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Rapid Voltammetric Identification and Determination of Simvastatin at Trace Levels in Pharmaceuticals and Biological Fluid

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Simvastatin is used as an antilipemic agent through inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A reductase. The reduction behavior of drug has been studied in different supporting electrolytes within the pH range 3–9. Based on the adsorptive character of simvastatin onto the mercury electrode surface, a new cathodic square-wave stripping voltammetry method for its direct determination at trace levels has been proposed. The voltammetric response could be used to determine drug concentration in the range 1.0×10^{-8} to 7.5×10^{-7} mol L^{-1}, with detection limit of 4.5×10^{-9} mol L^{-1}. Applicability to biological fluid analysis was illustrated. The method was successfully employed, without sample pretreatment, for quantitation of the active ingredient simvastatin in pharmaceuticals. The use of abrasive stripping voltammetry for rapid identification of this drug in pharmaceutical dosage forms using a paraffin-impregnated graphite electrode has been examined.

Keywords
simvastatin
square-wave voltammetry
abrasive stripping voltammetry
pharmaceuticals
biological fluid

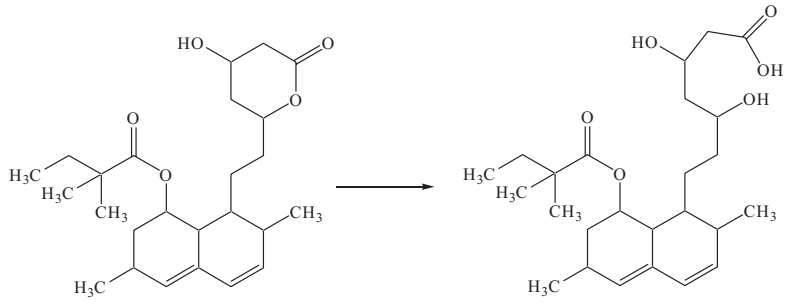
INTRODUCTION

Simvastatin belongs to a class of drugs called statins, which act by inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A reductase. This microsomal enzyme catalyzes the rate-limiting step of cholesterol biosynthesis. Also, simvastatin inhibits oxidation of native and modified low-density and high-density lipoproteins.[1] Statins are currently the most therapeutically effective drugs available for reducing LDL cholesterol and triglyceride levels in the blood stream of patients at risk of cardiovascular disease,[2] even they are now among the most frequently prescribed drugs.[3]

The chemical structure of simvastatin contains a β-hydroxy-lactone (Scheme 1). The physiologically active form of the drug is the β-hydroxy acid, which is formed by a ring-opening reaction of the lactone ring. *In vivo*, prodrug lactone form is enzymatically hydrolysed to its hydroxyl-acid pharmacophore.[4]

Developments of sensitive and selective analytical methods to the determination of drugs are highly required. Simvastatin has been determined in pharmaceutical preparations and biological fluids using several methods including, high-performance liquid chromatography combined with mass spectrometry,[5–8] fluorescence[9] or UV detection,[10] gas chromatography,[11] capillary electrophoresis[12] and UV spectroscopy.[13] However, some of these methods require expensive equipment and are time-consuming. In some cases, the methods entail an extraction

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1 **2**

Scheme 1. Molecular structures of simvastatin (**1**) and physiologically active simvastatin β-hydroxy acid form (**2**).

and derivatization procedures due to their relatively low sensitivities. Hence, a more rapid and simpler method for identification and determination of simvastatin at trace levels is highly desirable.

In a previous paper[14] we have been described the results of preliminary investigation of electrochemical properties of solid and dissolved simvastatin using cyclic and square-wave voltammetry. During the preparation of this manuscript, a paper dealing with the electrochemical determination of simvastatin appeared, but it is based on oxidation of drug at glassy carbon electrode.[15] Up to date no attempt has been made to study the adsorptive stripping voltammetric behaviour of simvastatin. In this work we extend our investigations to the development of a sensitive voltammetric method for the direct determination of this compound in bulk form, pharmaceutical formulation and human serum based on the reduction of simvastatin at a hanging mercury-drop electrode. A qualitative analysis of powders of pharmaceutical dosage forms using the abrasive stripping voltammetry has been performed.

EXPERIMENTAL

Materials and Reagents

Simvastatin, kindly supplied by Pliva (Zagreb, Croatia), was used without any purification. Stock solution (1×10^{-3} mol L^{-1}) was prepared in acetonitrile and stored at 4 °C in a refrigerator. Simvastatin and its acid form showed 1 % interconversion at 4 °C after 4 weeks.[6] Standard solutions were prepared daily by diluting the stock solution with a selected supporting electrolyte just before use.

The supporting electrolytes solutions, Britton-Robinson buffer (0.04 mol L^{-1} in each of acetic, phosphoric and boric acids) adjusted to the desired pH of 3–9 with 0.2 mol L^{-1} sodium hydroxide solution, 0.1 mol L^{-1} $Na_2B_4O_7$-KH_2PO_4 buffer (pH = 5–8) and McIlvain buffer (0.1 mol L^{-1} citric acid and 0.2 mol L^{-1} Na_2HPO_4; pH = 6–8) were used for square-wave voltammetry on the hanging mercury-drop electrode. The supporting electrolyte for abrasive stripping voltammetric measurements was prepared by adding 1 mL of 0.1 mol L^{-1} buffer solution and 0.1 mL of 0.1 % Triton-X-100 solution to 9 mL of 0.1 mol L^{-1} $NaClO_4$ solution. All the chemicals used were of analytical reagent grade quality (Aldrich or Kemika). Purified water from a Millipore Milli-Q system was used throughout the study.

Apparatus

A potentiostat Model 273 A and the SMDE in hanging mercury-drop electrode Model 303 A (both Princeton Applied Research) were used in the cyclic and square-wave voltammetry. The active area of the working mercury drop electrode was 0.026 cm^2. The Ag/AgCl (saturated KCl) served as a reference electrode and a platinum wire was used as a counter electrode. A magnetic stirrer (PAR Model 305) provided the convective mass transport during the accumulation step.

Abrasive stripping voltammetric measurements were performed by using a multimode polarograph Autolab 30 (EcoChemie, Utrecht). The working electrode was a spectral-grade paraffin-impregnated graphite rod (diameter 5 mm, length 50 mm). Its clean and carefully polished circular surface was contaminated with microparticles of simvastatin by pressing it into a small pile of substance powder on a highly glazed ceramic tile and moving it with a circular motion for about 10 s. Less than 1 mm of the graphite rod was immersed in the electrolyte only during the voltammetric measurements. The Pt wire was on auxiliary electrode and Ag/AgCl/3 mol L^{-1} KCl (Metrohm) was a reference electrode.

The pH measurements were made with a Radiometer PHM 85 pH-Meter using combined glass electrode (Radiometer PHC 2406L).

Procedure

Supporting electrolyte (10 mL) was placed in the electroanalytical cell and the required aliquot of standard simvastatin solution was added by a micropipette. The solution was deoxygenated prior to analysis by purging with purified nitrogen for 8 min with the stirrer on. The samples were blanketed with nitrogen during acquisition. After forming a new mercury drop, the square-wave voltamogram was recorded either immediately in quiescent solution or after adsorptive accumulation for a selected time at the predeter-

mined potential in stirred solution. A quiescent period of 15 s was allowed before commencing the potential scan. All measurements were carried out at the room temperature.

Analysis of Pharmaceutical Dosage Form

Statex® film-tablets, each containing 20 mg of simvastatin, were obtained from the commercial sources (Pliva). Excipients, such as lactose, microcrystalline cellulose, hydroxypropyl-methylcellulose, iron oxide and titanium dioxide, are added to dosage forms. Twenty tablets were weighed and powdered. A portion of powder equivalent to the average mass of one tablet was transferred into a 50 mL calibrated flask and 25 mL of acetonitril was added to dissolve the active material. After sonicating and shaking the mixture for 5 min, it was completed to volume with the same solvent, mixed and passed through a 0.5 μm mash filter. An aliquot of the filtrate was then transferred into a calibrated flask and a series of dilutions was made with 0.1 mol L^{-1} $Na_2B_4O_7$-KH_2PO_4 buffer at pH = 7 as supporting electrolyte, covering the working concentration range (1.0×10^{-6} to 1.0×10^{-5} mol L^{-1}). Solutions of the compound studied were subjected to voltammetric measurements as previously mentioned. For recovery experiments, known amounts of pure drug were added to the different preanalyzed samples of a commercial formulation and the mixtures were analysed by the proposed method. This step was repeated three times for determination of simvastatin by the standard addition technique.

For qualitative analysis, the surface of paraffin-impregnated graphite electrode was contaminated with microparticles of powders of simvastatin film-tablets. The voltamograms were recorded according to the above recommended procedure for simvastatin using abrasive stripping voltammetry.

Recovery Studies in Spiked Human Serum Samples

Serum samples were obtained from healthy volunteers and stored frozen until assay. A 500 μL aliquot of human serum samples was mixed with acetonitrile (1.5 mL) and with appropriate aliquot volume of simvastatin stock solution in centrifuge tube. The mixture was vortex for 5 min. After deproteination and centrifugation of the sample for 10 min at 6000 rpm the supernatant was separated. Appropriate volumes of clear supernatant solution were analysed in the voltammetric cell containing 0.1 mol L^{-1} $Na_2B_4O_7$-KH_2PO_4 buffer, pH = 7. A blank was prepared under the same conditions but without simvastatin. Measurements were obtained in the square-wave mode under the following optimized conditions: accumulation potential E_{acc} = –0.8 V; accumulation time t_{acc} = 60 s; frequency f = 500 Hz; pulse amplitude E_{SW} = 40 mV and scan increment $E_{s.inc.}$ = 2 mV.

RESULTS AND DISCUSSION

Voltammetric Behaviour of Simvastatin

The electrochemical reduction of simvastatin at the hanging mercury-drop electrode was studied by means of cyclic and square-wave voltammetry in different supporting electrolytes over a wide pH range (3–9) in Britton-Robinson, 0.1 mol L^{-1} $Na_2B_4O_7$-KH_2PO_4 and McIlvain buffers (Figure 1). Cyclic and square-wave voltamograms exhibited two peaks over the pH range 4–8. Cyclic voltammetric measurements show the reversible nature of the first reduction wave in the whole pH range investigated, while the second one is irreversible in the range of the scan rates between 100–5000 mV s^{-1}. Square-wave voltamograms of the drug contain a pair of well-defined cathodic and anodic peaks for both electrode reaction at the frequencies higher then 100 Hz. The forward and backward components of the responses indicate that the redox reactions are reversible below pH = 8.5. Such voltammetric behaviour, in agreement with our previous findings,[14] implies that the electroreduction of simvastatin proceeds via a surface EC mechanism in the whole pH range investigated.

The net peak potential of the reduction process was pH independent between pH = 3 and pH = 9 (slope of

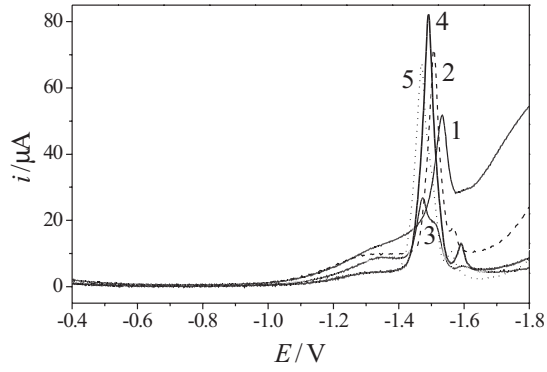


Figure 1. Influence of supporting electrolyte on simvastatin reduction: Britton-Robinson buffer pH = 3 (1), pH = 5 (2), pH = 9 (3); $Na_2B_4O_7$-KH_2PO_4 buffer pH = 7 (4) and McIlvain buffer pH = 6 (5). Conditions: $c = 1 \times 10^{-5}$ mol L^{-1}, E_{SW} = 50 mV, f = 400 Hz.

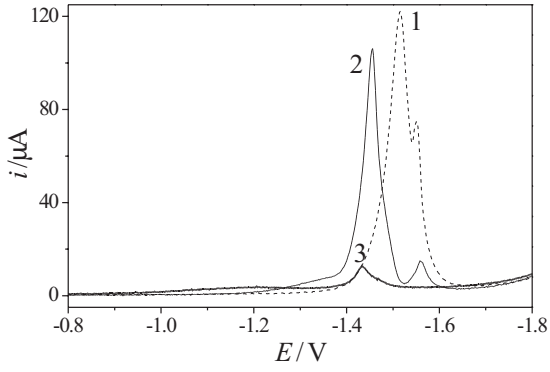


Figure 2. Dependence of peak potentials on simvastatin concentration at hanging mercury-drop electrode in 0.1 mol L^{-1} $Na_2B_4O_7$-KH_2PO_4 buffer, pH = 7; $c = 1 \times 10^{-4}$ (1), 1×10^{-5} (2) and 1×10^{-6} mol L^{-1} (3).

7.7 mV/pH) indicating that the protons are involved after the rate determination step, followed by the chemical reaction yielding the final product. Net square-wave voltammetric response of simvastatin is shifted towards more negative values by increasing the concentration of analytes (Figure 2) such as observed in the electroreduction of pravastatin.[16] The linear relationship between the peak potentials and the logarithm of simvastatin concentration with the slope of $\Delta E_p / \Delta \log c = -41$ mV indicates also that the reduction of the drug is followed by a chemical reaction. Pravastatin is administered to patients in its active hydroxyl acid form and the voltammetric response of pravastatin is related to reduction of its ester group in the side chain. However, simvastatin is lactone which can be converted to the corresponding hydroxyl acid form in alkaline condition. The effect of pH values in the pH range 3–9 on the reduction peak of simvastatin showed that the peak current increased gradually upon increasing the pH values from 3 to 6, and than remained nearly unchanged from 6.5 to 8. However, a sharp decrease in the current response upon increasing the pH values from 8 to 9 was observed. On the other hand, within the pH range 5–8 the peak current decays over time. Sample solution recorded after 24 h showed appreciable change in cathodic peak current. Simvastatin is in the prodrug lactone form in the solution used. Interconversion of β-hydroxy-lactone to the β-hydroxy acid is pH-dependent. The dependence of the voltammetric response on the pH values indicates that the degree of ring-opening increased with the pH values increasing from 8 to 9 to result in the peak current decrease. Samples stored in refrigerator for up to 24 h showed decreasing concentration of simvastatin lactone form over time, pointing to the hydrolysis of lactone to β-hydroxy acid form in aqueous media. Therefore, it could be concluded that the reduction of simvastatin on the mercury electrode occurred at the carbonyl group on the lactone ring.

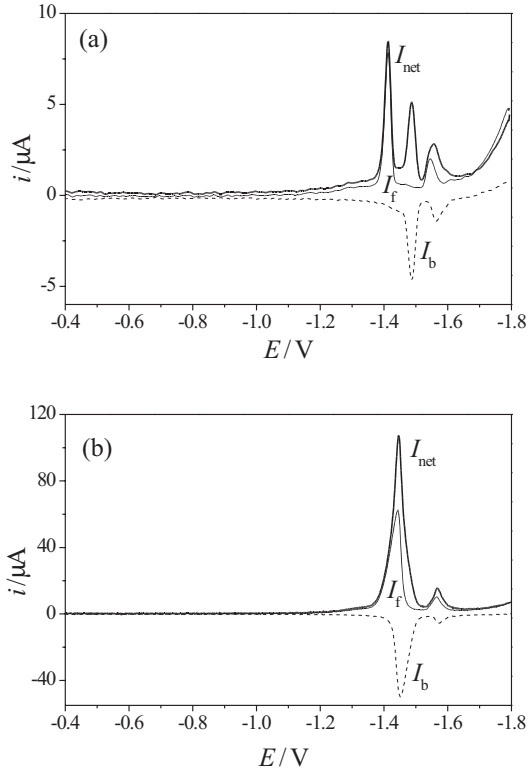


Figure 3. The effect of the square-wave frequency on the shape of the voltammetric response of 1×10^{-5} mol L^{-1} simvastatin solutions; frequencies are 100 Hz (a) and 400 Hz (b), $E_{SW} = 50$ mV. Net response (I_{net}) and its forward (I_f) and backward (I_b) components.

The first peak current was considered for the present analytical investigations owing to its high signal relative to that of the second one. Considering both the reduction current and the peak shape, 0.1 mol L^{-1} $Na_2B_4O_7$-KH_2PO_4 buffer pH = 7 was chosen in all subsequent analytical studies.

A corresponding analysis in square-wave voltammetry was undertaken by varying the frequency and amplitude of the signal. To obtain a much more sensitive peak current for analytical studies, the square-wave frequency and amplitude were changed between 50 and 900 Hz, and from 10 to 120 mV, respectively. At the frequencies lower than 300 Hz, the first response splits into two peaks (Figure 3). The separation of the peaks of the split response is proportional to the square-wave amplitude. The response of this type of reaction is the highest when the charge transfer rate is synchronized with the frequency of the square-wave signal. The sensitivity of the electroanalytical technique depends primarily on the kinetics of the redox reaction. As regards the change of capacitive currents, the best signal-to-noise ratio was obtained with the frequency of 500 Hz which was selected for analytical application. The best peak definition was recorded when using 40 mV pulse amplitude and 2 mV scan increment.

Application to the Trace Analysis

Electroanalytical procedures based on simvastatin reduction were developed, involving square-wave and adsorptive stripping square-wave voltammetry for quantitative determination of the drug at low levels. Since the reduction of simvastatin on mercury electrode is a surface redox reaction,[14] spontaneous adsorption of drug can be used as an effective preconcentration step before voltammetric measurement (Figure 4). It is necessary to select the variable affecting the adsorptive process. Different square-wave voltamograms with increasing accumulation times (between 0 s and 90 s) were recorded for solutions containing simvastatin at various concentration levels (5×10^{-7} and 1×10^{-7} mol L^{-1}). The peak current increased up to a maximum at 90 s and then remained constant suggesting saturation of the surface coverage of adsorbed simvastatin. The value of 60 s was found as the opti-

mum accumulation time because it provided the largest peak current in the linearity range. The influence of accumulation potential on the stripping peak current was evaluated from –0.2 to –1.0 V. A maximum was observed at –0.8 V, so this deposition potential was selected in all subsequent studies.

When all parameters that can affect simvastatin quantification had been studied, variation of the peak current with the bulk drug concentration was performed. In the case of a square-wave scan without any accumulation step, the reduction peak was linearly proportional to simvastatin concentration in the range of 1×10^{-6} to 1×10^{-5} mol L^{-1}. By using drug accumulation at the hanging mercury-drop electrode prior to square-wave voltammetric measurement, higher sensitivities can be readily achieved. The relation between the stripping peak current and concentration was found to be linear over the range 1×10^{-8} to 7.5×10^{-7} mol L^{-1}. The analytical characteristics and the related validation parameters of both methods are given in Table I. The limits of detection and quantification of both procedures were calculated from the calibration curves as 3 *s* / *m* and 10 *s* / *m*, respectively, where *s* is the standard deviation of the intercept and *m* is the slope of the calibration curve.[17] These values confirmed the sensitivity of the proposed methods for drug determination.

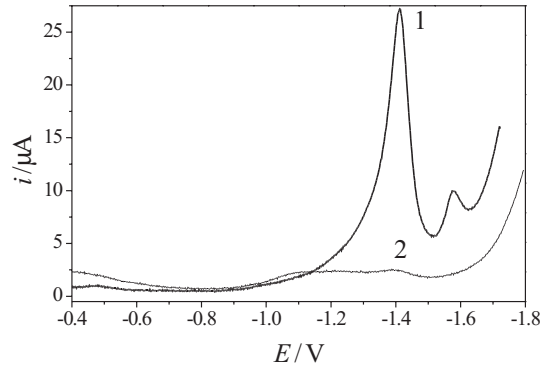


Figure 4. Square-wave voltamograms of simvastatin at hanging mercury-drop electrode after preconcentration time of 60 s (1) and without preconcentration (2). Conditions: $c = 7.5 \times 10^{-7}$ mol L^{-1}, $E_{acc} = -0.8$ V, $E_{SW} = 40$ mV, $f = 500$ Hz.

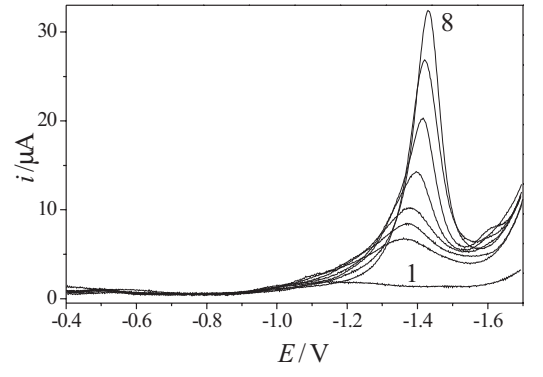


Figure 5. Stripping square-wave voltamograms in human serum samples: background (1) and different concentration of simvastatin over the range 5×10^{-8} to 7.5×10^{-7} mol L^{-1} (2–8). Accumulation time, 60 s; other conditions are the same as in Figure 4.

TABLE I. Analytical parameters of the calibration graph in the simvastatin determination by square-wave and adsorptive stripping square-wave voltammetry

Parameter	SWV	AdSWV
Linearity range / mol L^{-1}	1.0×10^{-6} to 1.0×10^{-5}	1.0×10^{-8} to 7.5×10^{-7}
Slope of calibration plot / μA mol^{-1} L	1.33×10^{7}	2.94×10^{7}
Intercept / μA	1.076	0.786
Correlation coefficient	0.999	0.999
$S_{y/x}$	1.955	0.079
S_a	0.279	0.119
S_b	1.549	0.045
Limit of detection / mol L^{-1}	3.5×10^{-7}	4.5×10^{-9}
Limit of quantitation / mol L^{-1}	1.1×10^{-6}	1.5×10^{-8}

In this study, square-wave voltammetry was proposed as an alternative method for drug quantitation, since applying the wave form allowed very rapid determination. The quantification limit is of the same order as for some chromatographic methods reported previously[8] and is better than for capillary electrophoresis,[12] UV spectrophotometry[13] and HPLC with UV detection[10] that is official method in assay procedures of simvastatin listed in European Pharmacopoeia[18] and its pharmaceutical product described in USP.[19] The detection limit is approximately two orders of magnitude better than the value reported for voltammetry based on the electrooxidation of the drug.[15]

The precision was evaluated by repeating seven independent measurements of 5×10^{-7} and 1×10^{-6} mol L^{-1} simvastatin solutions. Relative standard deviation ranged from 0.8 to 1.6 %. To evaluate the repeatability and reproducibility of the electrode response, analysis of standard simvastatin at three concentration levels of the calibration curve was tested by performing five experiments on the same day using the same analyte standard solution and over four consecutive days using different standard solutions. Mean recoveries of (99.5 ± 0.7) and (99.0 ± 1.2) %, square-wave, (98.4 ± 0.9) and (98.2 ± 1.4) %, adsorptive stripping square-wave voltammetry, were achieved by intra-day and inter-day determinations of simvastatin, respectively. The recovery results obtained indicate both the good precision of the proposed procedures and the stability of the solutions for the study period.

To check the applicability of the proposed method, a commercial film-tablet containing simvastatin was analyzed. Due to the high concentration of active ingredient in its dosage form (20 mg of simvastatin per tablet), the tablets assay was carried out directly by means of cathodic square-wave voltammetric technique. The simvastatin content in commercially available tablets was determined by estimating the recoveries at five different concentration levels using the corresponding calibration equation. Application of the square-wave voltammetric method to the determination of active ingredient in a pharmaceutical formulation, after a simple dilution step, resulted in acceptable deviation from the stated concentration. Recoveries of the drug from this type of matrix ranged from 98.2 to 99.9 % with relative standard deviations ranging from 1.6 to 2.5 %. To determine whether the excipients used in the dosage forms interfered with the current peak of interest, recovery experiments were carried out by the standard addition method. Each recovery was calculated by comparing the results obtained before and after addition. The mean concentration obtained was 19.85 mg per tablet with the relative standard deviation of 1.8 %, indicating adequate accuracy and precision of the proposed analysis procedures. Comparison of simvastatin recoveries obtained using the calibration curve and the standard addition method revealed that excipients did not interfere with the analysis. Moreover, the slope ratio between the slope of the standard calibration graph and the slope of the line obtained by standard additions of known quantities of pure drug to the pre-analyzed solution of formulations, and multiplied by 100, was 100.6 %. New developed method can therefore be used as a selective method that is very precise, rapid and inexpensive. The proposed voltammetric method might be applied as an alternative to more used HPLC or UV spectroscopic technique for formulation screening, release and dissolution testing of simvastatin in the solid dosage form.

The possibility of applying adsorptive stripping square-wave voltammetric procedures for the trace analysis of simvastatin in biological fluid was also tested (Figure 5). For determination of simvastatin in spiked serum samples three replicate samples containing three different levels of drug were processed. The mean recovery of 97.9±1.0 was achieved from this type of matrix. The proposed adsorptive stripping voltammetry is simpler, faster and required less expensive equipment than the known methods for simvastatin analysis in biological fluids and can be applied to the direct determination of drug in human serum samples. Using the proposed procedures, no sample pre-treatment was required, other than precipitation of the serum proteins with acetonitrile and a dilution step with the selected supporting electrolyte. The peak current of the first peak considered for the analytical purposes has been ascribed to reduction of carbonyl group on lactone ring of simvastatin prodrug. The degree of hydrolysis of lactone prodrug increased with the pH values increasing to result in the peak current decrease (Figure 6). Therefore, the voltammetric procedure shows the possibility of monitoring the interconversion of simvastatin to physiologically active simvastatin β-hydroxy acid form.

Electrooxidation of immobilized crystals of simvastatin at paraffin-impregnated graphite electrode has been discussed in our previous work.[14] Solid microparticles of the drug, mechanically immobilized on the surface of the paraffin impregnated graphite electrode, were oxidized in totally irreversible electrode reaction involving the β-hydroxyl group in lactone ring which is also an active site in the enzymatic β-oxidation of simvastatin.[20] Method for a quick detection of simvastatin has been developed using the abrasive stripping voltammetry. The voltammetric response of simvastatin was used for its rapid identification in pharmaceuticals (Figure 7). Net peak potential of the square-wave response of drug in bulk form is 1.107 V. The peak potential of simvastatin microparticles in film-tablet is 1.119 V. A qualitative analysis of powders

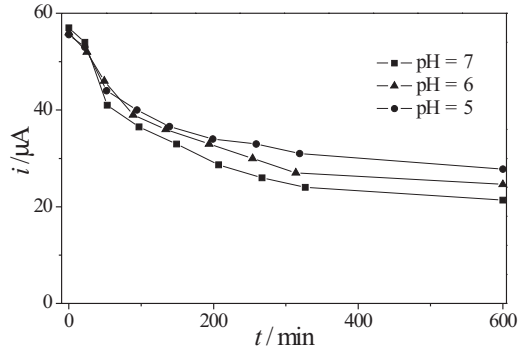


Figure 6. Stability profile of simvastatin prodrug lactone form as measured by square-wave voltammetry at different pH values of $Na_2B_4O_7$-KH_2PO_4 buffer. Conditions: $c = 4 \times 10^{-6}$ mol L^{-1}, $E_{SW} = 40$ mV, $f = 500$ Hz.

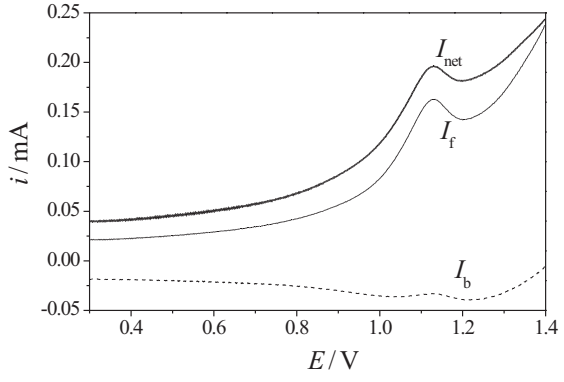


Figure 7. Square-wave voltammetric detection of simvastatin in pharmaceutical formulation on paraffin-impregnated graphite electrode. Frequency is 150 Hz, amplitude is 50 mV.

of pharmaceutical dosage forms revealed that the excipients present in tablet do not interfere with simvastatin detection.

CONCLUSIONS

A square-wave voltammetric procedure of sufficient sensitivity has been established and successfully applied to direct determination of the drug in a pharmaceutical formulation without interference from excipients. Rapid identification of active ingredient in dosage form using abrasive stripping voltammetry has been developed. Also, the adsorption process of simvastatin occurring on the mercury electrode surface can be used as an effective preconcentration step for drug determination at the trace level in human serum samples. Moreover, the voltammetric procedure could be applied for monitoring the interconversion of simvastatin to physiologically active simvastatin β-hydroxy acid form because the cathodic peak current considered for the analytical purposes has been ascribed to reduction of carbonyl group in lactone ring of simvastatin prodrug.

REFERENCES

1. G. Sobal and H. Sinzinger, *Biochem. Pharmacol*. **70** (2005) 1185–1191.
2. E. M. Balk, R. H. Karas, H. S. Jordan, B. Kupelnick, P. Chew, and J. Lau, *Am. J. Med*. **117** (2004) 775–790.
3. D. W. Kaufmann, J. P. Kelly, L. Rosenberg, T. E. Anderson, and A. A. Michell, *J. Am. Med. Assoc*. **287** (2002) 337–344.
4. A. T. Serajuddin, S. A. Ranadive, and E. M. Mahoney, *J. Pharm. Sci*. **80** (1991) 830–834.
5. A. Y. Yang, L. Sun, D. G. Musson, and J. J. Zhao, *J. Pharm. Biomed. Anal*. **38** (2005) 521–527.
6. X. S. Miao and C. D. Metcalfe, *J. Chromatogr.*, *A* **998** (2003) 133–141.
7. H. Yang, Y. Feng, and Y. Luan, *J. Chromatogr.*, *B* **785** (2003) 369–375.
8. S. Erturk, A. Onal, and S. M. Cetin, *J. Chromatogr.*, *B* **793** (2003) 193–205.
9. H. Ochiai, N. Uchiyama, K. Imagaki, S. Hata, and T. Kamei, *J. Chromatogr., B* **694** (1997) 211–217.
10. G. Carlucci, P. Mazzeo, L. Biordi, and M. Bologna, *J. Pharm. Biomed. Anal*. **10** (1992) 693–607.
11. T. Takano, S. Abe, and S. Hata, *Biomed. Environ. Mass Spectrom*. **19** (1990) 577–581.
12. M. K. Srinivasu, A. N. Raju, and G. O. Reddy, *J. Pharm. Biomed. Anal*. **29** (2002) 715–721.
13. L. Wang and M. Asgharnejad, *J. Pharm. Biomed. Anal*. **21** (2000) 1243–1248.
14. Š. Komorsky-Lovrić and B. Nigović, *J. Electroanal. Chem*. **593** (2006) 125–130.
15. O. Coruh and S. A. Ozkan, *Pharmazie* **61** (2006) 285–290.
16. B. Nigović, *Anal. Bioanal. Chem*. **384** (2006) 431–437.
17. J. C. Miller and J. N. Miller, *Statistics for Analytical Chemistry*, 4th ed., EllisHorwood, New York, 2002.
18. *European Pharmacopoeia*, 5th ed., Council of Europe, Strasbourg, 2004, pp 2413.
19. *The United States Pharmacopoeia*, 29 rd rev., USP Convention Inc., 2005.
20. T. Prueksaritanont, B. Ma, X. J. Fang, R. Subramanian, J. Yu, and J. H. Lin, *Drug Metab. Dispos*. **9** (2001) 1251–1255.

SAŽETAK

Brza identifikacija i određivanje tragova simvastatina u farmaceuticima i biološkoj tekućini

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Simvastatin je antihiperlipemik koji inhibira enzim 3-hidroksi-3-metilglutaril-koenzim A reduktazu. Istraživana je redukcija lijeka u različitim elektrolitima u rasponu pH 3–9. Na temelju adsorptivnog ponašanja na površini živine elektrode predložena je metoda za izravno određivanje tragova simvastatina korištenjem katodne pravokutnovalne voltametrije s adsorptivnom akumulacijom. Voltametrijski odaziv je linearna funkcija koncentracija lijeka u rasponu od $1{,}0 \times 10^{-8}$ do $7{,}5 \times 10^{-7}$ mol L^{-1}, s granicom detekcije od $4{,}5 \times 10^{-9}$ mol L^{-1}. Opisana je primjena metode za određivanje lijeka u biološkoj tekućini. Metoda je uspješno korištena za određivanje aktivne tvari u farmaceuticima bez prethodne obrade uzorka. Ispitana je primjena abrazivne voltametrije za brzu potvrdu identiteta lijeka u farmaceutskim dozirnim oblicima uporabom parafinom impregnirane grafitne elektrode.