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Anodic voltammetry of fluphenazine at different solid electrodes[1]

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Abstract

The electrochemical behaviour of fluphenazine based on its oxidation at platinum and glassy carbon electrodes was investigated by linear sweep and cyclic voltammetry. The influence of pH, concentration, nature of the buffer and scan rate was carefully examined. At both electrodes, three anodic steps (representing an irreversible oxidation) were obtained. The method was applied to the determination of fluphenazine in sugar-coated tablets.

Keywords: Fluphenazine; Platinum and glassy carbon electrodes; Tablets; Voltammetry

1. Introduction

Fluphenazine, a piperazine-type phenothiazine, is widely used in the control of symptoms of schizophrenia.

Methods for the determination of fluphenazine include gas–liquid chromatography [1,2], gas–liquid chromatography combined with mass spectrometry [3,4], high-performance liquid chromatography [5–7] and radioimmunoassays [8,9].

A common property of all N-substituted phenothiazines is that they are easily oxidized, either chemically or electrolytically. Investigation of the electro-oxidation of these drugs gives some information about their clinical activities. The explanation of the electrode reaction may provide information about the drug–receptor interaction. The interaction between the dopamine receptor and phenothiazines is very important in drug activity and the electrode can be accepted as a simple model of the receptor.

The electrochemical oxidation of fluphenazine and various tranquillizers at a wax-impregnated graphite electrode for the extraction–adsorption of the drugs by differential-pulse voltammetry was studied [10]. A sensitive method for the determination of fluphenazine and related compounds at carbon paste electrodes by differential-pulse voltammetry was also reported [11].

The aim of this study was to investigate the voltammetric behaviour of fluphenazine at platinum and glassy carbon electrodes in order to develop a method for the determination of this compound in dosage forms.

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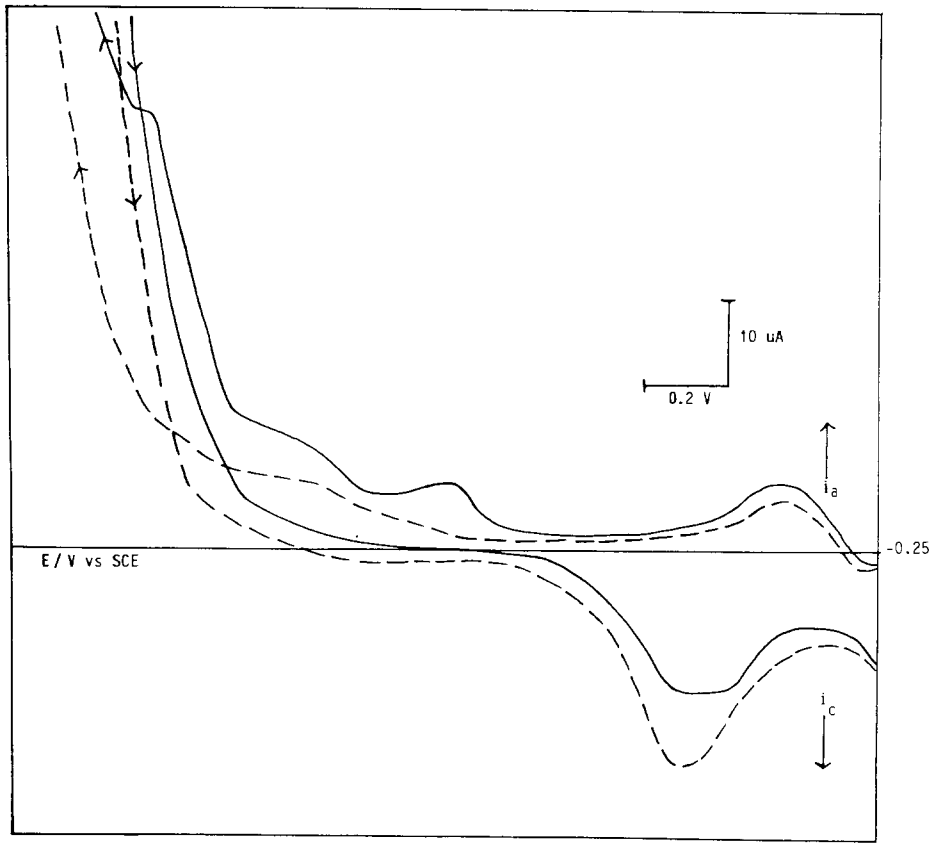


Fig. 1. Cyclic voltammogram of 1×10^{-3} M fluphenazine in 0.5 M H_2SO_4 at the platinum electrode. Scan rate: 100 mV s^{-1}. The broken line represents the residual current.

2. Experimental

2.1. Apparatus

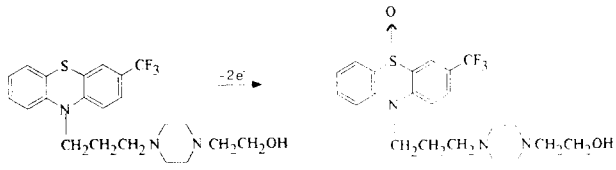
The voltammetric measurements were performed on a PRG-3 polarograph (Tacussel) connected to an EPL-2 recorder (Tacussel). All the potentials were reported vs. a saturated calomel electrode (SCE) and the auxiliary electrode was a platinum wire. Two working electrodes were used: a platinum wire (Tacussel, diameter 1 mm, height 15.7 mm) and a glassy carbon electrode (Tacussel XM 540, area 0.47 cm^2). The cell was covered with aluminium foil to protect from light.

2.2. Reagents

Fluphenazine dihydrochloride (generously provided by Fako Drugs Industries, İstanbul, Turkey) was used without further purification. All other reagents were of analytical grade. Stock solutions were prepared daily by dissolving fluphenazine in selected supporting electrolytes. Alkaline media were avoided as fluphenazine undergoes a precipitation reaction in such media. Doubly-distilled water was used to prepare the solutions.

2.3. Pre-treatment of the working electrodes

Pre-treatment of the platinum electrode was performed by anodising the electrode at +1.2 V for 5 min and, after washing it thoroughly with doubly-distilled water, allowing it to stand at +0.1 V for 15 min in de-aerated 0.5 M sulphuric acid. Activation of the glassy carbon electrode was achieved by polishing the electrode with alu-



Scheme 1.

mina every 10–15 measurements and polarising the electrode for 5 min at +1.5 V, followed by the application of −1.0 V for 2–3 s in 0.1 M potassium nitrate before each experiment. It was necessary to remove dissolved oxygen when working with the platinum electrode but this was not necessary with the glassy carbon electrode.

3. Results and discussion

3.1. Experiments on the platinum electrode

In 0.5 M sulphuric acid, the electro-oxidation of fluphenazine was well defined and occurred in three steps at about +0.75 V, +1.1 V and +1.45 V (Fig. 1). The half-wave potentials of the second and third waves were shifted towards more positive values with increasing concentration. This suggests that adsorption occurs after the first step. The most anodic wave disappeared at very low pH values owing to its overlap with the background electrolyte discharge. According to current knowledge of the electro-oxidation of phenothiazines [12,13], the first oxidation step of fluphenazine, resulting simply from the loss of an electron from the parent compound, produces the corresponding cation free radical which is stable in acidic solutions; however, its lifetime is shorter in less acidic media. The second step is a further one-electron oxidation of free radical to the sulphoxide (Scheme 1). The third step is related to the further oxidation of fluphenazine 5-sulphoxide [14]. On the cathodic branch, the current density of the peak at about +0.2 V, which corresponds to the reduction of the surface layers of the platinum electrode, was lower than that obtained in the supporting electrolyte. This phenomenon may occur because the formation of the oxidation products hinders the surface oxidation to some extent [15]. Moreover, in solutions more concentrated than 10^{-3} M, this single cathodic peak split into two overlapping peaks. Cyclic voltammetry demonstrated the total irreversibility of this system at scan rates from 10 mV s^{-1} to 100 mV s^{-1}.

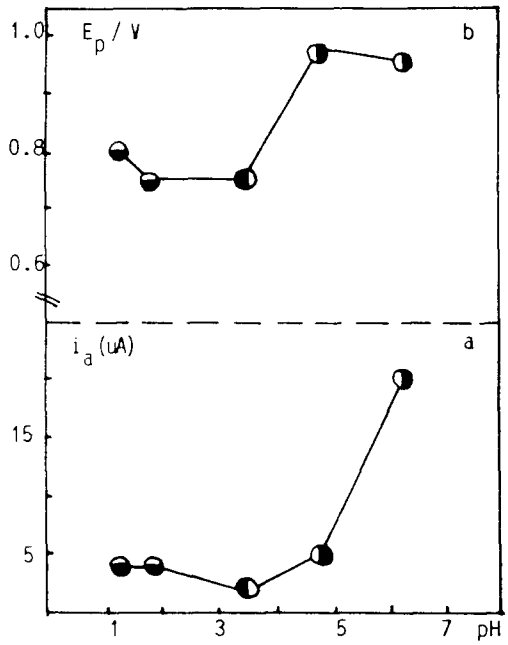


Fig. 2. Effects of pH on (a) the fluphenazine peak current and (b) the peak potential. Fluphenazine concentration, 4×10^{-4} M; scan rate: 100 mV s^{-1}; electrode, Pt. (◒) H_2SO_4; (◐) acetate buffer; (◑) phosphate buffer.

The least anodic wave was also the best defined, the peak becoming sharper with an increase in the concentration. For analytical purposes, the first anodic step was the most useful. Hence, all subsequent work was based on measurement of the magnitude of this step.

The effects of potential scan rate (v) on the peak potential and peak current for fluphenazine were evaluated. The linear increase in the oxida-

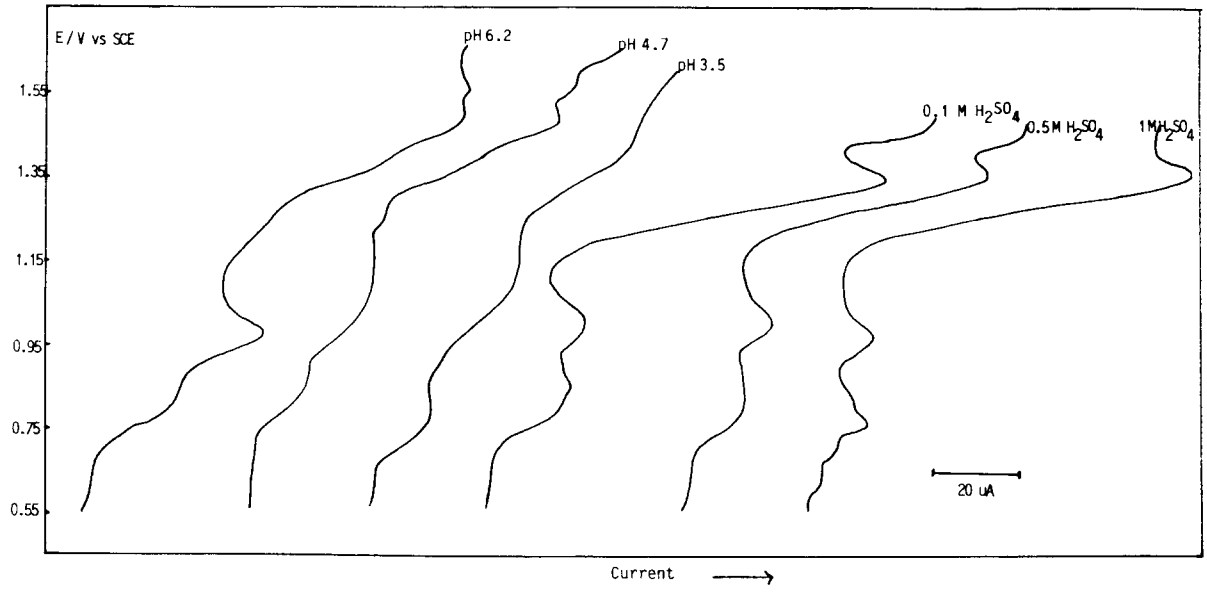


Fig. 3. Influence of pH on the anodic voltammograms of 4×10^{-4} M fluphenazine at the glassy carbon electrode. Scan rate: 100 mV s^{-1}.

tion peak current with the square root of the scan rate over the 10–100 mV s^{-1} range, with a slope of 2.70 (correlation coefficient 0.997), showed the diffusion control of the process. The plot of E_p vs. $v^{1/2}$ was also linear (correlation coefficient 0.994). A positive shift in the peak potential was observed when the scan rate was increased over the range given.

Fig. 2a shows the dependence of the peak enhancement on the solution acidity. Peak current remained constant in acidic media up to pH 3.5 and then showed a sharp increase up to pH 6.2. The effect of the solution pH on the peak potential is also shown in Fig. 2b. The peak exhibited three breaks, at pH 1.8, 3.5 and 4.7, which can be explained by changes in protonation of the acid–base functions in the molecule.

3.2. Experiments on glassy carbon electrode

When a glassy carbon electrode was used instead of a platinum electrode, the three oxidation steps were again observed by increasing the sensitivity of the measurement compared to that of the platinum electrode. However, the shapes of these waves were markedly dependent on pH (Fig. 3). The second wave was not well separated from the first at higher concentrations and disappeared at lower scan rates.

At the glassy carbon electrode, cathodic peaks were not detected by reversing the scan direction, indicating an irreversible process.

The shape of the most anodic wave changed in strongly acidic solutions and a peak appeared. The peak current was diffusion controlled and cyclic voltammograms presented evidence of slight adsorption, the oxidation peak height being not directly proportional to the square root of the scan rate. With increase in pH, the peak became ill-defined and quantitation of the peak was not possible. For this reason the peak in strongly acidic media was chosen for analytical purposes.

Table 1
Characteristics of fluphenazine calibration plots

Electrode	Medium	Concentration range (M)	Slope ($\mu A\ M^{-1}$)	Intercept (μA)	Correlation coefficient	SE of slope ($\mu A\ M^{-1}$)	SE of Intercept (μA)
Platinum	0.5 M H_2SO_4	4×10^{-4}–1×10^{-2} ($n=9$)	5.52×10^{3}	0.16	0.999	5.83×10	0.27
	Phosphate buffer (pH 6.2)	2×10^{-4}–4×10^{-3} ($n=7$)	1.64×10^{4}	5.39	0.998	4.12×10^{2}	0.73
Glassy carbon	0.5 M H_2SO_4	2×10^{-5}–8×10^{-4} ($n=9$)	1.60×10^{5}	5.26	0.999	2.58×10^{3}	0.95

3.3. Quantitative determination

Various electrolytes, e.g. sulphuric acid (0.1, 0.5 and 1 M), acetate buffer (0.2 M, pH 3.6–4.7) and phosphate buffer (0.2 M, pH 4.7–6.2), were evaluated as suitable media for the quantitative determination of fluphenazine. Best results (with respect to signal enhancement and peak shape) were obtained with 0.5 M sulphuric acid for both electrodes. Phosphate buffer (pH 6.2) was also used for the platinum electrode. Satisfactory results were obtained with a scan rate of 100 mV s^{-1}.

By choosing the optimum conditions mentioned above, calibration plots were drawn by spiking the blank solution with different amounts of the drug. The characteristics of these plots are listed in Table 1. The proposed method was applied to the direct determination of fluphenazine in Moditen sugar-coated tablets.

Table 2 compares the results of the analysis of fluphenazine by the proposed method and by the USP XXII procedure [16] which involves a spectrophotometric method. It is evident that the proposed method is as sensitive as the official method except for the result obtained with 0.5 M sulphuric acid at the platinum electrode. According to Student's t-test, the calculated t values were found to be 1.029 (0.5 M H_2SO_4) and 1.928 (phosphate buffer pH 6.2) for the platinum electrode and 1.979 for the glassy carbon electrode. The theoretical t value was 2.101 ($p=0.05$). This indicates that there is no significant difference between the two methods with respect to precision and accuracy. However, the voltammetric assay is simple and rapid in comparison with the UV spectrophotometric assay. No treatment of the sample is required before the voltammetric analysis. Excipients present in the tablet do not interfere with the analyses.

In summary, it is concluded that the electrochemical method for the determination of fluphenazine presented in this paper has the advantages of being rapid, simple and inexpensive.

Table 2
Comparative studies for fluphenazine sugar-coated tablets (declared amount: 1.0 mg per tablet)

Parameter	Voltammetric assay			Spectrophotometric assay
	Platinum		Glassy carbon	
	0.5 M H_2SO_4	Phosphate buffer (pH 6.2)	0.5 M H_2SO_4	
Amount found (mg)[a]	1.02	1.01	1.02	0.99
SD	0.11	0.04	0.05	0.02

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

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