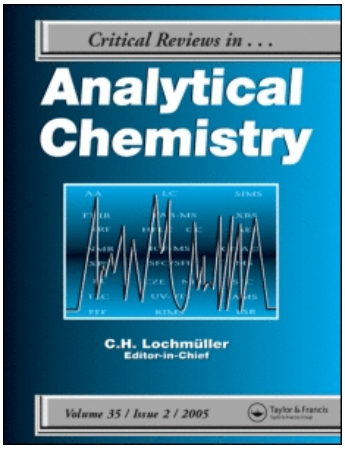

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Development of Electrochemical Methods for Determination of Atorvastatin and Analytical Application to Pharmaceutical Products and Spiked Human Plasma

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Atorvastatin is a new synthetic inhibitor of HMG-CoA reductase that has been recently and intensively prescribed as an antihyperlipoproteinemic drug. The property was exploited in developing a highly sensitive stripping voltammetric procedure for the determination of the drug. The anodic current of adsorbed compound is measured by differential pulse and Osteryoung square wave adsorptive stripping voltammetry, preceded by a period of preconcentration. The effect of various parameters such as supporting electrolyte composition, pH, initial potential, scan rate, accumulation time, and ionic strength are discussed to characterize the interfacial and redox behavior. The methods were performed in Britton-Robinson buffer, and the corresponding calibration graphs were constructed and statistical parameters evaluated. Applying the differential pulse adsorptive stripping voltammetry and Osteryoung square wave adsorptive stripping voltammetric method at pH 2.0 linearity was achieved from 3.5×10^{-8} to 4.6×10^{-7} M for square wave adsorptive stripping voltammetry with limit detection and limit quantitation of 4.0×10^{-9} M, 2.0×10^{-9} M and 1.0×10^{-8} M, 2.0×10^{-8} M, respectively. Since the proposed methods enabled lower concentrations of atorvastatin to be determined, this method was tested for atorvastatin determination in pharmaceutical products and spiked human plasma.

Keywords atorvastatin, differential pulse adsorptive stripping voltammetry, Osteryoung square wave adsorptive stripping voltammetry, pharmaceutical product, spiked human plasma

Atorvastatin, [(R-(R*,R*)]-2-(4-fluorophenyl)-β,δ,-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenyl-amino)-carbonyl]-1H-pyrrole-1-heptanoic acid, is an inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, a key enzyme in the biosynthesis of cholesterol and has clinical antihypercholesterolemic effects (1, 2). Atorvastatin is active in the administered form. This drug is absorbed from the gastrointestinal tract and undergoes extensive first-pass metabolism in the liver. Atorvastatin 98% is bound to plasma proteins. This drug is excreted mainly in feces via the bile, with a smaller proportion excreted in urine (3, 5).

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Considering that atorvastatin is a novel drug, few analytical methods for the determination of atorvastatin in pharmaceutical preparation and biological matrices relying on the use of chromatographic techniques such as liquid chromatography tandem mass spectrometry (LC/MS/MS), microbore liquid chromatography electrospray ionization tandem mass spectrometry (LC/ESI-MS/MS), and high-performance liquid chromatography (HPLC) with electrospray tandem mass spectrometry (6–13) have been described. The main problems encountered in using such methods are either the need for derivatization or the need for time-consuming extraction procedures. Since the these techniques have slightly expensive instrumentation and running costs, the use of simpler, faster, and less expensive, but still sensitive, electrochemical techniques (mainly those based on adsorptive stripping techniques) can be an interesting alternative.

Stripping voltammetry comprises a variety of electrochemical approaches, having a step of preconcentration onto the electrode surface prior to the voltammetric measurement. For the trace analysis of organic compounds that cannot be

accumulated by electrolysis, the stripping method proposed has been adsorptive stripping voltammetry. In adsorptive stripping voltammetry, the analyte is adsorbed on the working electrode by means of a nonelectrolytic process prior to the voltammetric scan. The high sensitivity of adsorptive stripping voltammetric methods makes it possible to work with very diluted samples with a corresponding decrease in possible interferences in the analysis.

To the best of my knowledge, there are no available literature data on electroanalytical investigations based on differential pulse adsorptive stripping voltammetry and Osteryoung square wave adsorptive stripping voltammetry for the determination of atorvastatin in pharmaceutical products and spiked human plasma. Furthermore, an official method for the determination of this compound in pharmaceutical dosage forms has not yet been described in any pharmacopoeia.

An investigation has been performed on the electrochemical behavior of atorvastatin at a glassy carbon electrode. The results were applied in the development of differential pulse adsorptive stripping and Osteryoung square wave adsorptive stripping voltammetric methods for determination of atorvastatin in pharmaceutical products and spiked human plasma. The voltammetric techniques data were compared with the HPLC method, according to the method referred to in the literature (13).

EXPERIMENT

Apparatus

Differential pulse adsorptive stripping, Osteryoung square wave adsorptive stripping, and cyclic voltammetry measurements were perfomed and curves were obtained using a BAS 100 W/B electrochemical analyzer. The three-electrode assembly cell consisted of a glassy carbon electrode with a diameter of 3 mm (BAS MF 2012) as the working electrode, a silver/silver chloride/saturated KCl (BAS MF 1063 type) as the reference electrode, and a platinum wire (BAS MV 1032) as an auxiliary electrode. The potentials in the text were given versus the silver/silver chloride electrode.

The HPLC system consisted of a membrane degasser, binary solvent delivery system, a Rheodyne injector equipped with a 20 μL sample loop, and a UV/Vis detector (1100 series, Agilent Technologies, New York, USA). The pH measurements were carried out with NEL model 890 pH meter digital equipped with a combined glass-calomel electrode and ultrasound generator.

Reagents and Solutions

Bulk atorvastatin drug was kindly supplied by Sanovel Pharm. Co., Istanbul, Turkey. The Atorvastatin tablets labeled as containing 20.0 mg/tablet, were purchased from the local market of Turkey. Analytical grade phosphoric acid and HPLC grade methanol, and acetonitrile were purchased from Merck Chem. Ind. (Darmstadt, Germany). All other chemicals were of analytical reagent grade and were used as received. Deionized water was obtained in the laboratory, using Milli-Q equipment.

Preparation of Solutions

Buffer Solutions

Used were 0.04 M Britton-Robinson buffer (acetic acid/boric acid/phosphoric acid), 0.2 M acetate buffer (sodium acetate-acetic acid) pH:3.2–5.2, and 0.05 M phosphate buffer solution (disodium hydrogen phosphate anhydrous salt) for voltammetric experiments. The desired pH was adjusted with concentrate solutions of NaOH or HCl.

Stock Drug Solution

Ten milligrams of atorvastatin were dissolved and diluted up to 100 mL with methanol to obtain a final concentration of 1.0×10^{-4} M atorvastatin. The stock solution was stored in brown bottles at $+4^{\circ}$C.

Working Solutions

The working solutions voltammetric investigations were prepared by dilution of the stock solution with selected 0.04 M Britton-Robinson buffer pH 2.0–10.0, 0.2 M acetate buffer (sodium acetate-acetic acid) pH:3.2–5.2, and 0.2 M phosphate buffer pH 5.3–8.3. The working solutions were prepared fresh every day. The atorvastatin solutions were stable and their concentrations did not change with time.

Pretreatment of the Working Electrode

The glassy carbon electrode was polished, at the start of the study, with aqueous slurry of 0.5 μm alumina powder on a damp silk cloth until a mirror-like finish was obtained. The accumulation of atorvastatin at the working electrode was carried for a selected time while the solution was stirred at 1,000 rpm. The stirring was then stopped, and after a 2 s rest period, a cyclic, differential pulse Osteryoung square wave stripping voltammetry, initiated in anodic direction, was performed. For electrode regeneration, the working electrode was transferred to a blank electrolyte solution and a series of cyclic scans was continued until a voltammogram corresponding to the residual current was obtained. The electrode was then ready for use in the next measurement cycle.

Analysis of Tablets

ATOR tablets were obtained in a local pharmacy. Ten ATOR tablets (amount declared of atorvastatin per tablet 20.0 mg) were placed in an agate mortar, ground, and finally the correct amount of powder was dissolved in methanol by stirring for 20 min. The excipient was separated by filtration and the residue washed three times with same solvent. The solution was transferred quantitatively into a calibrated flask and diluted to a final volume of 100 mL with same solvent; thus, a stock of 1.0×10^{-3} M was prepared. All the test solutions were obtained by diluting this stock solution with the selected supporting electrolyte. Voltammograms were recorded following the voltammetric procedure. The content of the drug in pharmaceutical products was determined referring to the regression equation.

Synthetic Samples

Excipients (cornstarch, magnesium stearate, lactose, sodium lauryl sulfate, polyethyleneglycol 6000, titanium dioxide, carboxymethylcellulose, hydroxypropylmethylcellulose, and talc) were added to the drug for recovery studies, according to the manufacturer's batch formulas for 20.0 mg atorvastatin per tablet.

Spiked Human Plasma Samples

Human plasma samples, obtained from healthy volunteers, were collected and stored frozen until the assay. A 100 μL aliquot of the human plasma sample was fortified with atorvastatin drug to achieve a final concentration of 1.0×10^{-3} M and treated with 0.2 mL methanol (as a protein precipitating agent), then the volume was completed to a 1.0 mL with human plasma. After vortexing for 30 s, the precipitated proteins were separated by centrifugation for 5 min at 5,000 rpm. The clear supernatant layer was filtrated through a 0.45 μm Millipore filter to produce a protein-free spiked human plasma, which was used as a standard solution.

RESULTS AND DISCUSSION

The optimum conditions for the determination of atorvastatin were investigated. The influence of different supporting electrolytes including Britton-Robinson buffer, acetate buffer, phosphate buffer, and 0.2 M H_2SO_4 were studied in order to obtain a reproducible current for the peak of the drug. The observed peak merges into the supporting electrolyte decay peaks for acetate buffer, 0.2 M H_2SO_4, and phosphate buffer investigated, except for Britton-Robinson buffer. It gave the highest signal owing to its low background current. The effect of different pH (between 2.0 and 10.0) on peak current were tested in Britton-Robinson buffer. The optimum pH for the determination of atorvastatin was about 2.0 as shown in Figure 1. The effect of the concentration of Britton-Robinson buffer as the supporting electrolyte (0.01, 0.02, 0.04, and 0.05 M) and also the influence of pH (2.0–10.0) were studied. The highest peak current was obtained at 0.04 M Britton-Robinson buffer at pH 2.0; this electrolyte was used throughout this study.

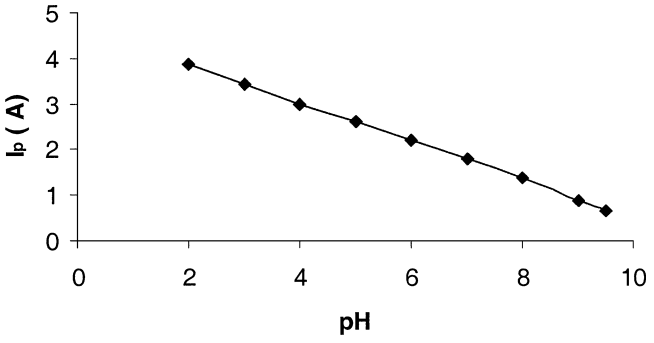

FIG. 1. Influence of pH on peak current for atorvastatin (1.2×10^{-7}) by means of differential pulse adsorptive stripping voltammetry at scan rate: scan rate 20 mV/s^{-1}, pulse amplitude 50 mV.

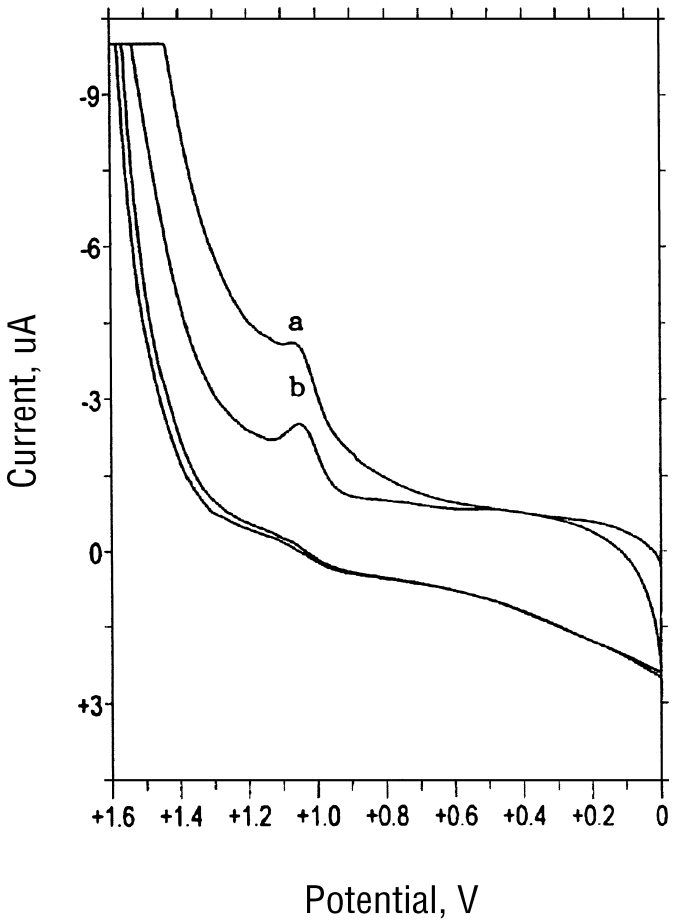

FIG. 2. Repetitive cyclic voltammograms for 1.2×10^{-7} M atorvastatin in Britton-Robinson buffer pH 2.0 at accumulation potential 0.4 V, accumulation time 20 s, and scan rate 100 mV/s^{-1}: (a) first cycle and (b) second cycle.

The cyclic voltammograms of 1.2×10^{-7} M atorvastatin at scan rate 100 mV/s^{-1} are shown in Figure 2. In Figure 2, only an oxidation peak at +1050 mV is observed, suggesting the electrode process is irreversible. The oxidative peak current of the first cycle is much higher than that of the second cycle. Two factors for the peak current decrease in the successive cyclic voltammograms are plausible. One is that the amount of atorvastatin on the glassy carbon electrode surface decreases gradually with the successive cyclic scanning. The other is that the working electrode surface is blocked by the reaction products, which may inhibit the adsorption of atorvastatin and its electron transfer with the working electrode. A study of the influence of the scan rate (ν) on stripping peak current (I_p) and peak potential (E_p) within the range 10 to 200 mV/s^{-1} was carried out. When accumulation time 20 s was applied, plotting log i_p versus log ν gave a straight line with a slope of 1.09 ($r = 0.9985$), close

to 1, which is the expected slope for an ideal reaction of surface species (14). So, in this case, the process appears to have an important adsorptive component. On the reverse scan, no cathodic peak was observed at scan rate of 10–200 mV/s^{-1}, a characteristic behavior of irreversible process. The peak potential shifted to more positive values on increasing the scan rate, which confirms the irreversibility of the oxidation process. The anodic peak may be due to the nature and position of the electrophilic substituents on the aromatic ring. A mechanism can be proposed that the redox process of atorvastatin occurs to yield dimer compounds, bonding the radical cations formed through the oxidation of the amine group.

The oxidation peak currents of 1.2×10^{-7} M atorvastatin were measured by differential pulse adsorptive stripping voltammetry after 20 s of accumulation at differential potential from 0.0 to 1.00 V. It was observed that the oxidation peak current almost remained stable, indicating that the accumulation potential did not influence the oxidation peak current of atorvastatin. The accumulation therefore was performed under open circuit. Figure 3 shows the influences of accumulation time on the oxidation peak current of 1.2×10^{-7} M atorvastatin. The oxidation peak current increases greatly at the first 20 s, and then levels off. The curved section after 20 s may be due to the fact that the adsorption of atorvastatin tends to saturation.

Differential pulse adsorptive stripping voltammetric behavior of atorvastatin at a glassy carbon electrode was examined at varying pH over a wide range of values from acidic to alkaline media (between 2.0 and 10.0). The differential pulse adsorptive stripping voltammograms obtained in Britton-Robinson buffer solutions were given. Best results were obtained in the solution of pH 2.0. To improve the sensitivity of the determination, differential pulse adsorptive stripping voltammetric conditions such as pulse amplitude, scan rate, and pulse width were investigated. It was found that the peak currents increased significantly with increasing pulse amplitude from 10 to 60 mV/s^{-1}, then improved slightly from 60 mV to 100 mV. The pulse amplitude chosen for practical determination was 60 mV. In these experiments faster scan rates resulted in higher peak currents, but background currents also increased. Taking peak current and background current into consideration, the scan rate chosen was 50 mV/s^{-1}. The effects of the atorvastatin concentration on peak current at 1004 mV were investigated. Differential pulse absorptive stripping voltammetry optimum conditions were found at pH 2.0 Britton-Robinson buffer: 9:1 v/v methanol:water; 20 mV/s^{-1} scan rate, 20 s accumulation time; 0.400 mV accumulation potential; 50 mV pulse amplitude, 17 ms sample width, 50 ms pulse width, 200 ms pulse period.

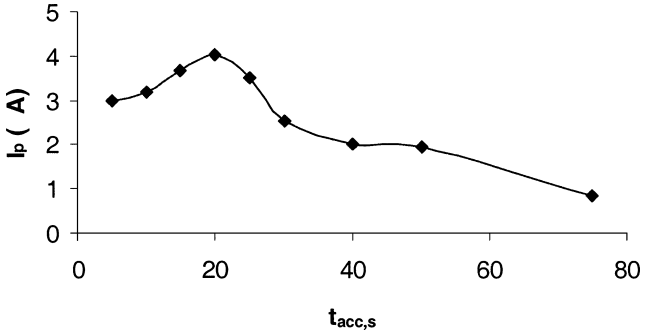

FIG. 3. Effects of accumulation time on the oxidation peak current of 6.0×10^{-6} M atorvastatin.

Osteryoung square wave adsorptive stripping voltammetric behavior of atorvastatin at a glassy carbon electrode was investigated at varying pH over a wide range of values from acidic to alkaline media (between 2.0 and 10.0). Best results were obtained in Britton-Robinson buffer of pH 2.0. Square wave voltammetry conditions were pulse amplitude 25 mV, frequency 15 Hz, accumulation time 20 s, accumulation potential 0.400 mV, potential step 4 mV. The methods were successfully applied to the pharmaceutical products and human plasma.

Analytical Applications

Based on the voltammetric behavior of atorvastatin, a quantitative method was developed. Using the optimum conditions described in the Experiment section, the relationship between the current and the concentration was found to be linear over the range 3.5×10^{-8} to 4.6×10^{-7} M for differential pulse adsorptive stripping voltammetry and 6.0×10^{-8} to 6.2×10^{-7} M for Osteryoung square wave adsorptive stripping voltammetry. The quantitative and statistic parameters obtained for the validation of the methods are collected in Table 1. The detection limit (LOD) estimated as 3 s/m was 4.0×10^{-9} M for differential pulse adsorptive stripping voltammetry and 2.0×10^{-9} for Osteryoung square wave adsorptive stripping voltammetry, with s representing the standard deviation of the peak current of the sample ($n = 5$) and m representing the slope of the calibration curve. Based on the signal-to-noise ratio of 10, the quantitation limit (LOQ) was calculated to be 1.1×10^{-8} M for differential pulse adsorptive stripping voltammetry and 2.0×10^{-8} M for Osteryoung square wave adsorptive stripping voltammetry. During the actual analysis, the analytical response was checked through the peak potential and its height. No change in peak potential was observed within an hour, while its height changed about $\pm 4\%$.

Robustness is the capacity to remain unaffected by small, but deliberate, variations in method parameters (15). The robustness of proposed methods was examined by varying the pH, the concentration of supporting electrolyte, temperature, and stability of sample solution. The results showed that none of these variables significantly affected the recovery of atorvastatin. These provided an indication of the reliability of the proposed procedures for assay of the drug, and these could be considered robust.

Precision of the methods was investigated by intra- and interday determination of atorvastatin at two different concentrations ($n = 5$) in the linear range (Table 2). Accuracy of the methods expressed as bias% for within and between days was

TABLE 1
Statistical Analysis of Calibration Curves in the Determination of Atorvastatin by Differential Pulse Adsorptive Stripping Voltammetry (DPASV) and Osteryoung Square Wave Adsorptive Stripping Voltammetry (OSWASV)

Parameters	DPASV	OSWASV
Range (M)	3.5×10^{-8}–4.6×10^{-7}	6.0×10^{-8}–6.2×10^{-7}
Limit of detection (M)	4.0×10^{-9}	2.0×10^{-9}
Limit of quantitation (M)	1.0×10^{-8}	2.0×10^{-8}
Regression equation (Y)[a]		
Slope (b)	4.53	2.31
SD on slope(S_b)	7.74×10^{-6}	1.32×10^{-6}
Intercept (a)	0.0148	0.385
SD on intercept (S_a)	2.83×10^{-5}	1.62×10^{-6}
SEE (S_e)	1.04×10^{-7}	1.65×10^{-7}
Correlation coefficient (r)	0.9995	0.9991

[a] $Y = a + bC$ where C is concentration in M and Y in peak current units for voltammetric methods.

less than 3.2% (Table 2); that indicated high precision of the proposed methods.

Specificity of the optimized procedures for assay atorvastatin was examined in presence of some common excipients in the same ratios usually used in pharmaceutical preparations (starch, lactose, glucose, sugar, talc, sodium chloride, titanium dioxide, and magnesium stearate). The mean percentage recovery of 1.2×10^{-7} M atorvastatin showed no significant excipient interference; thus the procedures were able to assay atorvastatin in the presence of excipients, and hence it can be considered specific. Besides, specificity of the proposed analytical methods was checked as its ability to specifically measure only the analyte, not the components that also may be expected in the in human plasma. In accordance with this, the blank human plasma was scanned before and after the addition of atorvastatin. Since no analytical response was obtained in the pure human plasma sample at the working potential, it might be concluded that there was no interference of the components of the human plasma matrix. This means that the method proposed shows the selectivity at the same time.

Assay of Atorvastatin in Tablets

The proposed procedures were successfully applied for the determination of atorvastatin in three batches of commercial formulations, respectively. The results presented in Table 3 are in good agreement with the labeled content. All data represent the average of ten determination.

Determination of Atorvastatin in Human Plasma Samples

The optimized differential pulse adsorptive stripping voltammetry and Osteryoung square wave adsorptive stripping voltammetry procedures were also successfully used for the determination of atorvastatin in protein-free spiked human plasma

TABLE 2
Analytical Precision and Accuracy of Atorvastatin Determination by Differential Pulse Adsorptive Stripping Voltammetry (DPASV) and Osteryoung Square Wave Adsorptive Stripping Voltammetry (OSWASV) ($n = 5$)

	Intraday				Interday			
Concentration (M)	Measured concentration (M)	*SD*	Accuracy bias%	Precision *RSD*%	Measured concentration (M)	*SD*	Accuracy bias%	Precision *RSD*%
				DPASV				
3.50×10^{-8}	3.41×10^{-8}	0.49	−3.24	1.20	3.36×10^{-8}	0.98	−3.85	1.42
4.60×10^{-7}	4.44×10^{-7}	0.78	−2.86	2.57	4.26×10^{-7}	1.63	−5.70	3.52
				OSWASV				
6.00×10^{-8}	5.98×10^{-8}	1.11	−2.84	0.98	6.16×10^{-8}	0.92	−3.35	2.47
6.20×10^{-7}	5.83×10^{-7}	1.03	−3.27	1.97	6.17×10^{-7}	1.82	−4.73	3.61

Bias% = [(Measured concentration−added concentration)/added concentration]×100; *RSD*% = relative standard deviation; *SD* = standard deviation.

TABLE 3
Comparative Studies for Atorvastatin Tablets

Drug[a]	DPASV Mean[b] ± RSD[c]	OSWASV	HPLC (13)
Batch no. 1	19.9 ± 0.45	20.3 ± 0.34	20.3 ± 0.42
Batch no. 2	20.5 ± 0.47	19.5 ± 0.46	20.1 ± 0.43
Batch no. 3	21.0 ± 0.33	19.9 ± 0.28	19.5 ± 0.45
t-test of significance[d]	0.67	0.96	

[a]ATOR tablets were labeled to contain 20.0 mg atorvastatin per tablet.

[b]Each value is the mean of 10 experiments.

[c]*RSD* = Relative standard deviation.

[d]Values in parentheses are the theoretical values at $p = 0.95$. Theoretical values at 0.95% confidence limits; $t = 2.26$.

Abbreviations: DPASV, differential pulse adsorptive stripping voltammetry, OSWASV, Osteryoung square wave adsorptive stripping voltammetry, HPCL, high-performance liquid chromatography.

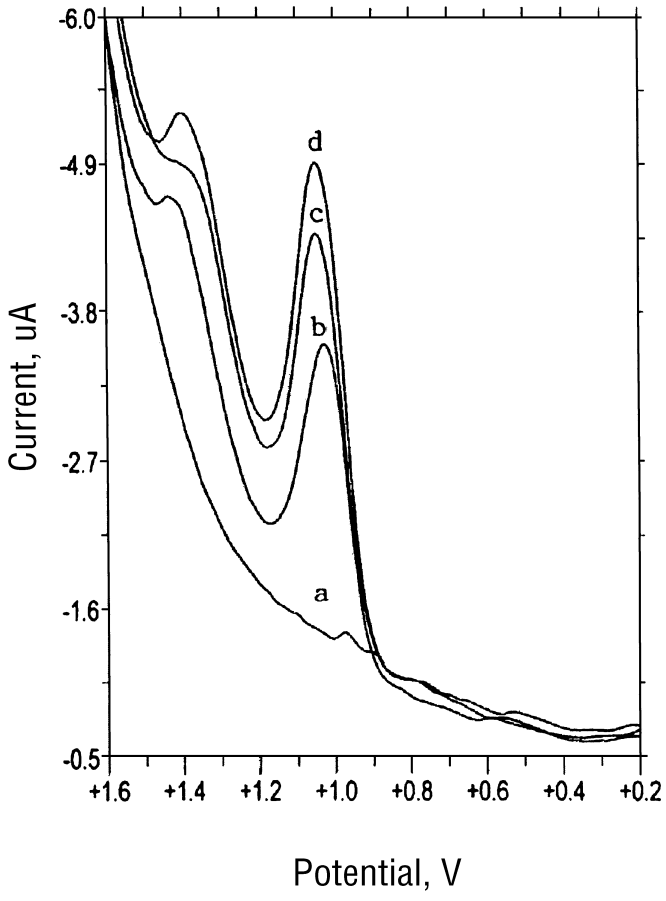

FIG. 4. Differential pulse adsorptive stripping voltammograms obtained for the determination of atorvastatin spiked to human plasma: (a) background, (b) 3.5×10^{-8} M, (c) 1.0×10^{-7} M, and (d) 4.6×10^{-7} M.

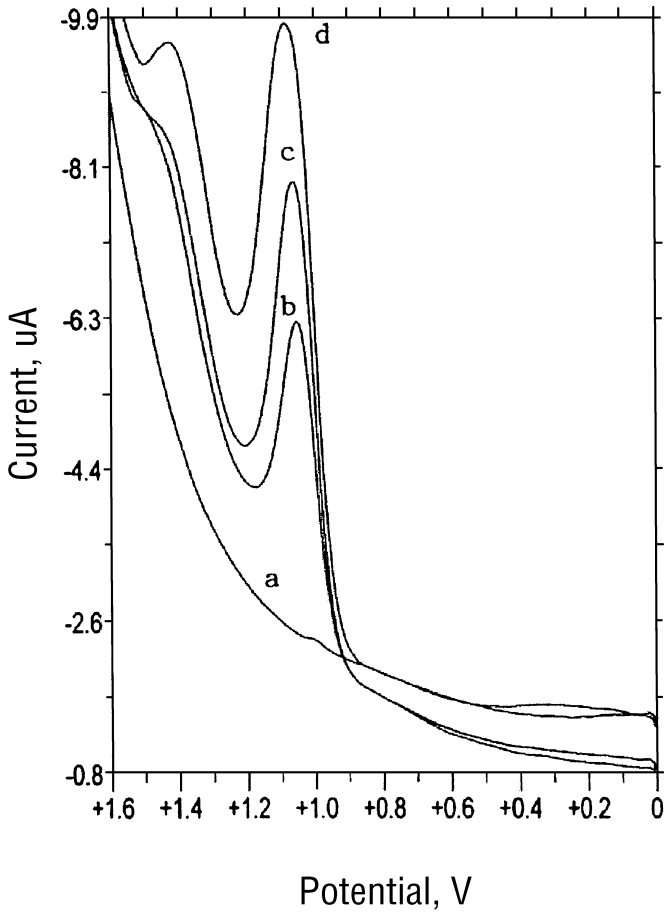

FIG. 5. Osteryoung square wave voltammograms obtained for the determination of atorvastatin spiked to human plasma: (a) background, (b) 6.0×10^{-8} M, (c) 1.2×10^{-7} M, and (d) 6.2×10^{-7} M.

(Figures 4 and 5). The generally poor selectivity of voltammetric techniques can expose difficulties in the analysis of biological fluids which contain oxidizable substances (glutathione, ascorbate, ureate, tryptophan, cycteine, and so forth). As can be seen from the figures, no oxidation of compounds present in human plasma occurs where the analytical peak appears. The determination of atorvastatin in spiked human plasma samples was carried out at three different levels of concentration: 6.2×10^{-8} M, 1.2×10^{-7} M, and 4.6×10^{-7} M for the differential pulse adsorptive stripping voltammetry and Osteryoung square wave adsorptive stripping voltammetric procedures described above. The recoveries obtained are shown in Table 4. Good recovery of atorvastatin was achieved from biological endogenous components in human plasma.

The HPLC method (13) was chosen as the analytical reference method. The proposed voltammetic techniques were compared with the HPLC method. The results obtained are summarized in Table 3. No significant differences were found between the results obtained by the HPLC method (13), the

TABLE 4
Recoveries of Atorvastatin from Spiked Human Plasma by Differential Pulse Adsorptive Voltammetry (DPASV) and Osteryoung Square Wave Adsorptive Stripping Voltammetry (OSWASV)

	Amount($x \pm SE$, $RSD\%$)[a]	
	DPASV	OSWASV
6.2×10^{-8} M	100.5 ± 1.24, 0.64%	99.9 ± 0.29, 1.02%
1.2×10^{-7} M	98.5 ± 1.08, 0.42%	$97.8.5 \pm 0.98$, 1.09%
4.6×10^{-7} M	101.1 ± 0.93, 0.82%	98.1 ± 1.04, 1.23%

[a] x, mean; *RSD*, relative standard deviation; *SE*, standard error.

voltammetric techniques, for same batch at the 95% confidence level (Student's t-test).

CONCLUSIONS

The electrochemical stripping methods developed for the quantification of the antihyperlipoproteinemic atorvastatin have proved to be a good alternative and advantageous over the reported analytical methods due to their sensitivity, rapidity, and accuracy. The good recoveries and low relative standard deviation reflect the high accuracy and precision of the described methods. On the other hand, the advantage of the proposed methods is that no prior separation procedures are required. These methods are simple, inexpensive, selective, and precise and do not require any complex pretreatment except polishing the electrode within a few minutes. The proposed methods might be preferred for the routine determination of atorvastatin in quality control laboratories.

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