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Determination of Fluvastatin Sodium by Differential Pulse Voltammetry

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Abstract: To establish method for the determination of fluvastatin sodium in *Loscol capsule*, the electrochemical behavior of fluvastatin sodium on a glassy carbon electrode was investigated by cyclic voltammetry, linear sweep voltammetry and differential pulse voltammetry. It was found that fluvastatin sodium would give a sensitive oxidation peak at +0. 64 V in the HAc-NaAc buffer solution (pH 5.10) under the Differential Pulse Voltammetric (DPV) mode. The peak current was linear with the concentration of fluvastatin sodium in the range of 2.0~40 mg L^{-1}. Based on which, a DPV method for determination of fluvastatin sodium with the detection limit of 0.24 mg L^{-1} has been developed. The proposed method has been used for determination of fluvastatin sodium in the Loscol capsule, the recovery was found to be in the range of 98.0~101.2%. The mechanism for this electrochemical reaction at the glassy carbon electrode was also discussed in this study. The electrochemical analysis method described here enables simple and rapid determination of fluvastatin sodium in real samples.

Key words: Fluvastatin sodium, electrochemistry, glassy carbon electrode

INTRODUCTION

Loscol (fluvastatin sodium), is a water-soluble cholesterol lowering agent which acts through the inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. Fluvastatin sodium is [R*, S*-(E)]-(±)-7-[3-(4-fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl]-3,5-dihydroxy -6-heptenoic acid (Fig. 1), monosodium salt. The empirical formula of fluvastatin sodium is $C_{24}H_{25}FNO_4Na$ and its molecular weight is 433.46. This molecular entity is the first entirely synthetic HMG-CoA reductase inhibitor, and is in part structurally distinct from the fungal derivatives of this therapeutic class. It is available by prescription only for the reduction of cholesterol levels. Specifically, Lescol is indicated for the use as an adjunct to diet to reduce elevated total cholesterol (total-C), LDL-C, TG, and Apo B levels and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia (Frederickson Type IIa and IIb) whose response to dietary restriction of saturated fat and cholesterol and other nonpharmacological measures has not been adequate and to slow the progression of coronary atherosclerosis in patients with coronary heart disease as part of a treatment strategy to lower total and LDL cholesterol to target levels (From FDA Label).

Sporadic publications on the identification of fluvastatin sodium by Spectrophotometric method (Erk, 2002), gas chromatography (Leis and Windischhofer, 2005), HPLC (Akinori *et al*., 2001) and electrochemical analysis method (Sibel and Benji, 2002) have appeared in the literature. In this work reported here the utility of electrochemical analysis method using glass carbon electrode as working electrode for the determination of fluvastatin sodium in HAc-NaAc buffer solution (pH5.10) for the first time. A sensitive differential pulse voltammetric peak of fluvastatin sodium at glass carbon electrode at about +0.64 V (vs Ag/AgCl) is found. The electrochemical behavior and reaction mechanism of this system have been studied by cyclic voltammetry, linear sweep voltammetry and differential pulse voltammetry. There is a good linear relationship between the peak current and the concentration of fluvastatin sodium in the range of 2.0~40 mg L^{-1}. The detection limit of the method is 0.24 mg L^{-1}. The electrochemical analysis method described here enables simple and rapid determination of fluvastatin sodium in real samples. The concentration of fluvastatin sodium in Loscol. capsule has been determined with recovery range 98.0~101.2% by this method.

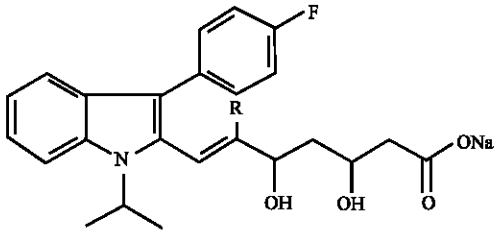

Fig. 1: Chemical structure of fluvastatin sodium

MATERIALS AND METHODS

Apparatus and Reagents: All measurements were carried out with a Model CHI832 multifunction voltammetric analyzer system (Shanghai Chenhua Electroanalysis Instruments Corporation, China). A glass carbon electrode with area 0.785 mm^2 was used as working electrode. An Ag/AgCl was used as a reference electrode together with a platinum wire as the counter-electrode. The pH measurements were carried out with a 25 pHS-2C model acidity meter (Leici Instrumental Factory, Shanghai, China), using a combination electrode. The electrolytic cell was a 50 mL beaker. A SRD-1 Model magnetic stirrer and a stirring bar (2.5 cm in length) provided the convective transport during the pre-concentration. All experiments were performed at room temperature, and dissolved oxygen was removed form the solutions by bubbling oxygen-free nitrogen through the cell for 10 min.

Fluvastatin sodium was obtained from Sigma and was used without further purification. A solution of 1.0×10^{-3} mol L^{-1} fluvastatin sodium was prepared by dissolving fluvastatin sodium in twice-distilled water. All of the chemicals were of reagent grade (Merck, Darmstadt). Twice-distilled deionized water served as a solvent.

Procedure: To evaluate the concentration of fluvastatin sodium, the standard curve method was used in the experiment. Transfer of the stock solution needed for assay into a 50 mL standard flask, followed by the addition 10.0 mL 1.0 mol L^{-1} HAc-NaAc buffer solution (pH5.10) and made up to volume with distilled water. The solution was transferred into the electrolytic cell, then the pre-concentration step was performed in a stirred (ca. 500 rev min^{-1}) solution for 120 sec. During this period, the glass carbon electrode was held at 0.40 V. The stirring was then stopped and after 10 seconds the voltamperogram was recorded by applying the Differential Pulse Voltammetry (DPV) from 0.40 to 0.8 V and measured the peak height at about +0.64 V.

RESULTS

Regression line and detection limit: Under the optimum conditions and over a concentration range of 2.0~40 mg L^{-1} for fluvastatin sodium, the DPV peak height varied linearly with concentration of fluvastatin sodium, and the equation of the regression line obtained was expressed as $i_p(\mu A) = 3.9232\times c(mg\ L^{-1})+3.4875$ (n = 6, R^2 = 0.992), the detection limit was 0.24 mg L^{-1} (S/N = 3).

Analysis of real sample: Dissolved the sample fluvastatin sodium tablets, which was purchased from market and nominal 0.04 g per tablet, in the water and diluted to the volume 20 mL. Transferred of the solution needed for assayed into the electrolytic cell, the concentration of fluvastatin sodium was determined using the method of standard additions according to the voltammetric method described above, and the results were shown in Table 1.

Table 1: Determination results of fluvastatin sodium in the Loscol capsule

No. of sample	Nominal (mg^{-1})	Determined (mg^{-1})	Added (mg^{-1})	Total (mg^{-1})	Recovery (%)
05037	40	40.8	20.0	60.4	98.0
			40.0	80.4	99.0
			60.0	101.5	101.2

DISCUSSION

Selection of the experimental conditions

Buffer solution: The pH value and the type of buffer were important parameters that greatly influence the voltammetric behaviors of fluvastatin sodium. In order to achieve the maximum sensitivity of the fluvastatin sodium, different supporting electrolytes such as hydrochloric acid, potassium chloride solution, sodium hydroxide solution, Britton-Robinson buffer solution, HAc-NaAc buffer solution and ammonia/ammonium chloride buffer solution, were compared and the results showed that there was a oxidation peak in neutral or acid solution. The voltammetric response of this experimental system was also affected by the concentration of the supporting electrolyte. A containing 0.20 mol L^{-1} HAc-NaAc buffer solution was found to be best and was used in the further experiments.

The voltrammograms of fluvastatin sodium were well defined and the sensitivity was reasonably high (Fig. 2) in 0.20 mol L^{-1} HAc-NaAc buffer solution.

Initial scan potential: the When the initial potential less than 0.40 V, the peak height decreased with the decreasing potential. Within the chosen range of 0.30 V to 0.50 V, the peak height kept stable, so 0.40 V was chosen as the initial potential. There was no effective affection on the peak height of the concentration of fluvastatin sodium when it was above 80 mg L^{-1}.

Pre-concentration time: The peak height increased with the pre-concentration time firstly, but reached stable after pre-concentration at 0.40 V for 120 sec if the concentration less than 80 mg L^{-1}, so pre-concentration for 120 sec and quite for 10 sec were selected in all these experiments.

Effects of interfering species: The effects of several types of interfering species on the determination of 5.0 mg L^{-1} fluvastatin sodium were examined. The relative error range was below ±5% in the presence of 1000 fold sodium chloride, ammonium chloride, oxalic acid, citrate

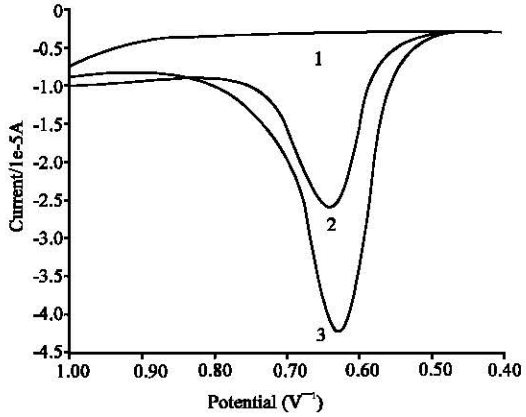

Fig. 2: Differential pulse voltammograms of fluvastatin sodium. 1) 0.1 mol L^{-1} HAc-NaAc (pH5.10), 2) 6.0 mg L^{-1} fluvastatin sodium +0.1 mol L^{-1} HAc-NaAc (pH5.10) and 3) 10.0 mg L^{-1} fluvastatin sodium +0.1 mol L^{-1} HAc-NaAc (pH5.10)

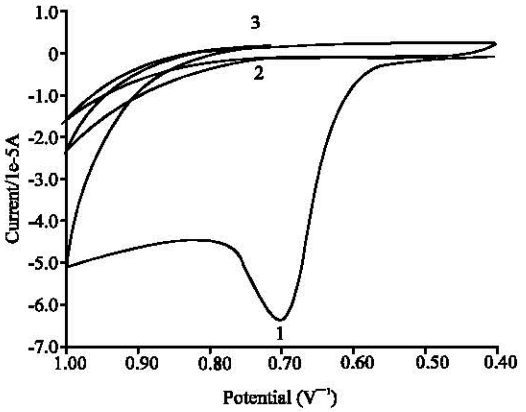

Fig. 3: Cyclic voltammogram of fluvastatin sodium, 10.0 mg L^{-1} fluvastatin sodium +0.1 mol L^{-1} HAc-NaAc (pH5.10), 1) first scan, 2) sec scan and 3) third scan

acid, tartaric acid, glucose, starch, or 100 fold histidine, glycine, glutamic acid, proline and 50 foldmethionine, tryptophan.

Mechanism of the electrochemical reaction

Repetitive cyclic voltammetry: The typical repetitive cyclic voltammetric curves were shown in Fig. 3. An oxidation peak was observed in ~+0.71 V and the oxidation peak in the first scan after an accumulation time of 120 sec which was much longer than in the second scan. No peak was observed in the catholic branch, indicating irreversibility of the oxidation.

Effect of the deposition time: The effect of the deposition time on the oxidation peak height of linear scan voltammetry was examined. The peak height increased with the adsorption time in the form of the adsorption isotherm. At relatively longer adsorption times, an equilibrium surface concentration was reached and the peak height became almost constant. Pre-concentration time of 120 sec the peak height, which varied linearly with concentration of the investigated compound, showed the process was diffusion controlled (Zhen and Hongyan, 1997).

CONCLUSIONS

The utility of electrochemical analysis method using glass carbon electrode as working electrode for the determination of fluvastatin sodium was reported for the first time. In the medium of HAc-NaAc buffer solution (pH5.10), a sensitive differential pulse voltammetric peak of fluvastatin sodium at glass carbon electrode at about +0.64 V (vs Ag/AgCl) is found. There is a good linear relationship between the peak current and the concentration of fluvastatin sodium in the range of 2.0~40 mg L^{-1}. The detection limit of the method is 0.24 mg L^{-1}. The electrochemical analysis method described here enables simple and rapid determination of fluvastatin sodium in real samples. The concentration of fluvastatin sodium in capsules has been determined with good results by this method.

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