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Short communication

The study of the voltammetric behaviour of flunarizine☆

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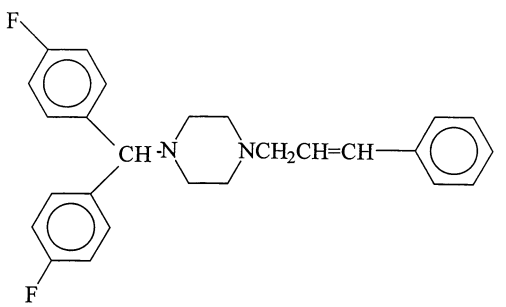
1. Introduction

Flunarizine, [(E)-1-[Bis (4-fluorophenyl) methyl]-4-(3-phenyl-2-propenyl) piperazine], a fluorinated derivative of cinnarizine, is a selective calcium entry blocker, widely used in cerebral and peripheral vascular disorders.



The compound has undergone the most extensive evaluation, and it may reduce the frequency of either classical or common migraine attacks by as much as 90%. It may also be effective in preventing more complicated syndromes, such as childhood hemiplegic migraine [1].

Chromatographic procedures including gas chromatography [2–5] and high pressure liquid chromatography [5–8] have been mainly used for the analysis of the drug and its metabolites in biological fluids. In recent years, capillary zone electrophoresis [9] has been applied to the determination of the drug in blood. Methods for the assay of flunarizine in pharmaceutically dosage forms are usually based on spectrophotometric determinations [10–12]. A potentiometric titration procedure using polymeric modified electrode has also been developed for the determination of the drug in pharmaceutical formulations [13]. There is no official method for the drug in any pharmacopoeia.

To our knowledge, no information about the electrochemical redox properties of flunarizine and related compound, cinnarizine, have appeared in the literature.

The aim of this study was to investigate the voltammetric behaviour of flunarizine at an activated glassy carbon electrode. The application of

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the method to the analysis of the drug in pharmaceutical formulations was also assessed. The results were compared statistically with a simple newly developed first derivative UV spectrophotometric procedure.

2. Experimental

2.1. Apparatus

Voltammetric analysis was performed with a PRG-3 polarograph and an EPL2 recorder (Tacussel Electronique). A saturated calomel electrode (SCE) and a platinum wire electrode were used as the reference and counter electrodes, respectively. A glassy carbon electrode (Tacussel XM540), 1.013 cm^2 in area was used as the working electrode. For the application of pretreatment to the glassy carbon electrode, a Wenking model HP 70 potentiostat and an exact-type 250 function generator were used. Electrode activation procedure was carried out as described previously [14].

A Shimadzu 1601 PC double beam UV–Vis spectrophotometer with a fixed slit width (2 nm) connected to an IBM computer loaded with Shimadzu UVPC software, and equipped with a Lexmark printer, was used for all the absorbance measurements and treatment of data.

2.2. Reagents

Flunarizine (generously provided by Eczacíbasí Pharmaceuticals Corporation, Istanbul, Turkey) was used without further purification.

All other chemicals used were of analytical reagent grade and supplied by Sigma or Merck.

All solutions were prepared with doubly distilled water.

Stock solutions were renewed daily and prepared in methanol. The working solutions under voltammetric investigations were prepared by dilution of the stock solution and contained 20% methanol. 0.5 M sulphuric acid, 0.2 M acetate buffer pH 3–5 and 0.2 M Britton–Robinson buffer pH 2–5 were used for the supporting electrolytes. Neutral and alkaline media were avoided as flunarizine undergoes a precipitation in such media.

Stock solutions for spectrophotometric measurements were used in the preparation of calibration graphs and for spectra after appropriate dilution with methanol.

2.3. Analysis of pharmaceutical capsules

The average mass of ten hard 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 1×10^{-3} M, was weighed, transferred into a 100 ml calibrated flask and completed to the volume with methanol. The content was filtered after stirring magnetically for 15 min.

Appropriate solutions were prepared by taking suitable aliquots of the clear filtrate and then diluting with the supporting electrolyte (0.5 M H_2SO_4). Each solution was analyzed by voltammetry as in pure drug.

Spectrophotometric analysis was carried out on an analogous solution with methanol (instead of 0.5 M H_2SO_4), by using the corresponding calibration curve.

3. Results and discussion

Flunarizine gave rise to a single oxidation process at the glassy carbon electrode in all the range of studied pH s ($1.2 < pH < 5$). This response was better resolved in sulphuric acid. In other electrolytes, however, dramatically decreased current response were found with a peak broadening. The cyclic voltammetric behaviour of flunarizine in 0.5 M sulphuric acid is shown in Fig. 1, indicating that the drug is irreversibly oxidized at the glassy carbon electrode.

Linear sweep voltammograms obtained for increasing values of the scan rate showed the existence of a linear dependence of the peak intensity upon the square root of the scan rate between 10 and 100 mVs^{-1}. The characteristics of this graph were slope 7.61 and correlation coefficient $r = 0.9999$. This consideration pointed to a diffusion-controlled process.

The relation of the peak height with pH is shown in Fig. 2. The peak potential was almost pH independent. By increasing the pH from 1.2 to 2.2, the peak current showed a sharp decrease and then remained constant up to pH 5.0.

Various electrolytes, such as sulphuric acid, Britton–Robinson and acetate buffers were examined. The influence of different supporting electrolytes is shown in Table 1. The best result with respect to signal enhancement accompanied by sharper response, was obtained with sulphuric acid.

Taking into account that as flunarizine contains an aliphatic tertiary amine in its molecular structure it represents a basic centre with the availability of non-bonding electron as donors, we assumed that the oxidation step of flunarizine is located on the piperazine ring.

3.1. Quantitative analysis

In order to develop a voltammetric methodology for determining the drug, we selected a supporting electrolyte of 0.5 M sulphuric acid (20% methanol) and a scan rate of 100 mVs^{-1}. The reproducibility of the measurement was calculated from four independent runs of 2×10^{-4} M flunarizine obtaining a relative standard deviation of 0.92%.

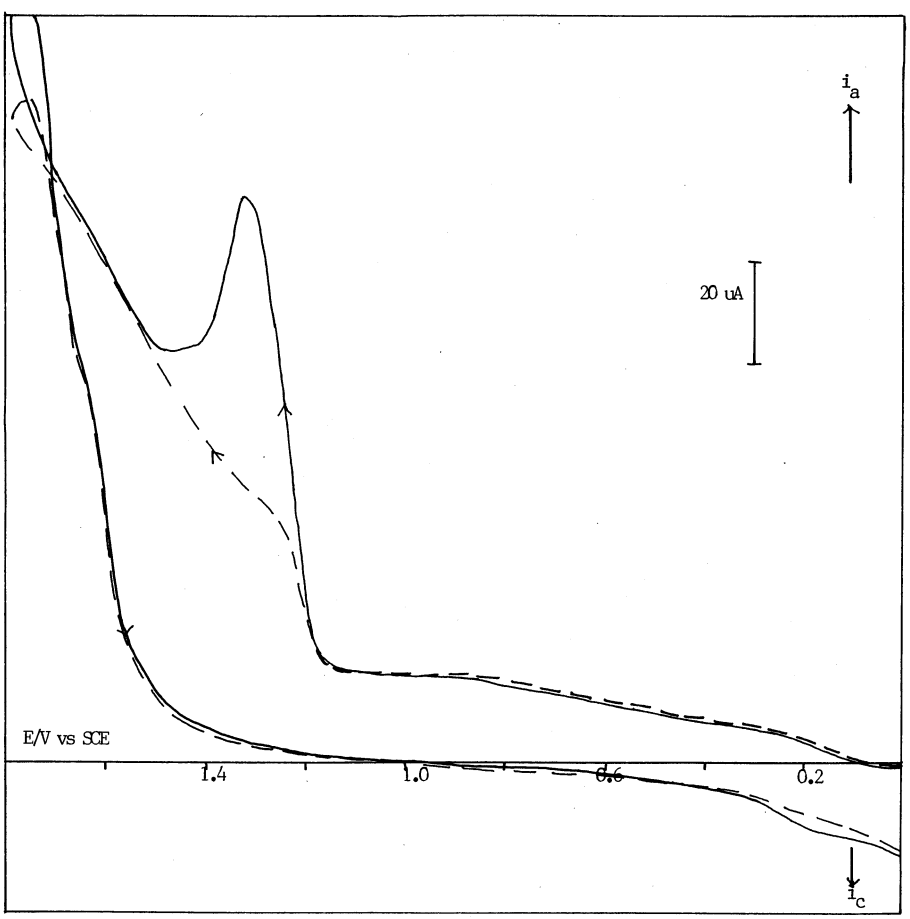

Fig. 1. Cyclic voltammogram of 2×10^{-4} M flunarizine solution in 0.5 M H_2SO_4 with 20% methanol. Scan rate, 100 mVs^{-1}. (Dashed line, supporting electrolyte).

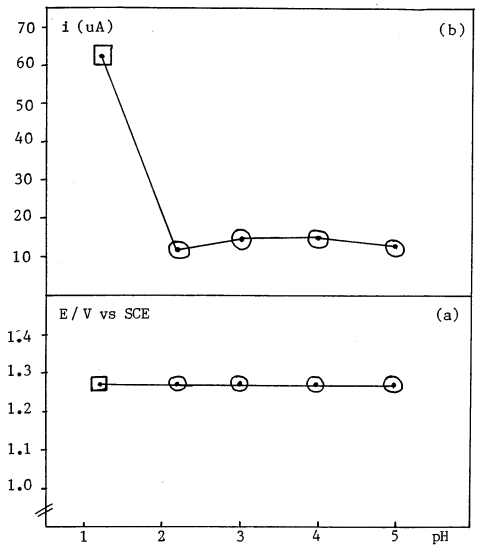

Fig. 2. Effect of the pH on flunarizine oxidation. Flunarizine concentration, 2×10^{-4} M; Scan rate, 100 mVs^{-1}. (□) H_2SO_4, (○) B–R buffer.

For quantitation, the calibration curve method, with concentrations ranging between 6×10^{-6} and 2×10^{-4} M, was used. The analytical characteristics of the method are summarized in Table 2.

Furthermore, to obtain comparative results, first derivative UV spectroscopic method was also developed. As shown in Fig. 3, the original (zero-order) UV spectrum of flunarizine in methanol has broad absorption bands between 208 and 285 nm.

In contrast, first order derivative UV spectrum (Fig. 4) has sharper and better defined peaks than the original, which is applicable to the drug avoiding any risks of matrix interferences. The determination was performed by reading the $dA/d\lambda$ values at 267.9 nm in the first derivative spectra of the sample solution in methanol. The concentration range for compliance with Beer's law was $1.5–6 \times 10^{-5}$ M. The results of statistical analysis of flunarizine using derivative spectroscopy are also listed in Table 2.

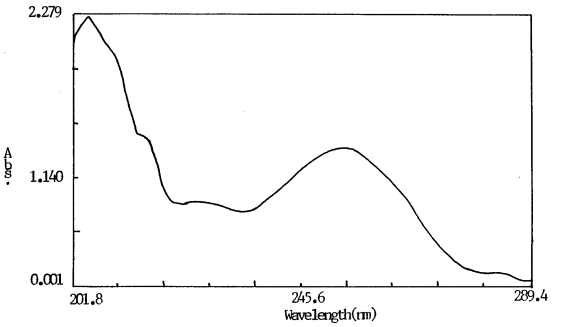

Fig. 3. Zero-order absorption spectra of 6×10^{-5} M flunarizine in methanol.

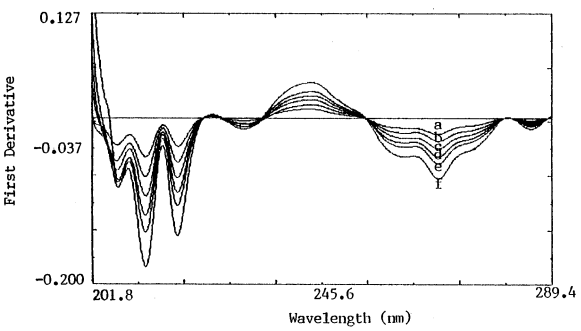

Fig. 4. First-derivative absorption spectra of (a) 1.48×10^{-5} M, (b) 2.2×10^{-5} M, (c) 2.97×10^{-5} M, (d) 3.71×10^{-5} M, (e) 4.45×10^{-5} M, (f) 6×10^{-5} M flunarizine in methanol.

The reported methods were applied to the commercial hard gelatine capsule preparations. In

Table 1
Voltammetric characteristics of flunarizine in different supporting electrolytes (20% methanol). Flunarizine concentration, 2×10^{-4} M.

Supporting electrolyte	Studied pH range	Selected pH	Ep/V	i/μA
Sulphuric acid		1.2	1.27	56
Britton–Robinson buffer	2–5	2.2	1.27	12
		3.0	1.27	15
Acetate buffer	3–5	3.0	1.27	10
		4.7	1.27	9

Table 2
Statistical analysis of flunarizine using both of the proposed methods

	Medium	Concentration range (M)	Slope	Intercept	Correlation coefficient	S.E. of slope	S.E. of intercept
Voltammetry	0.5 M H_2SO_4 (20% methanol)	6×10^{-6}–2×10^{-4}	2.92×10^{5}	2.80	0.9987	5.73×10^{3}	0.48
Spectrophotometry	Methanol	1.5×10^{-5}–6×10^{-5}	1.29×10^{3}	1.8×10^{-3}	0.9987	32.81	1.23×10^{-3}

Table 3
Comparative studies for flunarizine capsules

Drug[a] (Sibelium®)	Voltammetry	Derivative spectrophotometry
Mean (mg)[b]	4.97	5.02
S.D.	0.389	0.076
t-test of significant	$t_{calculated}$: 0.699	$t_{theoretical}$ (95%): 2.306

[a] Each capsule contains 5 mg flunarizine
[b] Each value is the mean of five experiments.

Table 3 the results obtained in the analysis of capsules are summarized. The methods for the determination of flunarizine in pharmaceutical formulations are very simple and rapid. According to the results of *t*-test at the 95% probability level, insignificant differences appeared between the methods. In comparison to the spectrophotometric method, the proposed voltammetric method is less sensitive, however, the linearity range was broader than that of compared method. Moreover, the accuracy of the methods was also evaluated by recovery studies after adding known amount of pure drug to various pre-analyzed formulations of flunarizine. Results from five determinations yielded mean recovery of 99.3 and 99.6% and the relative standard deviation of 1.41 and 0.67% using voltammetric and spectrophotometric method, respectively.

4. Conclusion

It is concluded that, the proposed voltammetric method has the advantages of being simpler, faster and less expensive than published procedures. The developed method is also sensitive enough to determine flunarizine in commercial preparations without any interference from the additives.

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