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Electrochemical behavior of valsartan and its determination in capsules

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ABSTRACT

Electrochemical behavior of valsartan has been carried out in Britton–Robinson (B–R) buffer solution at pH 7.0 at the mercury film electrode (MFE) by cyclic, linear sweep, differential-pulse and square-wave voltammetry. The property of valsartan adsorption at the MFE using accumulation potential of +0.10 V was observed. The effects of experimental parameters on electrochemical process at the MFE were discussed. Differential-pulse adsorptive stripping and square-wave adsorptive stripping voltammetry for the valsartan determination were proposed, linearity was found in the range of 6.0×10^{-8} to 4.0×10^{-6} mol/L. The detection limits were 2.93×10^{-9} and 3.27×10^{-9} mol/L, respectively. The proposed methods were also applied to the commercial valsartan with good recoveries.

1. Introduction

Valsartan, *N*-valeryl-*N*[[2-(1H-tetrazol-5-yl)biphenyl-4-yl] methyl]valine (Scheme 1), is a new antihypertensive drug belonging to the family of angiotensin II receptor antagonists acting at the ATI receptor, which mediates all known effects of angiotensin II on the cardiovascular system [1]. Its empirical formula is $C_{24}H_{29}N_5O_3$ and its molecular weight is 435.5. Valsartan is widely used in the treatment of hypertension [2]. The drug in unchanged form shows strong pharmacological activity with high affinity for the ATI receptor. Valsartan is metabolized only to a small extent (ca. 10%) and even its most abundant metabolite (M1) possesses negligible affinity for the ATI receptor (1/200 that of valsartan). In order to understand the relationship between exposure and receptor response, an analytical method for unchanged valsartan with high accuracy is of great importance.

There have been few reports for the determination of the drug in biological media or in pharmaceutical dosage forms including liquid chromatography–tandem mass spectrometry [2], high performance liquid chromatography (HPLC) with a fluorescence detector (FP) [3,4] and spectrophotometry [5].

So far, there are no electrochemical methods for the estimation of valsartan, either in pharmaceutical dosage forms and bulk form or in biological fluids have been reported.

Electroanalytical techniques, especially modern pulse techniques, such as differential-pulse and square-wave have been used for determination of a wide range of pharmaceuticals and biological media [6–10]. Voltammetric techniques are most suitable to investigate the redox properties of drugs. This can give insights into its metabolic fate or their in vivo redox process or pharmaceutical activity [11–13].

To determinate trace amounts of analytes in biological samples and in pharmaceuticals is highly desired. In order to eliminate the effects of interfering components and to enrich the analytes of interest, sample pretreatment is necessary in most case. Adsorptive stripping voltammetry has been demonstrated to be a useful technique for the study and determination of many molecules of biological importance [14]. The high sensitivity of adsorptive stripping methods is obviously their greatest advantage. If the sample contains interesting compounds that are electrochemically active but are not adsorbed on the electrode surface then classical separation procedures are not necessary. Another advantage is the possibility of working with high diluted samples with a consequent decrease in interferences in pharmaceutical analysis.

The main objective of this work is the development of simple, rapid, and selective stripping voltammetric methods for the determination of valsartan and applying it to the pharmaceuticals. There are no sample preparation and time-consuming extraction steps other than centrifugation for the determination of valsartan in capsule dosage form by the proposed differential-pulse adsorptive stripping and square-wave adsorptive stripping voltammetric methods. The obtained results by the proposed methods have been compared with the labeled values of the commercial oral

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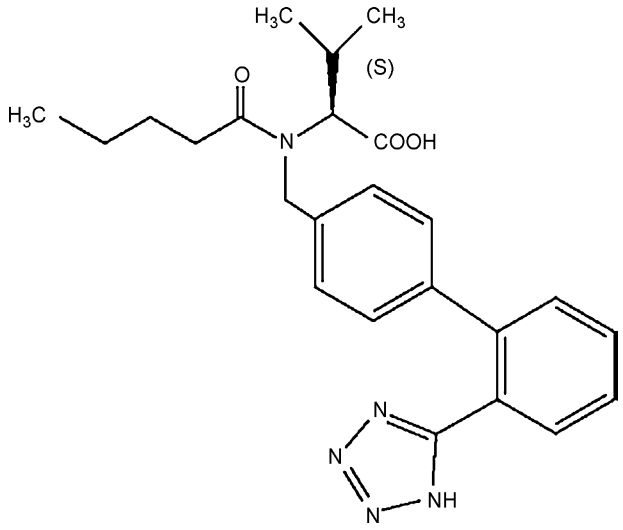

Scheme 1. Structure of valsartan.

contraceptives, and the proposed methods yield accurate, fast and reproducible results in capsule dosage.

2. Experimental

2.1. Apparatus

All measurements were carried out with a Model CHI832 multifunction voltammetric analyzer system (Shanghai Chenhua Electroanalysis Instruments Corporation, China). A mercury film electrode (MFE) using a Ag substrate with area 0.024 cm^2 was used as working electrode. Mercury films were deposited from solutions 1×10^{-3} mol/L Hg(II) and 0.1 mol/L $HClO_4$ at −0.5 V *vs.* SCE. Film thickness was calculated from the charge consumed during deposition and also from the current on stripping the film into 1.0 mol/L KSCN. A saturated calomel electrode (SCE) 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.

2.2. Reagents

Valsartan was obtained from Sigma and was used without further purification. All other chemicals were of analytical grade quality (Merck or Sigma) and used as received. Distilled deionized water was used throughout the experiments.

Valsartan stock solutions were prepared daily by direct dissolving a known amount of the chemically pure product in a specific volume of Methanol. The solutions under voltammetric investigations were prepared by dilution of the stock solution in the presence of methanol (25%). Britton–Robinson (B–R) buffer was brought to a constant ionic strength of 0.5 mol/L by the addition of $NaNO_3$ and adjusted to the desired pH.

2.3. Procedure

For voltammetric investigation, 2.5 mL of the B–R buffer solution and/or the valsartan stock solution needed for assayed were transferred into a 10.00 mL electrolytic cell, make up to volume with distilled water, and purged with oxygen-free nitrogen for 10 min. Pre-concentration was then achieved at a potential of +0.1 V for a giving time period, while the solution was stirred at 500 rpm. The stirring was then stopped and after 10 s the voltammogram was recorded by applying the differential-pulse and square-wave voltammetry from +0.10 to −0.90 V (*vs.* SCE), and the data was recorded at room temperature (approximately 25 °C).

Differential-pulse voltammetry conditions were: pulse amplitude, 50 mV; pulse width 50 ms; step potential of 4 mV and pulse period 0.2 s and square-wave voltammetry conditions were: square-wave potential (SW amplitude) E_{sw} = 25 mV, step potential of 4 mV, and square-wave frequency f = 25 Hz.

2.4. Pharmaceutical preparation

The average mass of seven capsules was determined. The capsule contents were emptied as completely as possible. An adequate amount of this powder, corresponding to a stock solution of concentration 1.0×10^{-4} mol/L was weighed, transferred into a 50-mL calibrated flask and completed to the volume with methanol. The resulting mixture was sonicated for 10 min to ensure that valsartan was dissolved completely. Appropriate solutions were prepared by taking suitable aliquots of the clear supernatant liquor and diluting with B–R solution. Differential-pulse and square-wave voltammograms were recorded as in pure valsartan.

2.5. Recovery experiments

To study the accuracy, reproducibility, precision and to check the interference from excipients used in the formulation of the above methods, recovery experiments were carried out. In order to know whether the excipients show any interference with the analysis, known amounts of the pure drug were added to pre-analyzed formulations of valsartan and the mixtures were analyzed by the proposed methods. The recoveries were calculated for both methods.

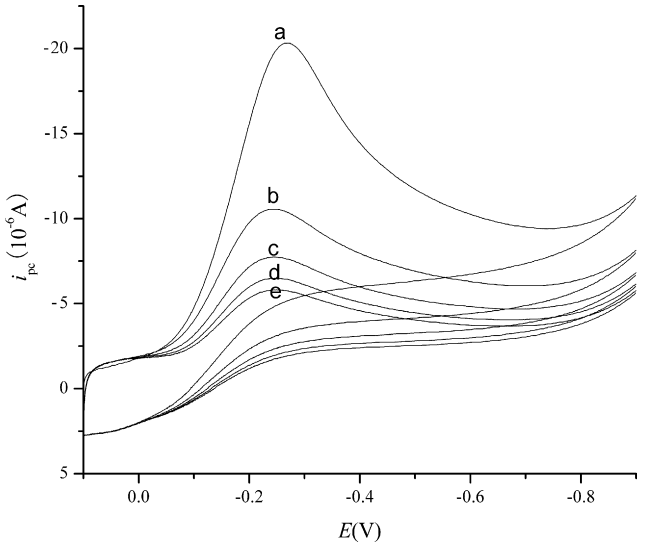

Fig. 1. Repetitive cyclic voltammograms obtained from a 2.0×10^{-6} mol/L solution of valsartan after accumulation 30 s in Britton–Robinson buffer at pH 7.0. Scan rate: 100 mV/s. Curve "a", first scan; curve "b", second scan; curve "c", third scan; curve "d", fourth scan and curve "e", fifth scan.

3. Results and discussion

3.1. Electrochemical behavior of valsartan

No previous electrochemical data were available concerning the redox mechanism of valsartan. Therefore, several measurements with different electrochemical techniques (cyclic, linear sweep, differential-pulse and square-wave voltammetry) were performed using B–R buffer as supporting electrolyte in order to obtain such information.

The voltammetric behavior of Valsartan at MFE was influenced by the characterizations of supporting electrolyte. Various supporting electrolytes, such as HOAc–NaOAc, KH_2PO_4–K_2HPO_4 and a B–R buffer solution, were tested. It was found that B–R buffer solution (pH 7.0) resulted in the highest signal.

The nature of the electrochemical process was studied by cyclic voltammetry (CV). Fig. 1 shows cyclic voltammograms obtained for repetitive cycle from a 2.0×10^{-6} mol/L solution of valsartan after accumulation 30 s in Britton–Robinson buffer at pH 7.0. One well-defined reduction peak was present at about +0.30 V and no anodic peak was observed, which indicated a certain degree of irreversibility [15]. Subsequent scans exhibit a dramatic decrease of the peak current to a stable value representing the response of the solution species. This is an obvious indication that valsartan has an adsorption characteristic at the MFE.

The effects of potential scan rate on linear sweep voltammograms were shown in Fig. 2A. The peak current of adsorbed valsartan (i_{pc}) increases linearly with scan rate from 5 to 100 mV/s. The corresponding plot of $\log i_{pc}$ *vs.* $\log \nu$ has a slop of 0.939 (Fig. 2B), which is in close proximity to 1.0, the value expected for an ideal reaction of surface species. A 72-mV negative shift in the peak potential was observed upon increasing the scan rate from 5 to 100 mV/s [16].

Fig. 3 shows plots of cathodic peak current i_{pc} (μA) of a linear sweep voltammetry *vs.* the accumulation time t_{acc} (s) for four different concentrations of valsartan. The longer the accumulation time, the more valsartan is adsorbed and the larger is the peak current. As the accumulation time increases, the peak current tends to level off, showing that adsorptive equilibrium is established. The larger is the concentration, the shorter is the time to reach equilibrium. As indicated from Fig. 3, it seems to be more probable that a full surface coverage is attained at 1.0×10^{-6} mol/L valsartan after a period of 30 s. The depression of the peak current for an accumulation period greater than 30 s can be explained in terms of a possible repulsion interaction of the polar molecules of valsartan in the adsorbed state, once full surface coverage of the electrode has been reached.

A marked increase in sensitivity results from stirring the solution during the pre-concentration step. For example, stirring of 8.0×10^{-7} mol/L valsartan at 500 rpm for 30 s resulted in a 3-fold current enhancement compared with quiescent solution. The dependence of the stripping peak current on the accumulation potential was examined over the range +0.10 to −0.10 V. Valsartan exhibits strong adsorption of comparable magnitude over the entire range. A potential of +0.10 V values was chosen for all subsequent analysis.

The application of the differential-pulse and square-wave modes yielded voltammograms in which the peak currents were greater than those obtained by cyclic and linear sweep voltammetry. As can be seen in Fig. 4, significant responses were obtained for differential-pulse and square-wave voltammetry after only 30 s of accumulation time for an assayed concentration of 8.0×10^{-7} mol/L of valsartan. The peak potential versus pH plots were similar to that

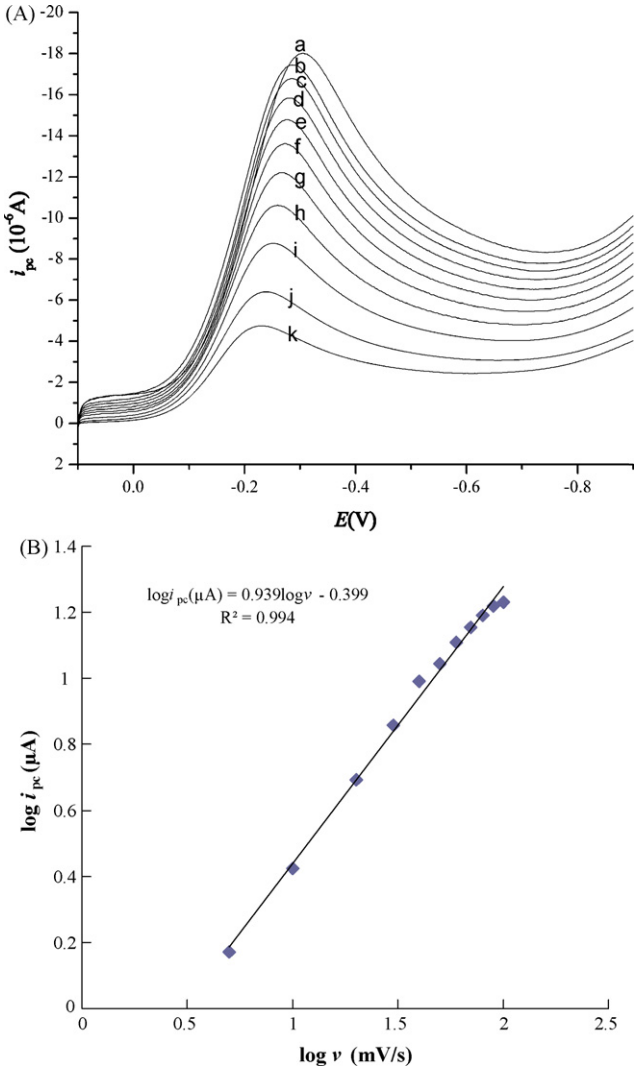

Fig. 2. Linear sweep voltammograms (A) obtained from a 2.0×10^{-6} mol/L solution of valsartan after accumulation 30 s in Britton–Robinson buffer at pH 7.0. Scan rate: curve "a", 100 mV/s; curve "b", 90 mV/s; curve "c", 80 mV/s; curve "d", 70 mV/s; curve "e", 60 mV/s; curve "f", 50 mV/s; curve "g", 40 mV/s; curve "h", 30 mV/s; curve "i", 20 mV/s; curve "j", 10 mV/s; curve "k", 5 mV/s. (B) Plot of $\log i_{pc}$ *vs.* $\log \nu$.

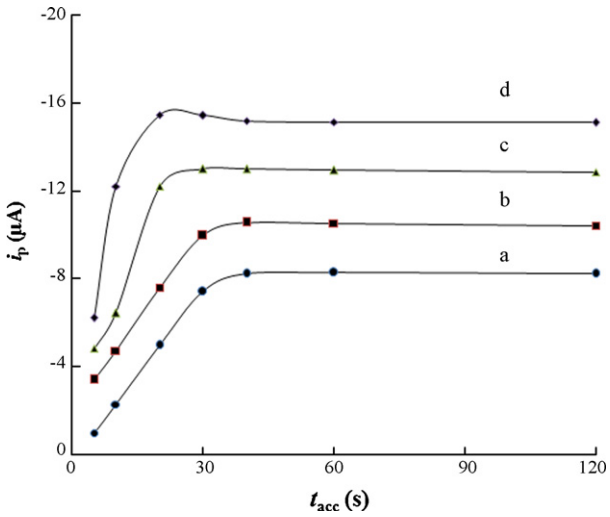

Fig. 3. Effect of accumulation time on the stripping cathodic peak current for 6.0×10^{-7} mol/L (a), 8.0×10^{-7} mol/L (b), 1.0×10^{-6} mol/L (c) and 1.2×10^{-6} mol/L (d) valsartan. Other conditions as in Fig. 2.

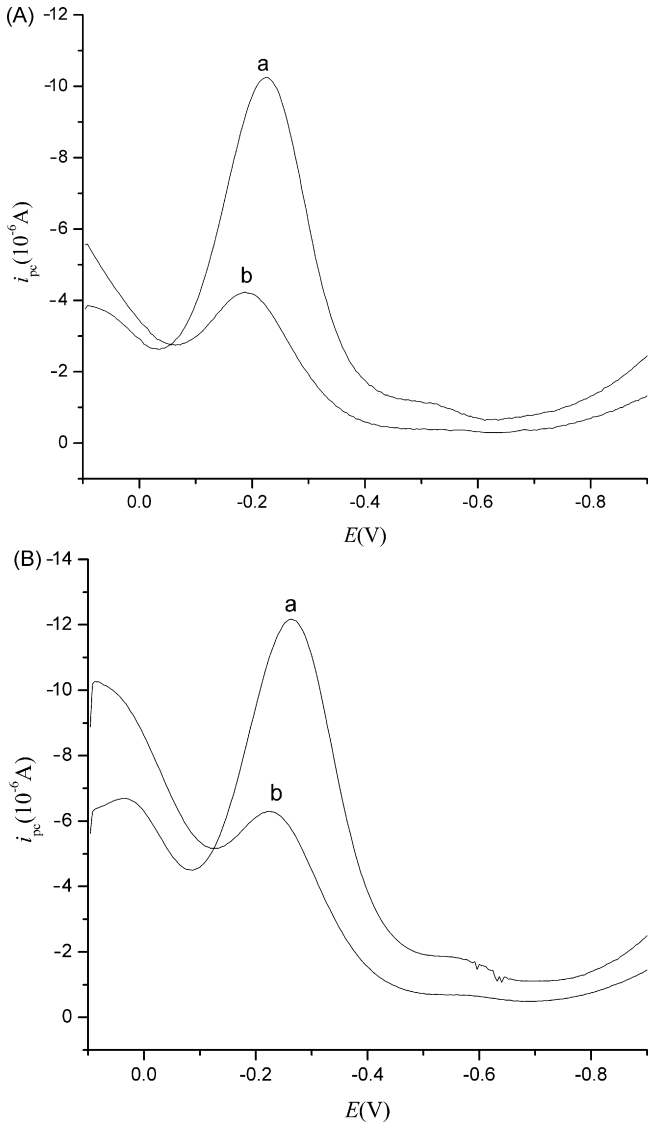

Fig. 4. Differential-pulse adsorptive stripping voltammograms (A) and square-wave adsorptive stripping voltammograms (B) obtained from a 8.0×10^{-7} mol/L solution of valsartan in Britton–Robinson buffer at pH 7.0. Curve "a" corresponds to the voltammogram after 30 s accumulation time and curve "b" corresponds to the voltammogram after 2 s accumulation time. Experimental conditions for differential-pulse adsorptive stripping voltammetry: accumulation potential E_{acc} = 0.1 V (*vs.* SCE), differential-pulse potential (DP amplitude) E_{dp} = 50 mV, step potential of 4 mV, pulse period 0.2 s and pulse width 0.05 s; Experimental conditions for square-wave adsorptive stripping voltammetry: accumulation potential E_{acc} = 0.1 V (*vs.* SCE), square-wave potential (SW amplitude) E_{sw} = 25 mV, step potential of 4 mV, and square-wave frequency f = 25 Hz.

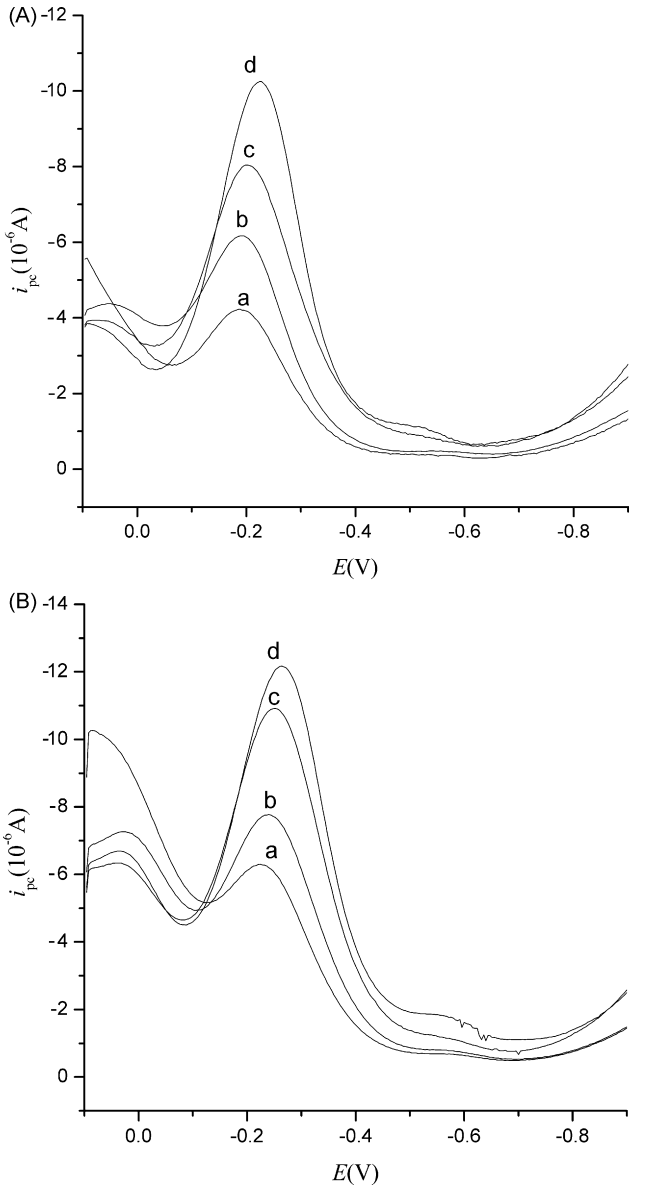

Fig. 5. Differential-pulse adsorptive stripping voltammograms (A) and square-wave adsorptive stripping voltammograms (B) in Britton–Robinson buffer at pH 7.0 after 30s of accumulation for 2.0×10^{-7} mol/L (a), 4.0×10^{-7} mol/L (b), 6.0×10^{-7} mol/L (c) and 8.0×10^{-7} mol/L (d) valsartan. Other conditions as in Fig. 4.

obtained by cyclic voltammetry for differential-pulse and square-wave voltammetric techniques.

3.2. Analytical application

The quantitative evaluation was based on the dependence of the peak current on valsartan concentration. The peak currents increased linearly with increasing amounts of valsartan by differential-pulse and square-wave voltammetry (Fig. 5A and B).

Under the optimal experimental parameters described in Section 2, linear calibration plots were obtained for valsartan in the range of 6.0×10^{-8} to 4.0×10^{-6} mol/L. The characteristics of the calibration plots are listed in Table 1. The detection (LOD) and determination limits (LOQ) of the procedures are also shown in Table 1, which were calculated on the peak current using the following equations:

$$\text{LOD} = \frac{3s}{m} \quad \text{LOQ} = \frac{10s}{m} \tag{1}$$

where s, the noise estimate, is the standard deviation of the peak currents (five runs) of the sample, m is the slope of the calibration plot. The values are close to that in the literature reported [2].

The intra-day reproducibility of peak potentials and peak currents was tested with 8.0×10^{-7} mol/L valsartan for both methods (n = 4). The relative standard deviations were calculated to be 0.24% and 0.19% for peak potentials and 0.37% and 0.39% for peak currents, for differential-pulse and square-wave voltammetric techniques, respectively. And the inter-day tests were also performed, the

Table 1
Regression data of the calibration lines for quantitative determination of valsartan in B–R buffer solution at pH 7.0 using differential-pulse adsorptive stripping and square-wave adsorptive stripping voltammetry

Method	Linearity range (mol/L)	Regression equation	Correlation coefficient (R^2)	R.S.D. (%)	LOD (mol/L)	LOQ (mol/L)
Differential-pulse adsorptive stripping voltammetry	6.0×10^{-8} to 4.0×10^{-6}	$-i_p$ (μA) = 9.93 C (μmol/L) + 0.11	0.994	0.97	2.93×10^{-9}	9.77×10^{-9}
Square-wave adsorptive stripping voltammetry	6.0×10^{-8} to 4.0×10^{-6}	$-i_p$ (μA) = 12.22 C (μmol/L) − 0.73	0.990	1.33	3.27×10^{-9}	1.09×10^{-8}

Table 2
Individual capsule assay results from commercial dosage forms and mean recoveries obtained for three determinations of valsartan in spiked valsartan capsules

	Differential-pulse adsorptive stripping voltammetry	Square-wave adsorptive stripping voltammetry
Labeled claim (mg)	80.0	80.0
Amount found	81.0	81.0
R.S.D. (%)	1.4	1.8
Added (mg)	20.0	20.0
Found (mg)	20.1	20.1
Recovered (%)	100.5	100.5
R.S.D. (%) of the recovery	1.6	1.9

relative standard deviations were 0.49% and 0.42% for peak potentials and 0.57% and 0.65% for peak currents for differential-pulse and square-wave voltammetry, respectively.

On the basis of these results, both proposed methods were applied to the direct determination of valsartan in capsules, using the calibration straight line without sample preparation and after an adequate dilution (Table 2). The proposed methods could be applied with great success to valsartan assay in capsules without any interference.

Recovery tests were employed to evaluate the interference of excipients. The application of the procedure is specified in Section 2. According to the data in Table 2, the results demonstrate the validity of the proposed method for the determination of valsartan in commercial dosage forms. The proposed methods proved to have precision and accuracy for the reliable analysis of valsartan.

4. Conclusion

Application of differential-pulse adsorptive stripping and square-wave adsorptive stripping voltammetric techniques at the MFE to pharmaceutical dosage form is possible after a simple dilution step. The analyses for valsartan in commercial capsules were performed without any interferences from the excipients in capsules. Both proposed methods are rapid, requires less than 5 min to run sample, and does not require filtration and expensive grades of solutions that are needed for other determination methods such as HPLC.

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