slope, µA µM^{-1}	0.018
Intercept, µA	0.015
Standard deviation of intercept, µA	0.002
Linear concentration range, µM	0.05–0.84
Coefficient of determination, R^2	0.990
LOD[a], nM	13
Repeatability[b], %	6.4

[a]Calculated as 3×$SD_{intercept}$/slope; [b]RSD calculated for 12 replicate DPV measurements at 0.11 µM ATOR

The repeatability of the DPV response was evaluated from twelve consecutive measurements of 0.11 µM ATOR under the optimized conditions. The relative standard deviation of the peak current was 6.4 %, which is acceptable for a method based on an unmodified GCE with mechanical surface renewal. Mechanical polishing with alumina suspension after each measurement was necessary to maintain the reproducibility of the electrode response and to remove possible

oxidation products or adsorbed species from the GCE surface. Although this regeneration step slightly increases the manual character of the procedure, it avoids the need for chemical modification, electrochemical activation, or nanomaterial-based electrode preparation.

The obtained analytical parameters show that the proposed DPV procedure can be applied to the determination of ATOR in tablet formulations when the sample extracts are appropriately diluted into the experimentally established linear concentration range. In addition, the method relies on an unmodified GCE and simple mechanical surface renewal, which reduces the complexity of the analytical procedure compared with approaches based on chemically modified or nanomaterial-based electrodes.

Interference study

The interference tolerance of the proposed DPV method was evaluated by investigating the influence of common tablet excipients on the oxidation signal of ATOR. Since the present method is intended for the assay of tablet formulations, the interference study was focused on compounds typically present in solid dosage forms rather than on biological interferents. The tested substances included glucose, sucrose, lactose, microcrystalline cellulose, starch, and magnesium stearate. These compounds were selected because they are frequently used as fillers, binders, disintegrants, lubricants, or sweetening agents in tablet formulations. The interference experiments were performed in BR buffer at pH 4 under the optimized DPV conditions.

A fixed concentration of 0.5 μM ATOR was used, and the tested excipients were added at ATOR-to-excipient mass ratios (*m*/*m*) of 1:1, 1:5, 1:10, 1:25, 1:50, and 1:100. The influence of each substance was evaluated by comparing the anodic peak current of ATOR recorded in the absence and presence of the potential interferent. A change in the ATOR peak current not exceeding ±5 % was considered negligible, whereas a larger deviation was interpreted as a measurable matrix effect.

For lactose, microcrystalline cellulose, starch, and magnesium stearate, the changes in the ATOR peak current remained within the predefined ±5 % tolerance limit over the investigated mass ratios. Even at the highest tested excipient excess of 1:100, the signal changes were 4.7 % for lactose, 3.4 % for microcrystalline cellulose, and below 3 % for starch and magnesium stearate. In the case of glucose and sucrose, the peak current remained practically unaffected up to the 1:50 ratio, whereas at the highest tested excess, corresponding to the 1:100 ratio, the change in the ATOR signal slightly exceeded 5 %. Glucose and sucrose did not produce additional oxidation peaks overlapping with the ATOR signal at approximately +1.05 V vs. Ag/AgCl/3 M KCl. Therefore, the observed effect at high excess is unlikely to originate from direct voltammetric interference. It is more likely related to matrix-induced changes at the electrode–solution interface or to slightly

hindered mass transport in the presence of a high saccharide excess, which may reduce the accessibility of ATOR to the GCE surface.

The absence of peak overlap is analytically important because it indicates that the tested excipients do not interfere directly at the oxidation potential of ATOR. The moderate signal change observed only for glucose and sucrose at very high excess is therefore not critical for the intended application to tablet analysis, especially because the determination of ATOR in tablet samples was performed using the standard addition method. This approach compensates for possible matrix effects and improves the reliability of quantification in the presence of excipients. Overall, the interference study supports the applicability of the developed DPV method to the determination of ATOR in tablet formulations.

Analysis of tablet formulations

The developed DPV method was applied to the determination of ATOR in commercial tablet formulations. *Torvacard Novum* tablets with three different declared contents of ATOR were selected as representative tablet samples. The tablet extracts were analyzed in BR buffer at pH 4 using the multiple standard addition method. This approach was used to compensate for possible matrix effects caused by tablet excipients and to improve the reliability of quantification in real pharmaceutical samples.

The results obtained for the analyzed tablets are summarized in Table II. The standard addition plots showed a proportional increase in the ATOR oxidation peak current after each addition of the standard solution, indicating a quantitative response in the presence of the tablet matrix under the selected experimental conditions. A representative DPV record obtained for *Torvacard Novum 10 mg* tablets using the multiple standard addition (SA) method is shown in Fig. 6. The determined ATOR contents were in good agreement with the declared values provided by the manufacturer, with the determined contents corresponding to 101.2–103.5 % of the respective label claims. Moreover, no additional voltammetric signal overlapping with the oxidation peak of ATOR was observed in the analyzed tablet samples. An independent comparison with a reference chromatographic method was not performed; therefore, the obtained results demonstrate agreement with the declared tablet contents but do not establish the trueness of the method against an independent analytical procedure. Within this limitation, these results indicate that simple dissolution, dilution, and standard addition are sufficient for ATOR assay in the tested tablet formulations. The main advantage of the procedure is that it uses an unmodified and easily renewable GCE, without requiring electrode modification, preconcentration, or complex sample preparation.

TABLE II. Analysis of *Torvacard Novum* tablets with different declared ATOR contents using the proposed method (n = 3)

Tablet formulation	Declared ATOR, mg	Found ATOR[a], mg	Recovery, %
Torvacard Novum	10	10.35 ± 0.39	103.5
	20	20.50 ± 1.81	102.5
	40	40.49 ± 2.28	101.2

[a]Results are expressed as mean ± standard deviation (n = 3)

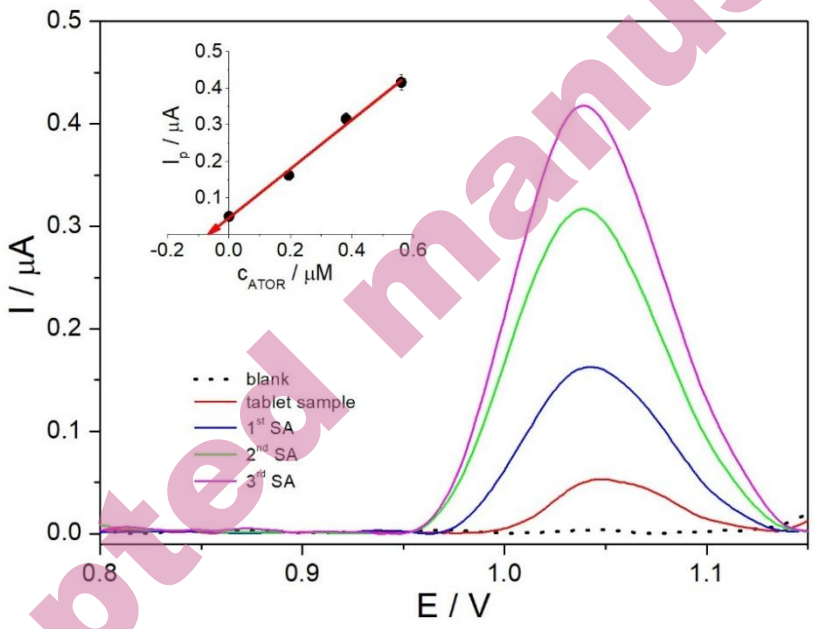

Fig. 6. DPV records for the determination of ATOR in *Torvacard Novum 10 mg* tablets using the multiple standard addition (SA) method. Measurements were performed at the unmodified GCE in BR buffer at pH 4 under optimized DPV conditions. The inset shows the corresponding standard addition plot of anodic peak current (I_p) versus ATOR concentration (c_{ATOR}). DPV parameters: modulation amplitude of 100 mV; modulation time of 10 ms; step potential of 5 mV.

Comparison with previously reported electroanalytical methods

The analytical performance of the developed DPV method was compared with previously reported electroanalytical methods for the determination of ATOR, as summarized in Table S1 in the Supplementary material. The comparison includes bare and modified GCEs, boron-doped diamond electrodes, carbon paste electrodes, screen-printed electrodes, 3D-printed electrodes, and several nanomaterial-modified sensing platforms. The main parameters considered were the working electrode, supporting electrolyte, peak potential, voltammetric technique, linear concentration range, LOD, and analyzed sample. Several published methods provide lower LOD values than the present approach,

particularly those based on adsorptive stripping procedures, accumulation steps, or nanomaterial-modified electrodes.[15,16,24,28] These platforms are analytically powerful, especially for trace-level determination or analysis of biological matrices. However, they usually require more complex electrode preparation, surface modification, accumulation procedures, or additional optimization steps.

Compared with previously reported methods based on bare GCEs[12,18], the present DPV procedure should be viewed as a complementary low-concentration protocol rather than as a substantially new electrochemical strategy. Earlier GCE-based approaches have already demonstrated the feasibility of ATOR oxidation and quantification. The present work therefore emphasizes simple mechanical renewal of the electrode surface, standard addition quantification, and applicability to diluted tablet extracts. More recent approaches based on disposable or advanced electrode platforms, such as AuNP-CNT/SPCE, MIP/SPCE, and 3D-printed graphite/polylactic acid electrodes, demonstrate the continuing interest in simple and portable ATOR sensing strategies.[17,29,30] These methods are attractive for specific applications, including environmental monitoring or high-throughput analysis, but they still require either modified disposable sensors, molecular imprinting, or 3D-printed electrode preparation. In contrast, the present method relies only on a commercially available unmodified GCE and mechanical surface renewal.

The aim of the method is not to achieve the lowest LOD, but to provide a reproducible and experimentally simple procedure for tablet assay. Its value lies in combining an unmodified, mechanically renewable GCE with straightforward DPV measurement and applicability to commercial tablets. Therefore, the method complements more complex electrode-modification approaches when the analytical task is limited to ATOR assay in tablet samples.

CONCLUSION

A simple DPV method was developed for the determination of ATOR in tablet formulations using an unmodified GCE. The electrochemical oxidation of ATOR proceeded irreversibly at approximately +1.05 V vs. Ag/AgCl/3 M KCl in BR buffer at pH 4. The effect of pH and scan rate indicated that the electrode reaction is influenced by proton participation and proceeds predominantly under diffusion-controlled conditions. BR buffer at pH 4 was selected as the optimal supporting electrolyte because it provided a well-defined oxidation signal with a favorable signal-to-background ratio. Under the optimized DPV conditions, the method showed a linear response in the submicromolar concentration range, with an LOD of 13 nM and acceptable repeatability for a mechanically renewed unmodified GCE surface. The use of simple mechanical polishing allowed reproducible renewal of the electrode surface without chemical modification, nanomaterial deposition, or electrochemical activation. The interference study confirmed that

common tablet excipients did not produce overlapping voltammetric signals at the oxidation potential of ATOR, supporting the applicability of the method to tablet analysis. The practical applicability of the method was demonstrated by the determination of ATOR in commercial *Torvacard Novum* tablets using the standard addition method. The obtained results were in good agreement with the declared tablet contents, with recoveries within the range acceptable for tablet assay. Together with the interference study, these results support the use of the method for ATOR determination in tablet formulations. Compared with more complex modified electrodes and stripping-based approaches, the proposed method does not aim to achieve the lowest possible LOD, but rather to provide a simple and experimentally robust alternative for tablet assay. Its value lies in combining an unmodified, mechanically renewable GCE with straightforward DPV measurement and standard addition quantification.

SUPPLEMENTARY MATERIAL

Additional data are available electronically at the pages of journal website: https://www.shd-pub.org.rs/index.php/JSCS/article/view/14081, or from the corresponding author on request.

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Conflict of interest. The authors declare that they have no commercial or financial relationships with the manufacturer of the analyzed tablets and no other conflicts of interest related to this work.

И З В О Д

ОДРЕЂИВАЊЕ АТОРВАСТАТИНА У ТАБЛЕТАМА МЕТОДОМ ДИФЕРЕНЦИЈАЛНЕ ПУЛСНЕ ВОЛТАМЕТРИЈЕ УЗ ПРИМЕНУ НЕМОДИФИКОВАНЕ ЕЛЕКТРОДЕ ОД СТАКЛАСТОГ УГЉЕНИКА

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Испитана је процедура одређивања аторвастатина (ATOR) у таблетама заснована на диференцијалној пулсној волтаметрији (DPV) уз употребу немодификоване електроде од стакластог угљеника. Електрохемијско понашање ATOR-а испитано је цикличном волтаметријом у Британ-Робинсоновом пуферу, при чему је за даља мерења одабрана pH вредност 4, јер је она обезбедила јасно дефинисан сигнал иреверзибилне оксидације на приближно +1,05 V у односу на електроду Ag/AgCl/3 M KCl. Испитивање утицаја брзине скенирања потврдило је да је процес оксидације претежно дифузионо контролисан. При оптимизованим условима DPV, струја анодног пика била је линеарна у опсегу концентрација ATOR-а од 0,05 до 0,84 μM. Граница детекције износила је 13 nM, а поновљивост 6,4 % за дванаест узастопних мерења раствора ATOR-а концентрације 0,11 μM.

Метода је примењена на комерцијалне таблете *Torvacard Novum* уз употребу методе стандардног додатка, при чему су добијени приноси износили од 101,2 до 103,5 %. Ова процедура је предвиђена за једноставно одређивање ниских концентрација у екстрактима таблета након одговарајућег разблаживања, без потребе за модификацијом електроде, преконцентрацијом или сложеном припремом узорка.

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