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Polarographic determination of flutamide

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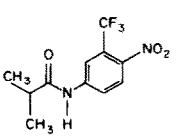
Abstract: The polarographic reduction of flutamide was investigated by direct current polarography (DCP), alternating current polarography (ACP), normal pulse polarography (NPP) and differential pulse polarography (DPP). The supporting solution was phosphate buffer containing 5% of 95% ethanol. The reduction process at the dropping mercury electrode was diffusion controlled and irreversible. Extraction with 95% ethanol followed by polarographic reduction was selected as the basis of a method for the determination of flutamide as a pure compound and in tablets.

Keywords: *Flutamide; direct current polarography; alternating current polarography; normal pulse polarography; differential pulse polarography.*

Introduction

Flutamide, 2-methyl-*N*-[4-nitro-3(trifluoromethyl)-phenyl]-propanamide is a synthetic antiandrogen agent used in tablets for the treatment of advanced prostatic cancer [1]. The literature on this compound is limited and only one reference to measurements has been traced using thin layer chromatography [2]. Polarographic analysis is a rapid and sensitive technique for the measurement of drugs in pure solutions, bulk materials, medicines and biological fluids. The polarographic behaviour of the nitro group is not constant for all nitro compounds, but is governed by a number of factors including molecular structure, pH, composition of supporting electrolyte and drop time at the dropping mercury electrode. The most useful polarographic wave for the analysis of nitro-containing drugs is that of four-electron reduction which generally occurs in the range $E_{1/2}$ −0.1–0.4 V (vs SCE) where many other compounds are polarographically inactive [3]. Flutamide has not so far been examined by any electrochemical methods. The aim of this research was to investigate some of the electrochemical properties of flutamide and to work out a new method for flutamide determination using polarography both for the pure chemical and when used as a drug.

Structure 1



*Presented at the "Third International Symposium on Drug Analysis", May 1989, Antwerp, Belgium.

Experimental

Materials and reagents

Flutamide standard was from Schering, and flutamide tablets of 250 mg were used as received. Stock solutions were prepared by dissolving 0.1 g of the standard in 100 ml of 95% ethanol. Aqueous buffer solutions 0.2 M were prepared with disodium hydrogen orthophosphate and sodium phosphate monobasic. The solubility of flutamide in water is low and stock solutions were diluted with appropriate amounts of aqueous buffer and 95° ethanol to give test solutions of the required concentration and pH. All the other chemicals were reagent grade.

Apparatus

Direct current polarographic (DCP) measurements were made with a PO-4 Radiometer polarograph with alternating current attachment made in the Academy of Mining and Metallurgy (Poland). This allowed the recording of alternating polarograms. Differential and normal pulse polarographic measurements were made with an Unitra-Telpod PP-04 apparatus and Kabid XYT recorder (Poland). Cyclic voltammetric curves were recorded with a Type-50 apparatus (Laboratornie Pristroje, Praha). Saturated calomel electrodes (SCE) were used for reference with a dropping mercury electrode (m = 1.97 mg s^{-1}) as cathode (with mechanical drop knocker of 2 s frequency). The third electrode used for measurement was a platinum wire set into a polarographic cell of 20 cm^3 vol (alternating current polarography, ACP). The pH values were measured with an Elpo N-512 pH meter. Oxygen in solutions was removed with nitrogen.

Procedures

The polarographic reduction of flutamide was investigated in various supporting electrolytes and 0.1 N phosphate buffer of pH 7.05 containing 5% of 95% ethanol was chosen. The dependence of current intensity, half-wave potentials and peak potentials upon pH (range 6.1–7.9), temperature (range 19–54°) and upon the square root of the level of the mercury container (DCP) was investigated in this solution (Table 1).

The concentration of flutamide was 7.2 × 10^{-5} M dm^{-3}. Cyclic voltammetric curves of flutamide at the speed of polarization: 2, 5, 20 and 50 mV s^{-1} were registered. The concentration of flutamide was 3 × 10^{-6} M dm^{-3}. Figure 1 shows the shape of curves recorded by normal pulse polarography (NPP) at different start potentials of polarization.

A relationship betwen the reduction current and the concentration of flutamide was investigated for the following ranges: DCP, 3.6 × 10^{-6}–1.44 × 10^{-4} M dm^{-3}; ACP,

Table 1
Polarographic characteristics of flutamide in phosphate buffer

Method (for abbreviations see text)	$\frac{\Delta i \times 100}{\Delta T \times i}$ (%)	$\frac{\Delta E}{\Delta T}$ (mV)	$\frac{\Delta E}{\Delta \text{pH}}$ (mV)	$E_{1/2}; E_p$ (V) vs SCE
DCP	2.12	1.0	40	−0.48
ACP	2.46	1.28	42	−0.63
DPP	2.19	1.45	38	−0.48
NPP	2.47	0.71	41	−0.56

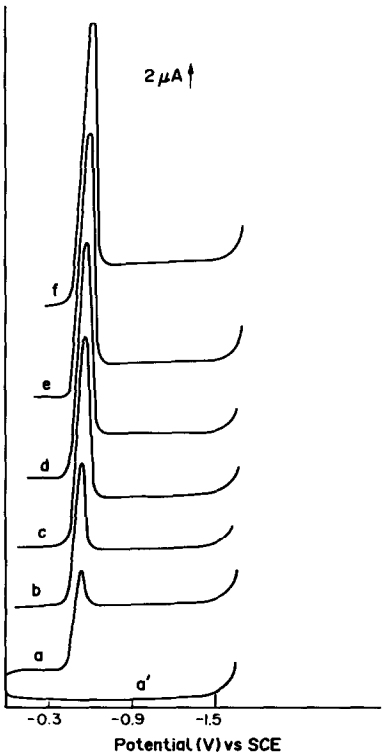


Figure 1
Polarograms of flutamide registered in 0.1 N phosphate buffer (pH 7.05) by NPP depending on the start potential of polarization. a, 0.0 V; b, 0.05 V; c, 0.1 V; d, 0.15 V; e, 0.2 V; f, 0.25 V. The concentration of flutamide was 7.2×10^{-5} M dcm^{-3}: a' polarogram without flutamide.

1.8×10^{-5}–1.44×10^{-4} M dcm^{-3}; NPP, 1.44×10^{-7}–7.2×10^{-6} M dcm^{-3}; and differential pulse polarography (DPP) 2.16×10^{-7}–3.6×10^{-6} M dcm^{-3}.

Determination of flutamide as a pure compound

Ten solutions containing 3.6×10^{-4} M dm^{-3} of flutamide in 95° ethanol (for DCP), 1.44×10^{-3} M dm^{-3} (for ACP), 3.6×10^{-5} M dm^{-3} (for DPP) and 7.2×10^{-5} M dm^{-3} (for NPP) were prepared. Portions of these solutions (0.5 ml) were placed in 10 ml volumetric flasks, 5 ml of 0.2 N supporting electrolyte were added, making up to volume with water. The polarograms were recorded using DCP, ACP, NPP and DPP for the de-aerated solutions. The content of depolarizer was found from calibration curves plotted for the ranges: 3.6×10^{-6}–3.6×10^{-5} M dm^{-3} for DCP, 1.8×10^{-5}–1.44×10^{-4} for ACP, 3.6×10^{-7}–3.6×10^{-6} M dm^{-3} for DPP and 1.44×10^{-6}–7.2×10^{-6} for NPP (Table 2).

Determination of flutamide in tablets

A quantity of powdered tablets equivalent to 25 mg of flutamide was placed in a 25 ml volumetric flask, 20 ml of 95% ethanol were added, the flask shaken for 1 min and made up to volume with ethanol. After stirring, 10 ml of this solution were transferred to a 25 ml volumetric flask and made up to the volume with ethanol. 0.25 ml of this solution was transferred to each of two 10-ml volumetric flasks, 0.25 ml of 95% ethanol and 5 ml of 0.2 M phosphate buffer were added to the first flask which was filled up to volume with water. After stirring, the contents of the flask were placed in the polarographic cell and after removing oxygen the polarogram was recorded. To the second volumetric flask

Table 2
Results of determination of flutamide as a pure compound (n = 10)

Method (for abbreviations see text)	Arithmetic mean $\bar{X}$	RSD (%)	Confidence interval of arithmetic mean $\bar{X} \pm t \times S_{\bar{x}}$ $\alpha = 0.95$
DCP (5 μg)	4.99	1.13	4.99 ± 0.04 99.9 ± 0.8%
ACP (20 μg)	20.32	2.24	20.32 ± 0.32 101.63 ± 1.63%
DPP (500 ng)	505.9	2.25	505.9 ± 8.16 101.2 ± 1.63%
NPP (1000 ng)	1020.7	1.46	1020.7 ± 10.67 102.07 ± 1.07%

0.25 ml of standard solution (concentration 0.4 mg ml^{-1}) was added and the procedure followed as described above. Ten repeat determinations were made. The methods of spectrophotometric* and polarographic determination of flutamide in tablets were compared.

Results and Discussion

Polarographic reduction of flutamide in a 0.1 M phosphate buffer (pH 7.05) containing 5% ethanol exhibits well-defined polarographic curves at potentials $E_{1/2}$–0.48 V (DCP); E_p–0.63 V (ACP); E_p–0.56 V (NPP); and E_p–0.48 V (DPP) (see Figs 2 and 3).

It was found that the heights of the polarographic curves are practically independent of pH in the range 6.1–7.9. With increase of pH the half-wave potentials in DCP and NPP, and peak potentials in ACP and DPP shifted toward more negative values. Temperature coefficient values of 2.12% (DCP), 2.46% (ACP), 2.19% (DPP), and 2.47% (NPP) were obtained upon investigation of the intensity current in the temperature range of 19–54°C. Increase of temperature led to the shifts of E_p and $E_{1/2}$ in the direction of positive potentials (Table 1). The limiting current of flutamide ws proportional to the square root of the level of the mercury container for DCP. A proportional relationship between the reduction current and the concentration of flutamide was observed. The results obtained indicated a diffusive type of limiting current. A cyclic voltammetric curve was recorded showing the irreversibility of the reduction process. During the investigation of flutamide by the cyclic voltammetric method, a good-shaped peak (−0.43 V, scan rate 5 mV s^{-1}) was observed only on the cathodic part, but on the anodic part a curve with a weak peak (−0.06 V) was observed. An increase of current intensity proportional to the square root of the potential scan rate was obtained. In the experiments carried out with NPP the presence of the adsorption peak on the polarographic wave was observed ([4] Fig. 1). It has been found that a relationship exists betwen the shapes of polarographic curves and the initial potential of polarization. At more negative values of the initial potential, the NPP peak increased with decreasing limiting current. The cyclic voltammetric curve of flutamide is similar to the cyclic voltammetric curve of nitrobenzene [5]. Based on the

*The spectrophotometric method comes from the producer's norm. It is the property of Schering Corporation, USA.

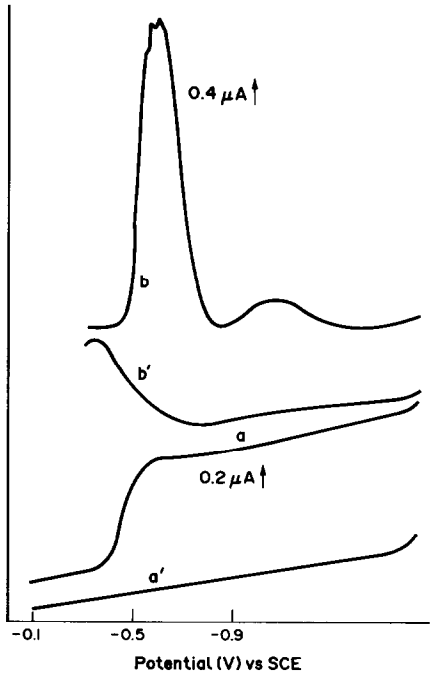


Figure 2
Polarograms of flutamide recorded in 0.1 M phosphate buffer (pH 7.05): a, by DCP; b, by ACP. The concentration of flutamide was 7.2×10^{-5} M dm^{-3}: a', b' polarograms without flutamide.

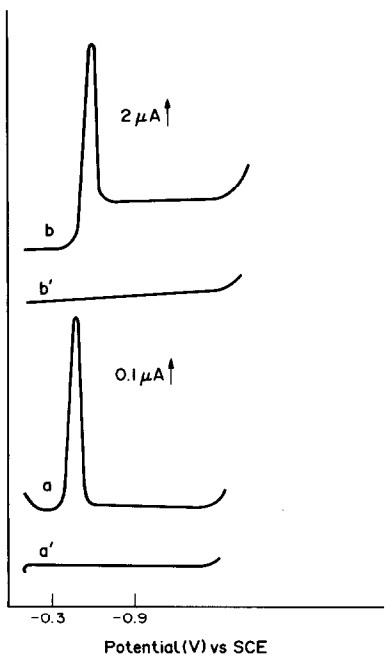


Figure 3
Polarograms of flutamide registered in 0.1 M phosphate buffer (pH 7.05); a, by DPP; b, by NPP. The concentration of flutamide was 7.2×10^{-5} M dm^{-3}; a', b' polarograms without flutamide.

literature [6] and on the findings of this investigation it can be suggested that the reduction process of flutamide involves four electrons and proceeds as follows:

$$R—NO_2 + 4H^+ + 4\,\bar{e} \rightarrow R—NHOH + H_2O.$$

The smallest quantities of the compound which can be detected by the various techniques are: 500 ng cm^{-3} for DCP; 20 ng cm^{-3} for DPP; 10 ng cm^{-3} for NPP and 5000 ng cm^{-3} for ACP.

The statistical analysis of the results obtained in the determination of flutamide as a pure compound is shown in Table 2. The standard error is: 0.03 for DCP; 0.14 for ACP; 3.6 for DPP and 4.7 for NPP. DCP is most suitable for the determination of flutamide as a pure compound. The statistical evaluation of the results for the determination of flutamide in tablets (250 mg) by polarographic and the standard spectrophotometric methods indicates similar precision for both methods. The mean results, respectively, were 244.8 ± 2.0 and 241.3 ± 3.7 mg with relative standard deviations 1.16 and 2.15. The recoveries obtained were 97.9 ± 0.8 and 94.5 ± 1.5%, respectively. The polarographic method is much faster because of the simple method of extraction from tablets.

References

[1] P. C. Sogari and W. F. Whitmore, *J. Urol.* **122**, 640–643 (1979).
[2] Ya. G. Balon, O. I. Lazebnaya and I. S. Dukhovnaya, *Khim.-Farm. Zh.* **19**, 626–627 (1985).
[3] J. T. Browne, in *Polarography of Molecules of Biological Significance* (W. Franklin Smyth, Ed.), pp. 111–113. Academic Press, London (1979).
[4] J. B. Flanagan, K. Takahashi and F. C. Anson, *J. Electroanalyt. Chem.* **257**, 257–266 (1977).
[5] W. Kemula and Z. Kublik, *Roczniki Chem.* **32**, 941–952 (1958).
[6] H. Lund, in *Organic Electrochemistry* (M. M. Bazier, Ed.), pp. 328–330. Marcel Dekker, New York (1973).

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