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Short communication

# Differential pulse cathodic voltammetric determination of floctafenine and metopimazine

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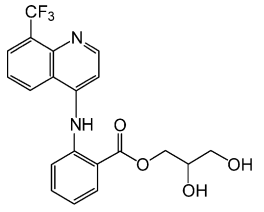
**Abstract**

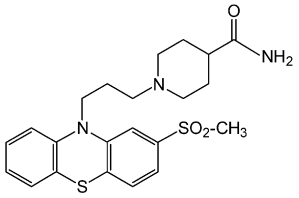
A simple, rapid and sensitive voltammetric method for the determination of floctafenine (FFN) and metopimazine (MPZ) was developed. Well-defined cathodic waves were obtained for both drugs in Britton–Robinson buffer pH 9.0 using the differential-pulse mode at the hanging mercury drop electrode (HMDE). The current–concentration relationship was found to be linear over the ranges 0.4–3.6 and 0.4–2.4 μg ml$^{-1}$ for FFN and MPZ, respectively. The quantification of the two drugs in their pharmaceutical formulations was carried out using the proposed voltammetric method and compared with spectrophotometric analysis data. The mechanisms of the electrode reactions for the two drugs were proposed.


*Keywords:* Floctafenine; Metopimazine; Differential-pulse; Voltammetric determination; HMDE

## 1. Introduction



Floctafenine



Metopimazine

Floctafenine (FFN) is a non-steroidal analgesic anti-inflammatory drug, used in musculoskeletal and joint disorders. It is given by mouth for the short-term relief of pain [1]. Few methods have been reported concerning the analysis of FFN. In biological fluids, FFN and its major metabolite, floctafenic acid, have been assayed using HPLC [2,3], derivative synchronous spectrofluorimetry [4] and direct and synchronous spectrofluorimetry [5]. Derivative spectrophotometry [6] has been applied for the determination of FFN and its degradation products. In pharmaceuticals, FFN has been determined using direct and synchronous spectrofluorimetry [5], derivative spectrophotometry [7], and spectrophotometry [8].

Metopimazine (MPZ) is a phenothiazine dopamine antagonist with an antiemetic action. It is used in the treatment of nausea and vomiting, including that associated with cancer chemotherapy [1]. Only single analytical procedure is available in the literature for its analysis. It involves the application of HPLC for the simultaneous determination of MPZ and its acid metabolite in serum [9].

No attempts have yet been made to determine either floctafenine or metopimazine by any electrochemical method. Both drugs contain reducible functional groups which can be the basis for a cathodic voltammetric procedure. The aim of this work is to develop a simple and reliable method for their determination; based on the differential-pulse cathodic voltammetric measurement of the two drugs on the hanging mercury drop electrode (HMDE).

## 2. Experimental

### 2.1. Apparatus

The voltammograms were obtained with a Metrohm 693 VA Processor. A Metrohm 694 VA Stand was used in the hanging mercury drop electrode (HMDE) mode. The three electrode system was completed by means of a Ag/AgCl (3 M KCl) reference electrode and a Pt auxiliary electrode. For pH measurements, a Jenway 3310 digital pH meter was used.

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### 2.2. Materials

All materials used were of analytical reagent grade. High purity distilled water was used allover the study. FFN was kindly donated by Roussel-Uclaf, Romainville, France and MPZ was kindly supplied by Amriya Pharmaceutical Industries, Alexandria, Egypt. Pharmaceutical formulations were purchased from the local market in Egypt. Idarac dispersible tablets (Batch no. 28202), Global Napi Pharmaceuticals, Egypt under licence of Aventis Pharma S.A.E., labeled to contain 200 mg floctafenine micronized per tablet. Vogalene syrup (Batch no. 853903), Amriya Pharmceutical Industries, Alexandria, Egypt under licence of Rhône-Poulenc-Rorer, Paris, France, labeled to contain 5 mg metopimazine per 5 ml.

### 2.3. Solutions and reagents

FFN stock solution, 400 μg ml$^{-1}$ and MPZ stock solution, 400 μg ml$^{-1}$, were prepared in methanol. Working solutions of either FFN or MPZ 100 μg ml$^{-1}$ were prepared by dilution of aliquots of the stock solutions in methanol and stored refrigerated at 4 °C.

The studies were carried out in Britton–Robinson buffer (0.04 M in each of acetic, *o*-phosphoric and boric acids) adjusted to the required pH with 0.2 M sodium hydroxide solution.

### 2.4. Procedure for voltammetric analysis

Aliquots from the working solutions of FFN and MPZ, within the concentration ranges shown in Table 1, were transferred into two separate sets of 10-ml volumetric flasks and completed to volume with Britton–Robinson buffer pH 9.0 for the two drugs. The content of each flask was transferred into the measuring vessel and purged with pure nitrogen for 5 min then the DP voltammograms were recorded using the HMDE as working electrode.

The differential-pulse voltammetric measurements were performed for both drugs with −100 mV pulse amplitude and maximum drop size, 9 (0.6 mm$^2$ drop area). For FFN assay, the voltammogram was recorded from 0 to −1600 mV at a scan rate of 25 mV/s versus Ag/AgCl reference electrode.For MPZ assay, the voltammogram was recorded from 0 to −2000 mV at a scan rate of 20 mV/s versus Ag/AgCl reference electrode.

### 2.5. Procedure for pharmaceutical preparations

#### 2.5.1. For FFN

A total of 20 tablets were massed and finely powdered. To an accurately weighed quantity of the powder containing the equivalent of 40 mg FFN, 60 ml methanol were added, stirred for 10 min then filtered into a 100-ml volumetric flask. The residue was washed with two 10 ml portions of methanol and washings were added to the filtrate and diluted to volume with methanol. Working tablet solution was prepared by dilution with methanol to reach a concentration of 100 μg ml$^{-1}$ FFN. Aliquots of the working tablet solution were diluted with Britton–Robinson buffer pH 9.0 to give the concentrations mentioned in Table 1. These final solutions were measured as under procedure for voltammetric analysis.

#### 2.5.2. For MPZ

An accurate volume (1.0 ml) of the syrup was transferred into a 10-ml volumetric flask and diluted to volume with Britton–Robinson buffer pH 9.0. Aliquots of this diluted solution were diluted with the same buffer to reach the concentrations mentioned in Table 1. These final solutions were measured as under procedure for voltammetric analysis.

## 3. Results and discussion

FFN exhibited a well defined differential pulse cathodic peak in the pH range 5–12, while the cathodic peak of MPZ was exhibited in a narrow pH range of 8–10. The FFN peak lied in the potential range of −1.05 to −1.27 V, while that of MPZ was shown at −1.85 V allover the studied pH range. Maximum peak current for both drugs was obtained using B–R buffer pH 9.0 which can be successfully used to determine FFN and MPZ by applying a differential-pulse voltammetric method and measuring the peak current at peak potential of −1.175 and −1.85 V for FFN and MPZ, respectively (Figs. 1 and 2).

Concerning the reversibility of the electrochemical reduction process, cyclic voltammetry is the best method to determine

Table 1
Experimental and analytical parameters for the differential-pulse voltammetric determination of FFN and MPZ

| Parameter | FFN | MPZ |
|---|---|---|
| Buffer | B–R pH 9.0 | B–R pH 9.0 |
| Pulse amplitude (mV) | −100 | −100 |
| Scan rate (mV/s) | 25 | 20 |
| $E_p$ (V) | −1.175 | −1.850 |
| Linearity range (μg ml$^{-1}$) | 0.4–3.6 | 0.4–2.4 |
| Regression equation $I_p = a + bC$ | $I_p = -1.250 + 133.69C$ | $I_p = -37.458 + 2903.81C$ |
| Correlation coefficient ($r$) | 0.99987 | 0.99983 |
| $S_a$ | 3.3176 | 56.637 |
| $S_b$ | 1.5143 | 37.509 |
| $S_{y/x}$ | 2.7088 | 57.622 |
| LOD (μg ml$^{-1}$) | 0.0286 | 0.0724 |
| LOQ (μg ml$^{-1}$) | 0.0953 | 0.2413 |

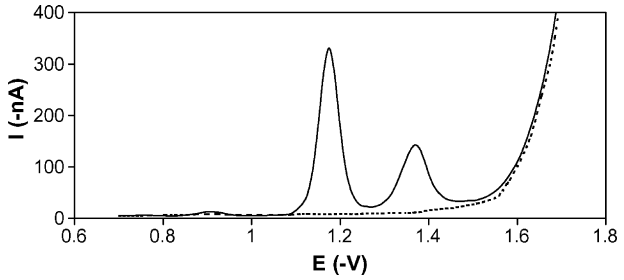



Fig. 1. Differential-pulse voltammogram of 2.4 μg ml$^{-1}$ FFN (—) and B–R buffer pH 9 (- - -), vs. Ag/AgCl reference electrode.

whether the electrode reaction is reversible or not, but unfortunately, it was not available in the instrument, therefore the reversibility of the electrode reaction was checked using the method reported by Birke et al. [10]. The DP voltammogram was recorded with a negative going potential pulse (−100 mV), then with a positive going potential pulse (+100 mV). It was found that both the FFN and MPZ reduction processes correspond to the quasi-reversible criteria: $E_p^c - E_p^a < |\Delta E|$, where $\Delta E$ is the pulse magnitude and $I_p^a/I_p^c < 1$. For FFN, these values were $E_p^c - E_p^a = 67$ ($\Delta E = 100$ mV) and $I_p^a/I_p^c = 0.41$ (<1) while for MPZ, these values were $E_p^c - E_p^a = 48$ ($\Delta E = 100$ mV) and $I_p^a/I_p^c = 0.77$ (<1). A further discussion of the reduction reversibility of the two drugs must be postponed until more evidence is available.

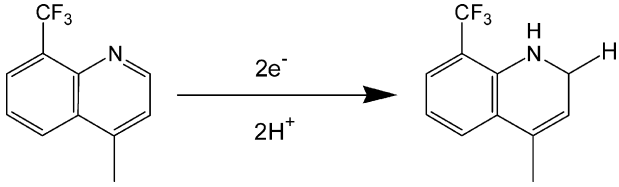
A linear plot of peak current ($I_p$) versus the square root of the scan rate ($\nu^{1/2}$) was obtained indicating that diffusion is the means of mass transport [11]. Correlation coefficients of the linear plots were 0.99740 and 0.99592 for FFN and MPZ, respectively.

### 3.1. The electrode reaction

FFN shows a voltammetric peak at −1.175 V using the HMDE versus Ag/AgCl electrode in B–R buffer pH 9.0. This cathodic peak is attributed to the reduction of the azomethine group located in the quinoline moiety.

It has been reported that compounds possessing azomethine group are polarographically reducible. Examples of these compounds are the closely related compound, glafenine [12] which showed a cathodic polarographic wave at −1.145 V in B–R buffer pH 8.5, doxazocin [13] giving a reduction peak at −1.33 V and buspirone hydrochloride and piribedil [14] which showed voltammetric signals at about −1.2 V in B–R buffer pH 7.0.

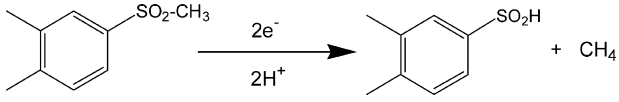
The reduction of the azomethine group involves two electrons and two protons. The following mechanism is proposed for the reduction behavior.




Another peak of lower sensitivity at −1.37 V can be seen in the voltammogram of FFN (Fig. 1). This peak was not observed in the polarogram of the closely related drug, glafenine [12], therefore this reduction peak can be attributed to the trifluoromethyl group which is located at $C_8$ in the quinoline moiety of FFN while glafenine lacks this group. A proposed mechanism concerning the reduction of this functional group is shown in the following scheme.

$$Ar - CF_3 \xrightarrow[2H^+]{2e^-} Ar - H + CHF_3$$

On the other hand, MPZ reduction peak at −1.85 V can be explained by the reductive cleavage of the C–S bond in the methylsulfone group. It has been reported that several arylsulfone compounds show polarographic reduction peaks at potentials ranging from −1.4 to −2.1 V [15]. A two electron reduction occurs with both aralkyl- and diarylsulfones, and is supposed to form a sulfinic acid derivative and a hydrocarbon [15,16]. Based on the above facts, a proposed pathway for the reduction of MPZ is demonstrated in the following scheme.




### 3.2. Optimum reaction conditions

Factors affecting the peak current were studied and optimized. Britton–Robinson buffer was chosen as a supporting electrolyte for the DP voltammetric determination of both drugs. The effect of pH on the peak current was studied over the pH range 5–12 for FFN and it was found that pH 9.0 gave the highest peak current (Fig. 3). In case of MPZ, the influence

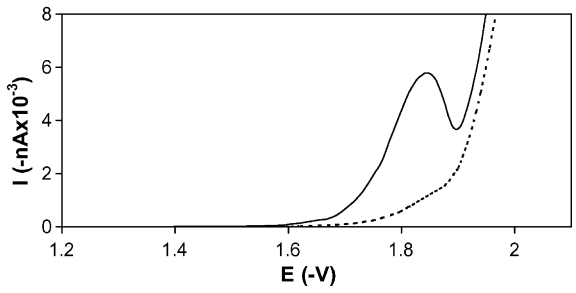



Fig. 2. Differential-pulse voltammogram of 1.6 μg ml$^{-1}$ MPZ (—) and B–R buffer pH 9 (- - -), vs. Ag/AgCl reference electrode.

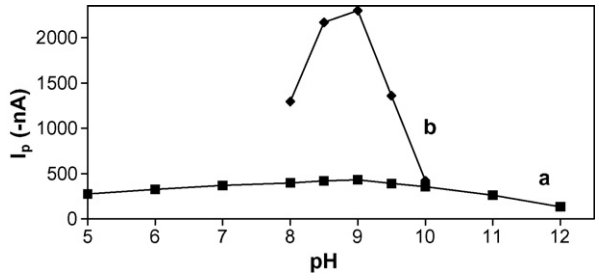



Fig. 3. Effect of buffer pH on the peak current ($I_p$) of the DP cathodic reduction of: (a) 3.2 μg ml$^{-1}$ FFN and (b) 0.8 μg ml$^{-1}$ MPZ using optimum conditions for each compound.

of pH on the peak current was studied in the range of 8–10. No peak could be observed below pH 8, this may be because the MPZ peak was completely overlapped by the very high current of the buffer. Maximum MPZ peak current was observed at pH 9.0, above which the current rapidly declined and the peak was completely vanished at pH higher than 10 (Fig. 3). The effect of pH on the peak potential ($E_p$) was also studied. In case of FFN, the $E_p$ values were shifted to more negative potential upon increasing the pH. The relationship was almost linear with slope of 0.033 V $pH^{-1}$ and correlation coefficient of 0.99552. On the other hand, the $E_p$ values of MPZ were found to be pH-independent, i.e., the peak potential was almost fixed at −1.85 V allover the pH range of 8–10.

Instrumental conditions affecting the peak current were also optimized. Maximum response was obtained at scan rate of 25 and 20 mV/s. for FFN and MPZ, respectively and pulse amplitude of −100 mV was chosen for analytical measurement of both drugs. The optimum assay parameters for FFN and MPZ were summarized in Table 1.

### 3.3. Statistical analysis of results

#### 3.3.1. Concentration ranges and calibration graphs

Under the optimized conditions previously mentioned, the peak current monitored was found to be proportional to the drug (FFN or MPZ) concentration. Data recorded in Table 1 summarizes the characteristics of the calibration plots of FFN and MPZ. Both plots are linear over the entire range examined (0.4–3.6 μg $ml^{-1}$ for FFN and 0.4–2.4 μg $ml^{-1}$ for MPZ) with slopes 133.69 and 2903.81 nA $\mu g^{-1}$ ml for FFN and MPZ, respectively. Other important statistical parameters such as the standard deviation of the intercept ($S_a$), the slope ($S_b$) and standard deviation of residuals ($S_{y/x}$) are also given in Table 1.

#### 3.3.2. Detection and quantitation limits

The detection and quantitation limits mentioned in Table 1 are calculated according to the formulae given by Miller [17]. Experimentally, detection limits were found to be 0.07 and 0.1 μg $ml^{-1}$ for FFN and MPZ, respectively while the quantitation limit for both drugs was 0.4 μg $ml^{-1}$ with a 2% R.S.D.

#### 3.3.3. Precision and accuracy

Precision (percentage relative standard deviation, R.S.D. (%)) and accuracy (percentage relative error, $E_r$ (%)) of the proposed voltammetric method were tested using different concentration levels of each drug repeated at least three times. The R.S.D. (%) and $E_r$ (%) values were less than 1.5% indicating good repeatability and accuracy of the proposed method (Table 2).

### 3.4. Assay of pharmaceutical preparations

The proposed voltammetric method was applied to the determination of FFN and MPZ in their dosage forms. The two drugs could be directly determined without any interference from the tablet excipients or the components of the syrup (sugar, flavor, preservative, etc.), and this clearly demonstrates the specificity and selectivity of the method. As shown in Table 3, the proposed method gave satisfactory recovery data and precision for both drugs.

Table 2
Precision and accuracy for the determination of FFN and MPZ using the proposed DP voltammetric method

| Analyte | Nominal value (μg $ml^{-1}$) | ($\bar{X}$ ± S.D.)[a] (μg $ml^{-1}$) | R.S.D. (%)[b] | $E_r$ (%)[c] |
|---|---|---|---|---|
| FFN | 0.8 | 0.806 ± 0.005 | 0.620 | 0.75 |
| | 1.6 | 1.590 ± 0.011 | 0.692 | −0.62 |
| | 2.4 | 2.385 ± 0.020 | 0.839 | −0.62 |
| | 3.2 | 3.220 ± 0.025 | 0.776 | 0.63 |
| MPZ | 0.8 | 0.810 ± 0.008 | 0.988 | 1.25 |
| | 1.2 | 1.206 ± 0.009 | 0.746 | 0.50 |
| | 1.6 | 1.591 ± 0.011 | 0.691 | −0.56 |
| | 2.0 | 2.011 ± 0.016 | 0.796 | 0.55 |

[a] Mean ± S.D. for three determinations.
[b] % Relative standard deviation.
[c] % Relative error.

Table 3
Application of the proposed voltammetric method for the determination of FFN and MPZ in their pharmaceutical preparations

| | Voltammetric method | Reference method |
|---|---|---|
| Idarac-D® tablets | | |
| % Recovery ± S.D.[a] | 99.48 ± 0.950 | 100.20 ± 0.634 |
| R.S.D. (%)[b] | 0.955 | 0.633 |
| $E_r$ (%)[c] | −0.52 | 0.20 |
| $t$[d] | 1.414 | |
| $F$[d] | 2.249 | |
| Vogalene® syrup | | |
| % Recovery ± S.D.[a] | 99.65 ± 1.297 | 98.96 ± 0.797 |
| R.S.D. (%)[b] | 1.302 | 0.805 |
| $E_r$ (%)[c] | −0.35 | −1.04 |
| $t$[d] | 1.005 | |
| $F$[d] | 2.645 | |

[a] Mean % recovery ± S.D. for five determinations.
[b] % Relative standard deviation.
[c] % Relative error.
[d] Theoretical values for $t$ and $F$ at $P = 0.05$ are 2.31 and 6.39, respectively.

Reference methods were adopted for the assay of FFN in tablets and MPZ in syrup form. FFN in Idarac-D® tablets was assayed spectrophotometrically through the reaction with *p*-chloranilic acid and measuring the $^1D$ of the product at 375 nm [7]. MPZ in Vogalene® syrup was assayed using a difference spectrophotometric technique based on measuring the $\Delta A$ at 358 nm after the addition of a solution of hydrogen peroxide and glacial acetic acid [18,19]. Applying the Student's *t*- and the variance ratio *F*-tests, the calculated values did not exceed the theoretical ones at $P = 0.05$, demonstrating that the proposed method is as accurate and precise as the reference spectrophotometric methods.

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