POTENTIOMETRIC AND SPECTROPHOTOMETRIC DETERMINATION OF PHENOTHIAZINE DERIVATIVES BASED ON THEIR TITRATION WITH 2,3-DICHLORO-5,6-DICYANO-1,4-BENZOQUINONE

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Abstract

The reaction between phenothiazine and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in the presence of *p*-toluenesulfonic acid in chloroform was investigated by potentiometry, voltammetry and spectrophotometry, and the reaction pathways were proposed. The conditions for the oxidimetric titration of phenothiazines with a standard chloroform solution of DDQ were optimized and the potentiometric and spectrophotometric detections of the reaction end point were utilized. The relative standard deviations for the potentiometric determination of 3-5 mg phenothiazines and for the spectrophotometric determination of 0.1-0.2 mg phenothiazines were found to be about 1.2-1.7% and 0.8-1.2%, respectively. The proposed methods were applied to the determination of phenothiazine derivatives in pharmaceutical preparations after their extraction into chloroform.

Introduction

Phenothiazine derivatives are widely used as antihistamines, tranquilizers, antiemetics and antiparkinson drugs. The vital importance of these drugs prompted the development of many analytical methods for their determination.[1-3] These methods include a variety of spectrophotometric and fluorimetric[4-14] and electroanalytical procedures.[15-29] Some of the reported methods for the determination of different phenothiazine derivatives involve a preliminary separation by solvent extraction into a proper organic solvent. The direct application of potentiometric titration method by using suitable reagents to the extracts can then provide fast and sensitive methods for the drugs' analysis.[23,25,26,29]

The oxidation of phenothiazine derivatives is known to involve a series of one-electron steps providing free radicals and cations.[30-32] Thus, exploring suitable oxidizing agents for the potentiometric titration of these drugs is of increasing interest.[1-3] Quinones belong to a group of mild oxidizing reagents whose oxidizing power is seriously related to the acidity of the medium.[33] In this paper we studied the reaction between

2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and phenothiazines in acidic chloroform solution by different potentiometric, voltammetric and spectrophotometric methods, in order to develop new analytical methods on the basis of the oxidimetric titration for the determination of phenothiazine derivatives. The phenothiazine derivatives investigated include chlorpromazine, promethazine, thioridazine, perphenazine, and trifluperazine.

Experimental

Apparatus. Potential measurements were carried out with a model E632 Metrohm pH/Ion-meter. A Metrohm multipurpose instrument model 693 VA processor equipped with a model 694 stand and a thermal printer was used to record the voltammograms via a three-electrode system. A Metrohm drive shaft was used for rotating disk electrodes. A GBC911 UV-Vis spectrophotometer with 1 cm matched cells was used for recording the electronic spectra. A model 662 Metrohm probe-type spectrophotometer was used for spectrophotometric titrations at fixed wavelengths. All experiments were carried out at 25.0 ± 0.1 °C using a D1 Haake thermostat.

Electrodes. A Pt indicator electrode and a Pt disk working electrode (both from Metrohm) were used in potentiometric and voltammetric experiments, respectively. The reference electrode Ag/AgCl (satd) in 0.5 M tetrabutylammonium perchlorate (TBAP) in chloroform prepared in a separated compartment with a dense ceramic plug in the bottom was used.

Reagents. Reagent grade chloroform (Merck) was used as received. DDQ, TBAP, phenothiazine, chlorpromazine.HCl, promethazine.HCl, trifluperazine.HCl and perphenazine (all from Fluka) were of the highest purity available and used without any further purification. *p*-Toluenesulfonic acid (TSO_3H, Merck) or perchloric acid were used as suitable strong acid for acidifying the test solutions up to 0.1 M. A standardized solution of DDQ (about 1.0×10^{-3} M) in chloroform was used as titrant. This solution was stable in refrigerator for at least two days.

Standardization of DDQ.[34] A 10-mL portion of 1.0×10^{-3} M solution of DDQ in chloroform was filtered and evaporated at room temperature to dryness. The residue was dissolved in methanol and enough phosphoric acid was added to reach a final concentration of 10 M. The resulting solution was then titrated with a solution of

ammoniumiron(II) sulfate (1.0×10^{-3} M), standardized with potassium dichromate. The end point of titration was determined either potentiometrically or by using methylen blue as a suitable redox indicator.

Extraction and separation of phenothiazines from pharmaceutical preparations. The pharmaceutical preparations were obtained from local sources in various forms (tablet, syrup and injection), and their phenothiazines were extracted as follows. An accurately measured volume of syrup and injection solutions or weighed portions of finely powdered tablets equivalent to about 25 mg of phenothiazine drugs were transferred into a 100-mL separation funnel. A 5-mL portion of 1 M NaOH was added and extracted with three 10-, 10- and 5-mL portions of chloroform, shaking gently for 2-5 min to avoid emulsion formation. The extracts were combined in a 25-mL volumetric flask.

Potentiometric titration of phenothiazine drugs. A 10-mL portion of chloroform extracts, obtained from the extraction of sample pharmaceutical preparations, was pipetted into the reaction vessel and a required amount of *p*-toluenesulfonic acid or perchloric acid was added up to 0.1 M. The solution was titrated with a DDQ solution (about 1.0×10^{-3} M) in chloroform using a 10.0±0.1 mL burette or a 100±2 μL syringe. The quantitative determination of phenothiazine drugs in the extract is achieved in one of the following ways:

1. A standardized solution of DDQ is used in titration.
2. Another titration is carried out with a second 10-mL aliquot of the corresponding pure phenothiazine drug. The quantity of phenothiazine is calculated by comparison of the volumes of titrant consumed in the two titrations.

Spectrophotometric titration of phenothiazine drugs. A 0.1-1.0 mL portion of chloroform extract was transferred into the titration cell, diluted to about 5 mL with chloroform and a required amount of TSO_3H (0.1 M) or 0.1 mL of concentrated $HClO_4$ was added. The probe of the spectrophotometer was immersed into the resulting solution while it was stirred by a small magnetic stirrer. The solution was then titrated with a standard 1.0×10^{-3} M DDQ solution in chloroform using a calibrated micropipette at a suitable wavelength for each phenothiazine derivative.

Results and discussion

Voltammetric and potentiometric studies. The cyclic voltammograms of phenothiazine and DDQ in a chloroform solution of 0.1 M TSO_3H and 0.2 M TBAP at a stationary Pt disk electrode are shown in Figure 1. As is obvious, under the experimental conditions used, phenothiazine is oxidized in two one-electron steps at $(E_p)_a$ values of about 0.6 and 1.2 V vs. the reference electrode, respectively (Figure 1A), while the reduction of DDQ occurs in a single two-electrons step. Previous electrochemical studies have also revealed that the oxidation of phenothiazines in chloroform solutions of TBAP occurs in two one-electron reversible steps.[21,23,35] In this case, the products of the two electrochemical processes are a cation radical and a dication, respectively.

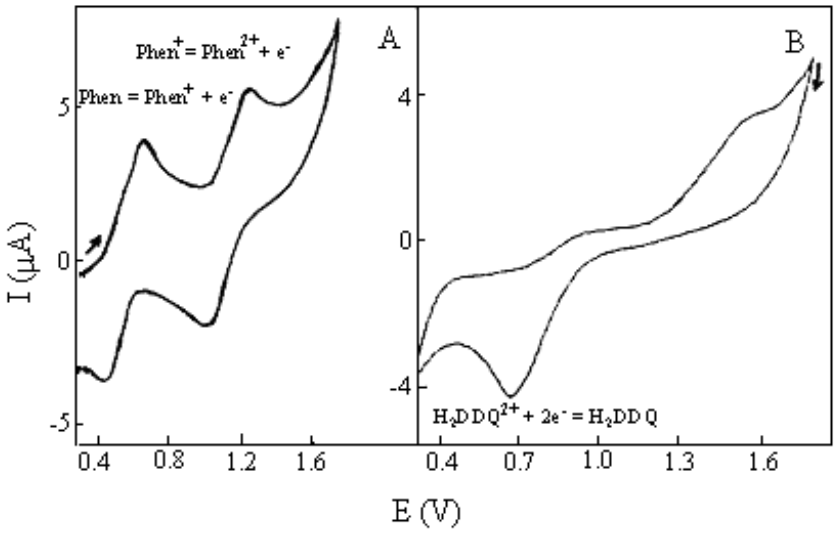

Figure 1. Cyclic voltammograms of (A) phenothiazine and (B) DDQ in 0.1 M TSO_3H in chloroform on a Pt disk electrode at a scan rate of 100 mVs^{-1}.

Previous electrochemical studies of quinone derivatives under nonaqueous conditions demonstrated that these compounds are reduced in two one-electron steps.[36-39] The first reduction step to a semiquinone anion radical is generally reversible, while the second step to a dianion is a nearly reversible or irreversible process, depending on the experimental conditions employed. However, in the presence of proton donors, the reduction of quinone derivatives is well known to occur via a single two-electron reversible or quasireversible process. Figure 1B shows the electrochemical reduction of DDQ in chloroform solution containing TSO_3H, as a proton donor reagent,

and TBAP, as a suitable supporting electrolyte. As it is seen, in contrast to common benzoquinone derivatives, at this condition DDQ is reduced in one completely irreversible step at a $(E_p)_c$ about 0.7 V. The reduction product is most possibly a hydroquinone molecule H_2DDQ. From Figure 1 it is immediately obvious that the reduction of DDQ occurs at a more positive potential than the first step oxidation potential of phenothiazine.

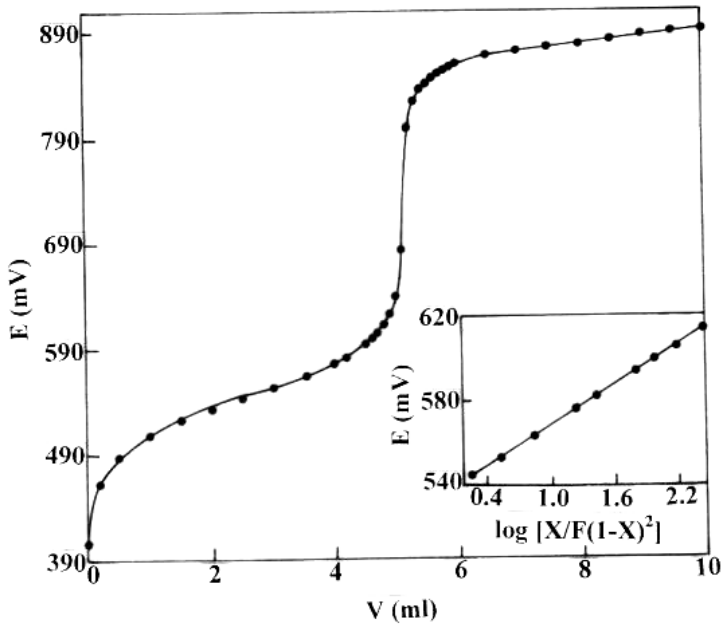

Figure 2. Potentiometric titration of 5 mL of 2.0×10^{-3} M phenothiazine + 5 mL of 0.2 M TSO_3H with a 9.7×10^{-4} M DDQ solution in chloroform. Inset is a plot of E vs log $[X/F(1-X^2)]$.

The potentiometric plot for the titration of 10 mL of 1.0×10^{-3} M phenothiazine in chloroform with a standardized chloroform solution of DDQ (9.7×10^{-4} M) in the presence of 0.1 M TSO_3H is shown in Figure 2. As seen, the potential ranges from 400 to 900 mV vs the reference electrode and only one sharp inflection point is observed at a phenothiazine/DDQ molar ratio of 2. Based on the results thus obtained, the titration reaction may proceed via the oxidation of phenothiazine (Phen) to a cation radical involving a single-step process and two-electron reduction of DDQ to a hydroquinone H_2DDQ as follows:

$$2\text{Phen} + (\text{HDDQ}^+)(\text{TSO}_3^-) + \text{TSO}_3\text{H} \leftrightarrow 2\text{PhenTSO}_3 + \text{H}_2\text{DDQ} \qquad \textbf{(I)}$$

or

$$2\text{Phen} + \text{H}_2\text{DDQ}(\text{TSO}_3)_2 \leftrightarrow 2\text{PhenTSO}_3 + \text{H}_2\text{DDQ} \qquad \textbf{(II)}$$

Alternatively, the proposed pathway can be tested by the analysis of the experimental titration curve. The electrode potential on the two sides of the equivalence point at 25 °C can be expressed as follows. Before the equivalent point:

$$\text{Phen}^+ + \text{e}^- \leftrightarrow \text{Phen}$$

$$E = E^\circ_{\text{Phen}} + 0.0591 \log \frac{[\text{Phen}^+]}{[\text{Phen}]} \qquad \textbf{(1)}$$

Because of the ion-pair formation, dissociation equilibrium should also be considered for PhenTSO_3 as:

$$\text{PhenTSO}_3 \overset{K_1}{\leftrightarrow} \text{Phen}^+ + \text{TSO}_3^-$$

$$K_1 = \frac{[\text{Phen}^+][\text{TSO}_3^-]}{[\text{PhenTSO}_3]} \qquad \textbf{(2)}$$

where $[\text{Phen}^+] = [\text{TSO}_3^-]$ and thus, $[\text{Phen}^+]^2 = K_1\,[\text{PhenTSO}_3]$. Equation (1) can then be written as:

$$E = E^\circ_{\text{Phen}} + \frac{0.0591}{2} \log \frac{K_1[\text{PhenTSO}_3]}{[\text{Phen}]^2} \qquad \textbf{(3)}$$

Considering X = (added DDQ)/(C_o/2), where C_o is the initial concentration of Phen, and on the basis of the reactions (I) or (II), at any point of titration, we can write:

$$[\text{Phen}] = F\,(C_o - XC_o) = FC_o(1 - X) \text{ and } [\text{PhenTSO}_3] = FXC_o, \qquad \textbf{(4)}$$

where F = V/(V + v), V is the initial volume of test solution and v is the volume of added DDQ. Thus,

$$E = E^\circ_{\text{Phen}} + \frac{0.0591}{2} \log \frac{K_1 FXC_o}{F^2 C_o^2 (1 - X)^2} \qquad \textbf{(5)}$$

or

$$E = a_1 + \frac{0.0591}{2}\log\frac{X}{F(1-X)^2} \quad \textbf{(6)}$$

with

$$a_1 = E^{o}_{Phen} + \frac{0.0591}{2}\log\frac{K_1}{C_o} \quad \textbf{(7)}$$

According to equation (6), the plot of E vs. log $(X/F(1-X)^2)$ for $0 < X < 1$ resulted in a straight line with a slope of 30-32 mV decade^{-1} (see the inset of Figure 2).

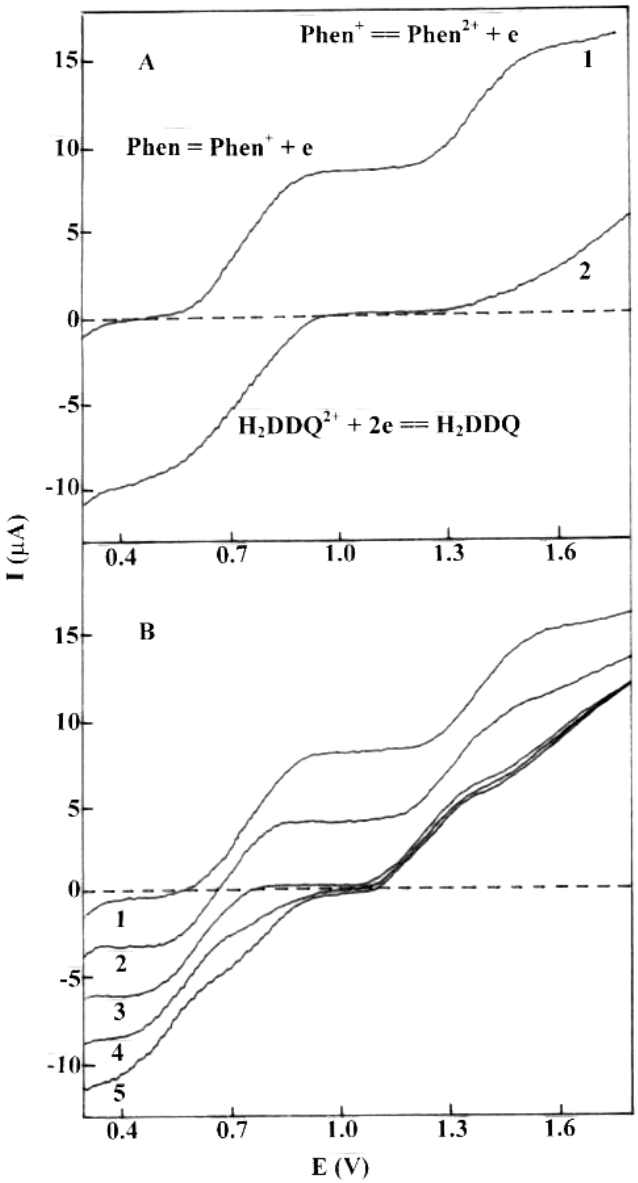

Figure 3. Potential-current curves of (A1) phenothiazine (0.5 mM), (A2) DDQ (0.5 mM) alone and (B) during titration of phenothiazine with DDQ: 1, X = 0; 2, X = 0.5; 3, X = 1.0; 4, X = 1.5; 5, X = 2.0.

After the equivalence point (i.e. X > 1), the potentials are expected to be corresponded to the equilibrium potential between DDQ added and H_2DDQ formed till the equivalence point. Any deviation from this potential will be due to the existence of excess amount of DDQ present after the equivalence point, which, of course, will not affect the accuracy of the titration.

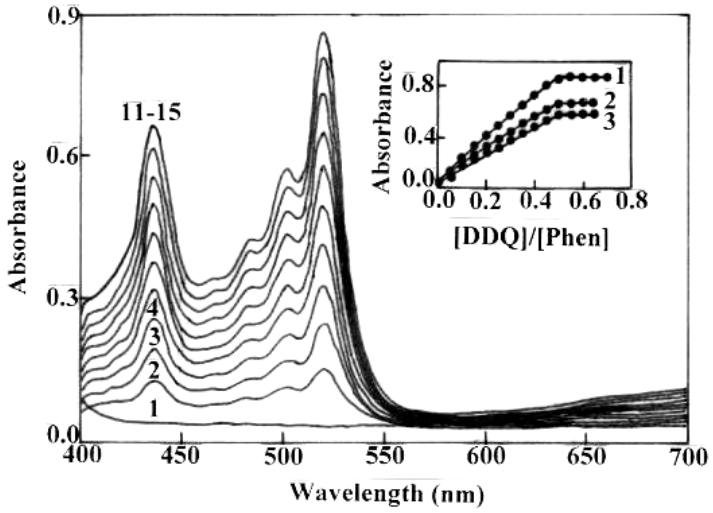

Figure 4. Visible spectra for the titration of 3 mL of 1.0×10^{-4} M phenothiazine + 0.1 M of TSO_3H with varying volume of 1.0×10^{-3} M DDQ in chloroform. The volume of titrant added (in μL) is: 2, 0; 3, 15; 4, 45; 5, 90; 6, 135; 7, 180; 8, 225; 9, 270; 10, 315; 11, 360; 12, 510; 13, 525; 14, 540; 15, 555. Curve 1 is the spectrum of 1.0×10^{-3} M DDQ in chloroform. Inset shows the corresponding absorbance-mole ratio plots at 1, 520 nm; 2, 502 nm; 3, 436 nm.

The RDE voltammograms of phenothiazine and DDQ alone, in the presence of 0.1 M TSO_3H and 0.5 M TBAP in chloroform, and those obtained during the titration of phenothiazine with DDQ, at various X values under the same experimental conditions, are shown in Figures 3A and 3B, respectively. As it is obvious from Figure 3A, according to the cyclic voltammograms shown in Figure 1, while DDQ is reduced in one step at an $E_{1/2} \cong 700$ mV vs. the reference electrode, phenothiazine is oxidized in two one-electron steps at $E_{1/2} \cong 600$ and 1300 mV. On the other hand, from Figure 3B, it is seen that upon addition of DDQ to an acidic solution of phenothiazine in chloroform, a new cathodic $Phen^+$/Phen wave is gradually appeared in the expense of decreasing height of the anodic $Phen^+$/Phen wave. It is interesting to note that, the equilibrium potential of the system at I = 0, at each X value during titration, exactly matches that obtained from

the potentiometric titration curve shown in Figure 2. However, the equilibrium potential at X > 1 values (i.e. curves 4 and 5 in Figure 3B) becomes constant at a value belonging to a mixed potential of the two redox systems $Phen^{2+}/Phen^{+}$ and H_2DDQ^{2+}/H_2DDQ. Such a mixed potential can be seen when one of the redox systems, or both of them, involve slow or irreversible steps.

Spectrophotometric studies. The absorption spectra of DDQ, phenothiazine and their mixture in an acidic chloroform solution are shown in Figure 4. As it is seen, while DDQ and phenothiazine have negligible absorption at 400-650 nm spectral region, the spectrum of their mixture in an acidic chloroform shows three absorption maxima at 436, 502 and 520 nm. These three absorption peaks are reported to be characteristics of a phenothiazine cation radical.[29]

The spectra of a 1.0×10^{-4} M phenothiazine in 0.1 M TSO_3H chloroform solution with varying volume of a standardized 1.0×10^{-3} DDQ in chloroform are given in Figure 4. The corresponding absorbance-[DDQ]/[Phen] mole ratio plots at wavelengths 520, 502 and 436 nm are shown in the inset of Figure 4. As it is obvious, at all three wavelengths, the absorbance of solution increases linearly until a [DDQ]/[Phen] mole ratio of 0.5 is reached. Further addition of DDQ solution resulted in no change in the measured absorbance of the solution.

Table 1. Determination of pure phenothiazine drugs by potentiometry, spectrophotometry and the official USP method.[a]

	Potentiometry			Spectrophotometry			USP method			
Phenothiazine	Taken (mg)[b]	Recovery (%)	RSD (%)	Taken (mg)[c]	Recovery (%)	RSD (%)	λ_{max} (nm)	Taken (mg)	Recovery (%)	RSD (%)
Chlorpromazine.HCl	5.0	101.2	1.4	0.2	99.5	0.7	537	50	100.7	0.8
Promethazine.HCl	5.5	100.8	1.6	0.2	101.6	1.4	535	50	101.5	0.5
Thioridazine.HCl	5.0	100.4	1.2	0.2	100.8	0.9	660	50	101.8	0.4
Perphenazine	5.0	99.9	1.2	0.2	98.7	1.1	537	50	100.2	0.2
Trifluperazine.2HCl	5.0	100.8	1.7	0.2	102.4	0.9	515	50	101.8	0.6

[a] Mean of three replicate analyses.
[b] 5 mL extract phase corresponding to the extraction of 25 mg of the phenothiazine drug in 25 mL chloroform.
[c] 2 mL extract phase corresponding to the extraction of 25 mg of the phenothiazine drug in 25 mL chloroform.

Table 2. Determination of phenothiazine drugs in pharmaceutical preparations.[a]

Phenothiazines	Declared amount	Found		
		Potentiometry	Spectrophotometry	USP Method
Promethazine tablet	25 mg/tablet	25.7 ± 0.5	26.2 ± 0.8	26.0 ± 0.5
Perphenazine tablet	8 mg/tablet	9.0 ± 0.1	9.1 ± 0.4	8.7 ± 0.3
Trifluperazine tablet	1 mg/tablet	1.1 ± 0.2	1.1 ± 0.3	1.2 ± 0.2
Trifluperazine ampoule	1 mg/mL	1.0 ± 0.2	1.1 ± 0.4	1.0 ± 0.4
Chlorpromazine tablet	25 mg/tablet	26.5 ± 0.5	25.2 ± 1.2	26.7 ± 0.3
Chlorpromazine ampoule	25 mg/mL	25.7 ± 0.7	26.2 ± 0.5	25.5 ± 0.7
Thoridazine tablet	10 mg/tablet	10.7 ± 0.8	11.0 ± 1.0	10.6 ± 0.5

[a] Mean of three replicate analyses.

Application to pharmaceutical analysis. The nature of acid used was found to influence the proposed potentiometric method. Of the various acids tested, *p*-toluenesulfonic acid, perchloric acid and sulfuric acid (~0.1 M of each) resulted in the most sensitive and stable potentiometric response for phenothiazine (Figure 2). However, for N-substituted phenothiazines the titration reaction proceeded successfully only in the presence of 0.1 M perchloric acid.

On the other hand, the spectrophotometric titration of the optimized concentration of drugs (i.e. about 1.0×10^{-4} M) was preformed successfully in the presence of 0.05-0.10 M TSO_3H for the case of phenothiazine, thioridazine and perphenazine. While the titration of trifluperazine and promethazine was only proceeded in the presence of 0.1 mL of concentrated perchloric acid. In should be noted that, in this case, addition of excess perchloric acid resulted in either a two-phase mixture or darkening of the sample solution. The absorbance measurements were performed at λ_{max} of each phenothiazine derivative, as mentioned in Table 1.

The precision and accuracy of the proposed methods were evaluated by analysis of three pure samples of each phenothiazine derivative and comparing by the official USP method based on their acidimetric titration in anhydrous acetic acid.[40] The results are summarized in Table 1. As seen, the recoveries and relative standard deviations, ranging from 1.2% to 1.7%, obtained emphasize a satisfactory agreement between the results obtained and the real values, as confirmed by statistical analysis (i.e. F-test and t-test).

It was found that, with the relative standard deviations mentioned, satisfactory results for the determination of the phenothiazines used can be obtained in the range of

1.0×10^{-3}-2.0×10^{-2} M by the potentiometric method, and in the range of 5.0×10^{-5}-1.0×10^{-4} M by the spectrophotometric method proposed.

The proposed methods were applied to the determination of several phenothiazine drugs obtained from the local sources and the results are shown in Table 2. As seen, the declared dosage amounts of different phenothiazine derivatives ranging from 1-25 mg per tablet and 1-25 mg mL^{-1} for injections can be conveniently determined by the proposed potentiometric and spectrophotometric methods. Some of the potentiometric and spectrophotometric titration curves for different phenothiazines extracted from the dosage forms into chloroform are illustrated in Figures 5 and 6, respectively.

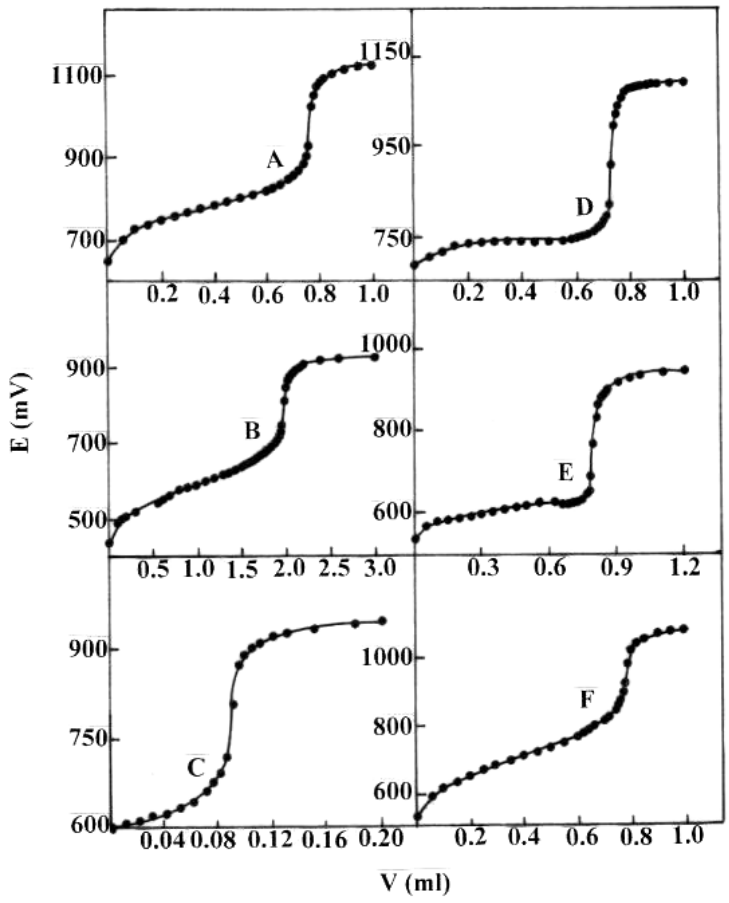

Figure 5. Potentiometric titration of 10-mL portion of chloroform extracts containing about 5 mg of different phenothiazine drugs + 0.1 M $HClO_4$ with 9.7×10^{-4} M DDQ in chloroform. The extracts correspond to the extraction of about 25 mg of phenothiazines from (A) chlorpromazine tablet (25 mg $tablet^{-1}$), (B) promethazine tablet (25 mg $tablet^{-1}$), (C) trifluperazine ampoule (1 mg mL^{-1}), (D) perphenazine tablet (8 mg $tablet^{-1}$), (E) thioridazine tablet (10 mg $tablet^{-1}$) and (F) chlopromazine ampoule (25 mg mL^{-1}), into 25 mL (10+10+5 mL) of chloroform.

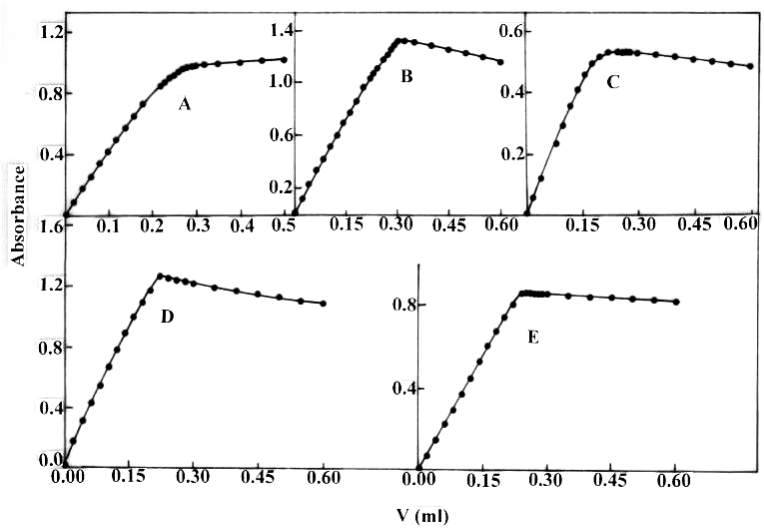

Figure 6. Spectrophotometric titration curves of 5-mL of chloroform solution containing about 0.2 mg of phenothiazine drugs (0.2 mL of chloroform extraction) with a 9.7×10^{-4} M of DDQ in the presence of 1 drop of concentrated $HClO_4$. The extracts correspond to the extraction of about 25 ng of phenothiazine derivatives from (a) Thioridazine 10 mg tablet^{-1} (b) chlorpromazine 25 ng tablet^{-1}. (c) Perphenazine 5 mg 1 mL^{-1}, (d) Trifluperazine 5 mg tablet^{-1} and (e) promethazine 25 ng tablet^{-1} into 25 mL (10, 10, 5 mL) of chloroform.

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Povzetek

Oksidacija fenotiazina z 2,3-dikloro-5,6-diciano-1,4-benzokinonom (DDQ) v kloroformu in prisotnosti *p*-toluensulfonske kisline, je bila raziskovana z voltametrijo, potenciometrijo in spektrofotometrijo. Nakazan je potek reakcije in izdelan optimalen postopek za titracijo derivatov fenotiazina z raztopino DDQ v kloroformu ter potenciometrično in spektrofotometrično indikacijo končne točke. Ponovljivost rezultatov je znašala pri potenciometrični titraciji od 3-5 mg fenotiazina od 1,2-1,7 % (RSD), pri spektrofotometrični indikaciji pa je bila pri vsebnosti 0,1-0,2 mg fenotiazina, od 0,8-1,2%. Metoda je bila uporabljena za določanje nekaterih derivatov fenotiazina v farmacevtskih preparatih po ekstrakciji učinkovine v kloroform.