

SQUARE-WAVE VOLTAMMETRIC DETERMINATION OF SULPIRIDE

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ABSTRACT

The basic redox properties of sulpiride are investigated by means of cyclic (CV) and square-wave voltammetry at a hanging mercury drop electrode (HMDE). Sulpiride undergoes electrochemical reduction in a basic medium. The voltammetric response strongly depends on pH of the medium. A square-wave voltammetric method for quantitative determination of sulpiride is developed. A detection limit of 1.9×10^{-6} mol/l sulpiride was obtained at the static mercury drop electrode in 2 mol/l KOH. The correlation coefficients of the calibration curves at concentration levels of 10^{-5} and 10^{-6} mol/l are greater than 0.99. The results of recovery tests for added sulpiride from 5.7 to 11.1×10^{-5} mol/l ranged from 91.3 to 106 %, with relative standard deviations from 0.3 to 2.1 %.

INTRODUCTION

Polarographic and voltammetric methods have been frequently applied for studying the redox properties of various pharmacologically active compounds [1-5]. Moreover, these techniques have been extensively explored for quantitative determination of numerous drugs [6-16]. It has been shown that the pulse voltammetric techniques provide higher sensitivity in comparison with the classical *dc* polarography or linear potential scan voltammetry [17]. Among them, the square-wave voltammetry is one of the most advanced electroanalytical techniques [18, 19]. It is particularly appealing because of its fast scan-rate, high frequency, large amplitude, and relatively low residual current. In this paper, the square-wave voltammetry together with the cyclic voltammetry have been utilized for characterization of the redox properties of sulpiride at a static mercury drop electrode in an aqueous medium.

Sulpiride (N-[(1-ethyl-2-pyrrolidinyl) methyl]-2-methoxy-5-sulfamoylbenzamide, see Fig.1) is an important antipsychotic drug [20]. Due to its dopaminergic blocking activity, it has been frequently used in the therapy of schizophrenia. [21-23]. Most of the investigations of sulpiride have been focused around its pharmacological activity [21-27]. Chromatographic methods have been applied for its quantification and separation in biological fluids [28-31]. Its redox properties have not been a subject of investigations so far. The aim of this work is to investigate the basic redox and voltammetric properties of sulpiride, as well as to develop a voltammetric method for its quantitative determination using the square-wave voltammetry.

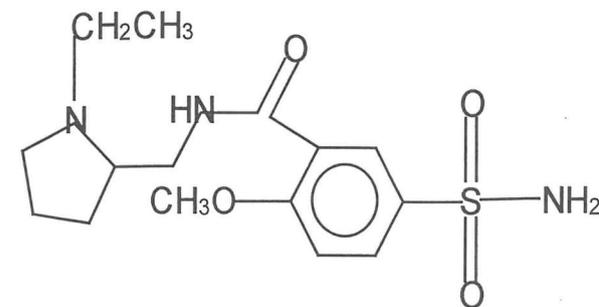


Fig. 1. Structure of sulpiride.

EXPERIMENTAL

Sulpiride, potassium hydroxide, sodium hydroxide, boric acid, phosphorous acid, acetic acid, and methanol (all MERCK) were used as received.

The supporting electrolytes were 0.1 mol/l Britton-Robinson buffers and 2 mol/l KOH. The Britton-Robinson buffers were prepared as a mixture of H_3BO_3 , H_3PO_4 and CH_3COOH and particular pH values were adjusted by adding 0.2 mol/l NaOH. Water was double distilled. A stock solution of sulpiride was prepared by dissolving in an appropriate amount of 96 % (volumic parts) methanol.

All voltammograms were recorded with a polarographic analyzer PAR 384B equipped with a static mercury drop electrode (PAR 303A). A small renewable mercury drop with a surface area of 0.0149 cm^2 was used as a working electrode. The reference was the saturated (KCl) Ag/AgCl and a Pt wire was a counter electrode. Solutions were degassed with high-purity nitrogen for 8 minutes prior to each measurement and nitrogen blanket was maintained thereafter. All measurements were performed at room temperature.

RESULTS AND DISCUSSION

The basic redox properties of sulpiride have been investigated applying both the cyclic and the square-wave voltammetry. Sulpiride undergoes electrochemical reduction in a medium with $\text{pH} > 10$. Cyclic voltammograms of 2×10^{-4} mol/l sulpiride solution, recorded in Britton-Robinson buffers at various pH values are presented in Fig. 2. Over the range from $\text{pH} = 10.1$ to $\text{pH} = 10.5$ sulpiride undergoes two-step reduction. According to the cyclic voltammograms, peak I in the Fig. 2 is attributed to a totally irreversible redox process. An increase of pH caused the peak I to shift slightly towards more negative potentials, while its peak current remains virtually the same. For instances, if pH was increased from $\text{pH} = 10.1$ to $\text{pH} = 10.4$, the peak potential changes from -1.28 V to -1.29 V , respectively. At pH higher than 10.5, this peak vanishes.

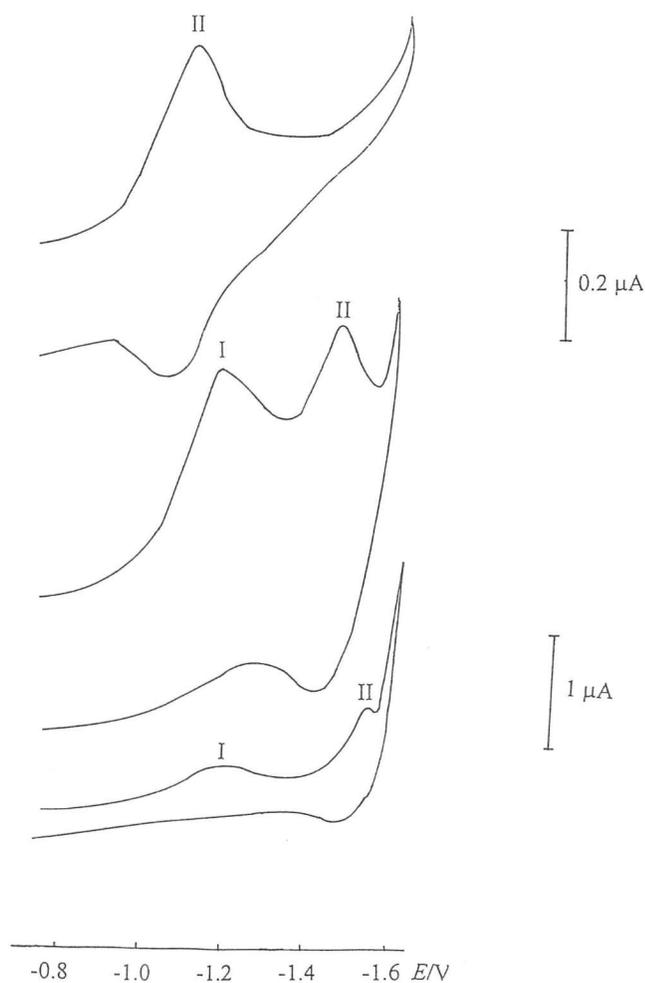


Fig. 2. Cyclic voltammograms of 2×10^{-4} mol/l sulphiride solution recorded in Britton-Robinson buffers with pH = 10.1 (1); 10.4 (2) and 11.5 (3). The scan rate was $\nu = 1$ V/s. The voltammograms were recorded starting from the potential $E_s = -0.70$ V towards final potential $E_f = -1.80$ V and back to the starting potential. The scan increment was $dE = 4$ mV.

According to the cyclic voltammetric measurements, the second redox reaction of sulphiride (peak II in the Fig. 2) seems to be a chemically reversible electrode process. The second redox reaction of sulphiride is markedly dependent on pH of the buffers. At pH < 10, this redox process does not occur. In the medium with pH = 10.1 (Fig. 2, curve 1) this redox process appears at rather negative potentials, as illustrated by curve 1 in the Fig. 2. An increase of pH, caused the second redox process to occur at more positive potentials. In the same time, the peak currents of both cathodic and anodic CV peaks are significantly enhanced (see curves 2 and 3 in the Fig. 2). For instance, the formal redox potential of this process in Britton-Robinson buffers at pH = 10.4 and at 11.5 are $E_f = -1.59$ V and -1.15 V, respectively (see curve 2 and 3 in the Fig. 2).

In order to investigate the electrochemical reversibility of this process, a scan rate analysis using cyclic voltammetry was attempted. The results are listed in Table I. The peak currents of both cathodic and anodic peaks increase with scan rate, however they are not proportional to the square-root of the scan rate. The peak potentials of the cathodic peak shift in a negative direction with an increase of the scan rate. The ratio $i_{p,c}/i_{p,a}$ (where $i_{p,c}$ and $i_{p,a}$ are peak currents of cathodic and anodic peaks, respectively) was changed from 0.84 for to 1.08 at the scan rate $\nu = 0.27$ V/s and $\nu = 1.00$ V/s, respectively. The average value of this ratio is 0.97. The potential separation ΔE_p between cathodic and anodic peak ($\Delta E_p = |E_{p,c} - E_{p,a}|$) varies from $\Delta E_p = 51$ mV at $\nu = 0.27$ V/s to $\Delta E_p = 58$ mV at $\nu = 1.00$ V/s. The average value of the peak separation is 55.60 mV.

Table I. A scan rate analysis of the cyclic voltammograms of 2×10^{-4} mol/l solution of sulphiride recorded in 2 mol/l KOH. The voltammograms were recorded starting from the potential $E_s = -0.90$ V towards final potential $E_f = -1.50$ V and back to the starting potential. The scan increment was $dE = 4$ mV.

ν/Vs^{-1}	$i_{p,c}/\mu A$	$i_{p,a}/\mu A$	$i_{p,c}/i_{p,a}$	$\Delta E_p/mV$
0.27	0.04	0.05	0.84	50
0.33	0.05	0.07	0.81	50
0.40	0.08	0.08	1.05	58
0.50	0.10	0.11	0.96	57
0.66	0.17	0.17	1.00	56
0.80	0.23	0.21	1.07	59
1.00	0.36	0.33	1.08	58

According to the theoretical criterion [32] for an electrochemically reversible redox process, the ratio of the peak currents is $i_{p,c}/i_{p,a} = 1$, while the potential separation between cathodic and anodic peaks is $\Delta E_p = 2.303 RT/nF$. According to the results listed in the Table I, it can be concluded that the redox reaction does not satisfy the criterions for an electrochemically reversible redox process. Therefore, these results confirm that the response II of sulphiride corresponds to a quasireversible redox reaction controlled by the charge transfer rate. Nevertheless, from analytical point of view it is important to emphasize that the strong basic medium would be more convenient for quantitative determination of sulphiride.

Additional information about the dependence of the voltammetric response of sulphiride on pH of the medium were collected applying the SW voltammetry. At pH = 10.2, the SW voltammetric response consists of two peaks with the peak potentials of E_p (I) = -1.17 V and E_p (II) = -1.63 V. The SW peak (I) which is attributed to the irreversible redox process of sulphiride is ill-shaped, with a half-peak width of about 280 mV. If pH value was higher than 10.5, the first SW peak (I) vanishes, and only the second

peak (II) which corresponds to the chemically reversible redox process of sulphiride can be observed. Obviously, the second SW peak (II), which is attributed to the chemically reversible redox process of sulphiride, is more convenient for analytical purposes and hence, our interest was focused to this electrode process.

Increasing pH caused the peak II to shift in positive direction and its peak current to increase. When pH was increased from 10.4 to 11.3, the peak potential alters from $E_p(\text{II}) = -1.53 \text{ V}$ to $E_p(\text{II}) = -1.16 \text{ V}$, while the peak current increases from $i_p(\text{II}) = 0.25 \text{ }\mu\text{A}$ to $i_p(\text{II}) = 0.50 \text{ }\mu\text{A}$, respectively. In the same time, the ratio $i_p/\Delta E_{p/2}$ (where $\Delta E_{p/2}$ is a half-peak width) enhances from $0.146 \text{ }\mu\text{A/mV}$ to $0.236 \text{ }\mu\text{A/mV}$. Fig. 3 illustrates the dependence of the SW peak potentials on pH of the buffers. The relationship between E_p and pH deviates from linearity over the pH range from 10.5 to 10.8 (see Fig. 3). This phenomenon could be associated with the second dissociation constant of amine group of sulphiride which reads $\text{p}K_2 = 10.20$ [20]. All these results suggest that the response II of sulphiride at a mercury electrode corresponds most probably to a CE electrode mechanism.

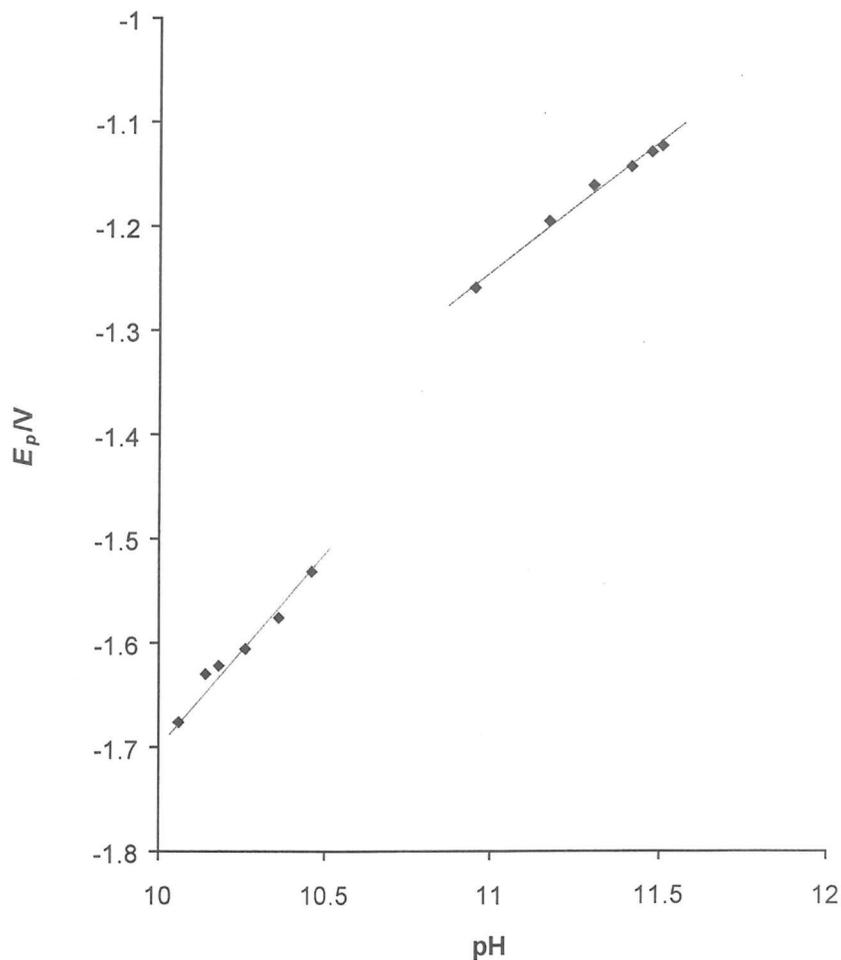


Fig. 3. The effect of pH of the buffers on the SW peak potentials of sulphiride. The concentration of sulphiride was $2 \times 10^{-4} \text{ mol/l}$. The frequency of the signal, the amplitude, and the scan increment were 100 Hz, 20 mV and 4 mV, respectively. The starting potential was $E_s = -0.90 \text{ V}$ and the final potential was $E_f = -1.50 \text{ V}$.

Presumably, the dissociation of the amine group precedes the electron transfer step. However, it is still not clear, why the peak potential depends so strongly on pH. It is reasonable to suppose that the quasireversibility of the electron transfer step is a reason for such behavior.

In order to achieve the best-defined SW response of sulphiride, which could be useful for analytical purposes, an optimization of the instrumental parameters such as the frequency f , the pulse height E_{sw} and the scan increment dE of the SW signal was attempted. The effect of the SW frequency on the peak currents of sulphiride is illustrated in Fig. 4. The peak current-frequency dependence is linear with the correlation coefficient of regression line $R^2 = 0.99$. The peak potential depends linearly on the logarithm of the frequency of the signal. The slope of this line is $\Delta E_p/\Delta \log(f) = -0.069 \text{ V}$, with a correlation coefficient of linear regression $R^2 = 0.99$.

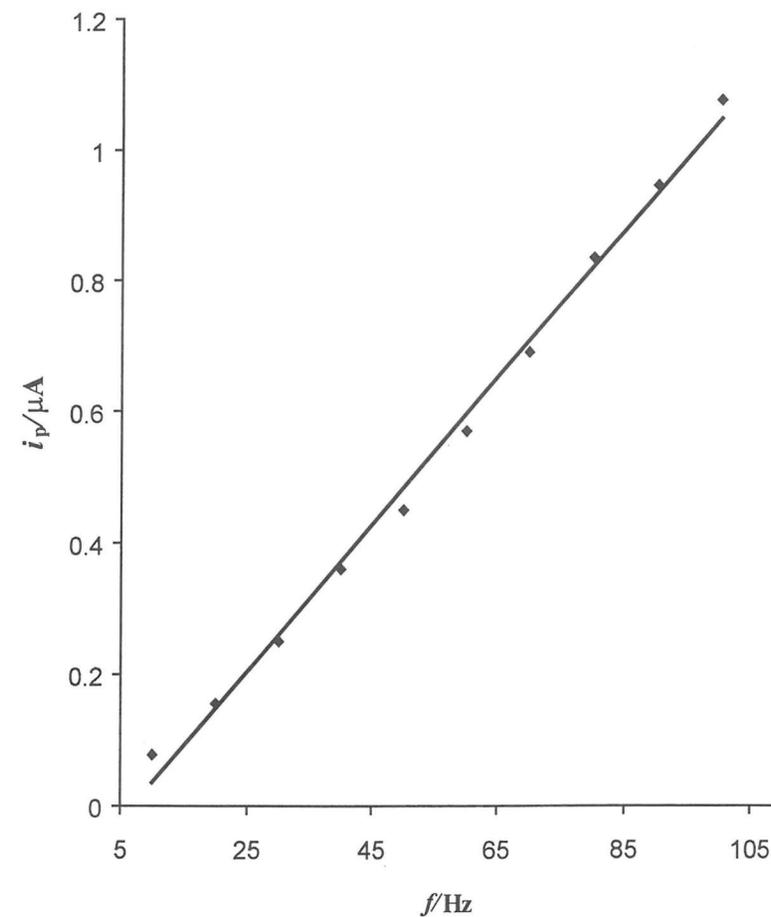


Fig. 4. Effect of the frequency of the signal on the SW peak currents of sulphiride. The supporting electrolyte was 2 mol/l KOH. All other conditions as in the caption of the Fig. 3.

The effect of the SW amplitude on both the SW peak currents and the peak potentials is presented in Fig. 5. The peak currents increases in proportion with the SW amplitude over the range from 5 to 60 mV (Fig. 5, curve 1). If the amplitude was larger than 70 mV, deviations from linearity occur. The peak potential shifts towards more positive values with an enhancement of the amplitude (Fig. 5, curve 2). The shape of the

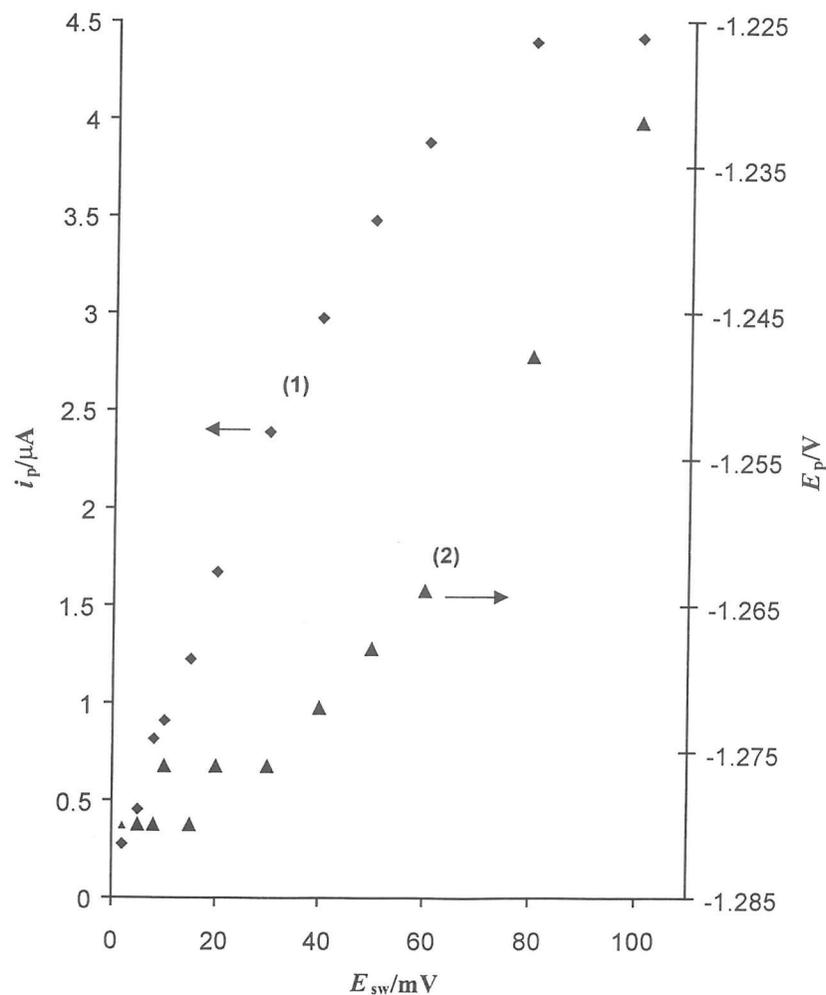


Fig. 5. Effect of the amplitude of the signal on the SW peak currents (curve 1, left axis) and the peak potentials (curve 2, right axis) of sulphiride. The supporting electrolyte was 2 mol/l KOH. . All other conditions as in the caption of the Fig. 3.

peak is also sensitive on the SW amplitude. For SW amplitude higher than 80 mV, a broad and ill-shaped SW peak, which is unsuitable for analytical purposes, is obtained. The narrowest peak, with half-peak width of 170 mV, was obtained for amplitude of 20 mV. Hence, the SW amplitude of 20 mV was considered as an optimal value for analytical measurements.

The scan increment affects mainly the peak current of the SW peak. When the scan increment was increased from 2 mV to 10 mV, the peak potential slightly changes from $E_p = -1.208$ V to $E_p = -1.200$ V, respectively. However, the peak current depends parabolically on the scan increment with the maximum located around $dE = 5$ mV. The

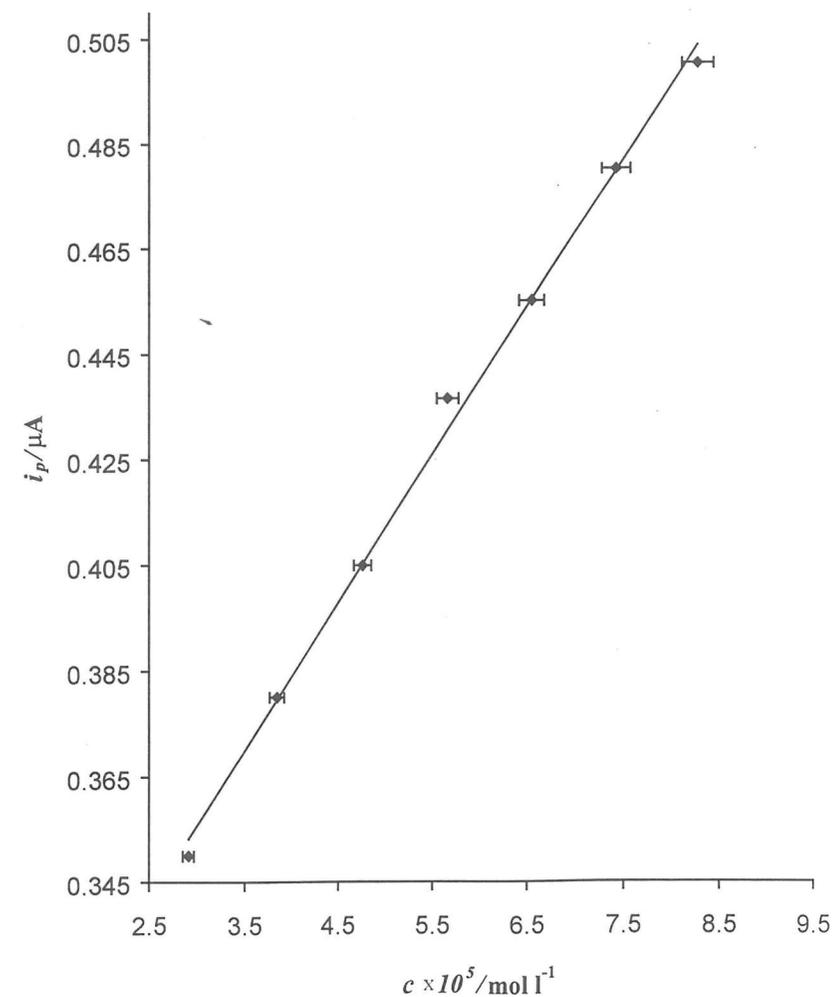


Fig. 6. Calibration curve recorded within the concentration range of sulphiride from 2 to 9×10^{-5} mol/l. The supporting electrolyte was 2 mol/l KOH. The frequency of the signal, the amplitude, and the scan increment were 100 Hz, 20 mV and 4 mV, respectively. The starting potential was $E_s = -0.90$ V and the final potential was $E_f = -1.50$ V.

scan increment also affects the half-peak width. The half-peak width changes from 140 mV to 190 mV when the scan increment was increased from 2 to 10 mV, respectively. The narrowest SW peak was obtained for a scan increment of 4 mV, and consequently the ratio $\Delta i_p/\Delta E_{p/2}$ reaches the maximum for this value of the scan increment.

Therefore, the dependence of the SW peak current on the concentration of sulphiride was investigated in 2 mol/l KOH, at the frequency of the signal of 100 Hz, the pulse height of 20 mV and the scan increment of 4 mV. Over the concentration range from 2 to 9×10^{-5} mol/l a linear dependence was observed with a correlation coefficient of linear regression line $R^2 = 0.996$ (Fig. 6). The regression line is described with the following equation: $\Delta i_p = 0.0281 \times 10^5 c + 0.2714$, where Δi_p is expressed in μA and c in mol l^{-1} . The linear dependence also exists within the concentration range from 2.6 to 8.5×10^{-6} mol/l (Fig. 7). The correlation coefficient of linear regression line is $R^2 = 0.992$ (Fig. 7). The slope of the line is different in comparison to the previously concentration range and the regression line is described with the following equation: $\Delta i_p = 0.0204 \times 10^6 c \pm 0.0265$.

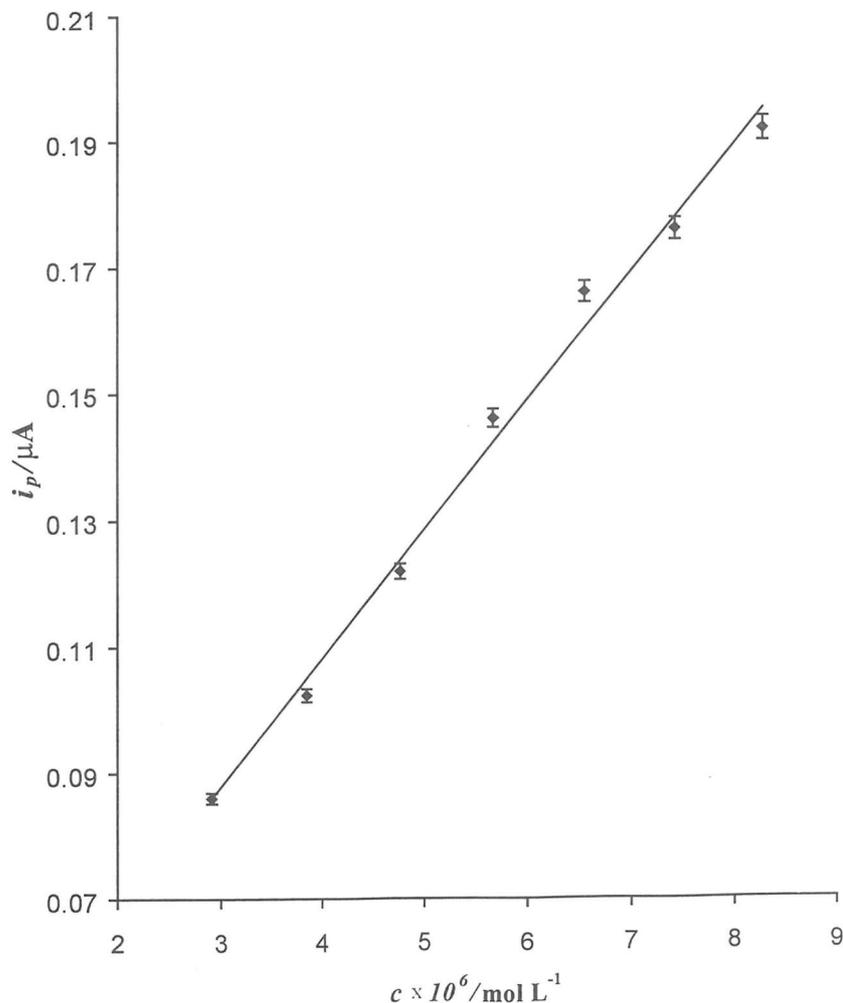


Fig. 7. Calibration curve of sulphiride recorded in the concentration range from 2.6 to 8.5×10^{-6} mol/l. All other conditions as in the caption of the Fig. 6.

In order to estimate the detection limit of sulphiride in 2 mol/l KOH, 18 measurements of the supporting electrolyte were carried out. The minimal current, i_{\min} , which could be detected, is calculated according to the formula: $i_{\min} = i_b + k S_b$, where i_b is an average value of the currents of the supporting electrolyte, k is confidence level factor (for this calculation, $k = 3$, which means that the confidence level is 99.6 %) and S_b is standard deviation of the current values [33]. This procedure gives an estimate of 1.9×10^{-6} mol/l for the detection limit. The sensitivities of the method at concentration level of 10^{-5} and 10^{-6} mol l^{-1} are $2.8 \mu A \text{ l/mmol}$ and $2.04 \mu A \text{ l/mmol}$, respectively. In addition, the recovery and the relative standard deviation (RSD) tests have been carried out. The results are listed in Table II. The recovery test is based on the addition of a known amount of sulphiride to the blank solution and determination of this amount by calibration curves in carried out parallel with the determinations. The results of recovery test with addition of amounts from 5.7×10^{-5} mol/l to 11.1×10^{-5} mol/l are listed in the Table II. Each entry in the table represents the median of four potential scans. Recoveries ranging from 91.3 % to 106 % were obtained. The reproducibility of the results in terms of the relative standard deviation ranged from 0.3 to 2.1 %.

Table II. Recovery and RSD test for sulphiride. The frequency of the signal, the amplitude, and the scan increment were 100 Hz, 20 mV and 4 mV, respectively. The starting potential was $E_s = -0.90$ V and the final potential was $E_f = -1.50$ V. The supporting electrolyte was 2 mol/l KOH.

$c \times 10^5 / \text{mol L}^{-1}$ added	$c \times 10^5 / \text{mol L}^{-1}$ founded	Recovery (%)	RSD (%)
5.66	6.00	106	0.33
6.97	7.02	100.62	1.96
7.83	8.01	102.24	0.76
8.67	8.61	99.25	0.63
9.50	9.32	98.08	1.54
11.11	10.15	91.35	2.07

In summary, square-wave voltammetry is a sensitive, rapid, precise, and accurate analytical technique for determination of sulphiride, and by extension, of other organic compounds. This technique is also attractive due to the relatively low cost of the instrumentation and short time required for the analysis. The disadvantage of this approach is addressed to the problems presented by complex sample types. In principle, problem of interference can be addressed by means of separation techniques. These problems will need to be addressed case by case, as the specific nature of the problem depends on the type of the sample.

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