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Reviews

Efficient Oxidizing Agents for Determination of 2,10-Disubstituted Phenothiazines

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2,10-Disubstituted phenothiazines are the best drugs in psychiatry. Several methods for their analysis have been reported in the literature. The official methods are based on non-aqueous titration or spectrophotometry. Various oxidizing agents have been used for the spectrophotometric determination of 2,10-disubstituted phenothiazines, *e.g.* $Ce(SO_4)_2$, NH_4VO_3, $K_2S_2O_8$, KIO_4, KIO_3, $KBrO_3$, $FeCl_3$, $NaNO_2$, H_2O_2, chloramine T, *p*-benzoquinone, *N*-bromosuccinimide. Oxidation reactions of phenothiazines were also used for their determination by flow-injection methods.

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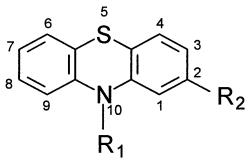
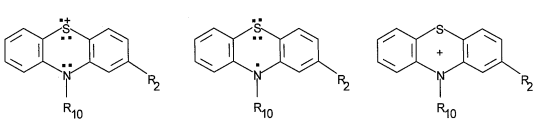
1 Introduction

2,10-Disubstituted phenothiazines are characterized by a tricyclic rings with sulfur and nitrogen atoms at positions 5 and 10.



They exhibit certain interesting analytical properties, *e.g.* a liability to oxidation by many oxidizing agents with the formation of colored oxidation products. These products are easily formed by chemical,[1-3] electrochemical,[4,5] enzymatic[6] and photochemical[7] oxidation. A number of papers[8] have been devoted to the oxidation behavior of *N*-substituted phenothiazines. The oxidation involves a series of one-electron steps providing free radicals and cations.[9] The distribution of π electrons in the 2,10-disubstituted phenothiazines molecules, according to theoretical considerations, may lead to the formation of free radical forms:[9]



The stability of cationic radicals depends on the following factors:

• Type and position of substituents on the phenothiazines skeleton;[10]

• Acidity of the reaction medium; the stability depends on the type and concentration of acid and buffer used;[11,12]

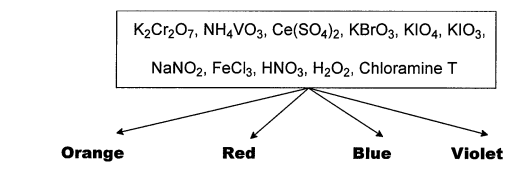
• Presence of cations and anions of various salts, *e.g.* $NaClO_4$, LiCl, NaCl, KCl, NH_4Cl, Na_2SO_4.[13]

It was found that cationic radicals are stable in acidic media. This property was the basis for the development of a number of spectrophotometric methods for the determination of phenothiazines.[14] Phenothiazines were also used as spectrophotometric reagents[2,8] and indicators in various redox titrations with $K_2Cr_2O_7$, $Ce(SO_4)_2$, NH_4VO_3, $KBrO_3$.[1,3,15]

In the presented paper the applications of some oxidizing agents for the spectrophotometric and flow-injection determination of 2,10-disubstituted phenothiazines have been described.

2 Spectrophotometric Methods

As mentioned previously, 2,10-disubstituted phenothiazines are easily oxidized in an acidic medium by some oxidizing agents, *e.g.*



Promazine	Chlorpromazine	Thioridazine	Levomepromazine
Triflupromazine	Perphenazine		Methopromazine
Perazine	Propericiazine		
Trifluoperazine	Prochlorperazine		
Fluphenazine			

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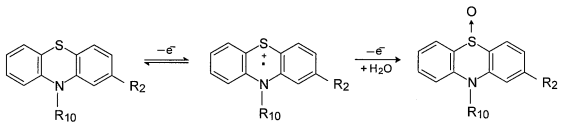
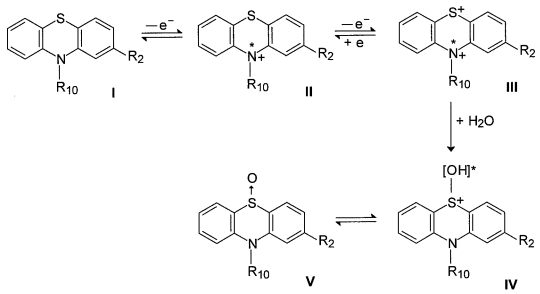
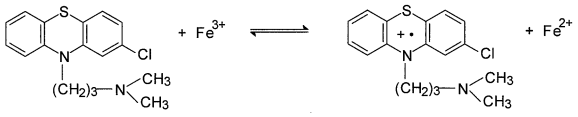


Scheme 1 Oxidation process of 2,10-disubsituted phenothiazines.



Scheme 2 Detailed scheme of the oxidation process of 2,10-disubstituted phenothiazines.



Scheme 3 Oxidation of chlorpromazine with $FeCl_3$.

with the formation of colored oxidation products.[2]

According to the literature,[16] the oxidation reactions of 2,10-disubstituted phenothiazines, are generally represented as follows:

It appears from Scheme 1, that the radicals of most phenothiazines decompose to yield an approximately equimolar mixture of the original derivative and its sulfoxide.[17,19] Scheme 2 represents the most probable detailed mechanism of the phenothiazines(I) oxidation process.

The first step of the phenothiazines oxidation reaction is the loss of an electron, giving a color semiquinone free radical(II). This reaction is reversible. The free radical can lose another electron, giving the colorless phenothiazonium ion(III). Next, compound(III) is hydrolyzing to the phenothiazine derivative S-oxide(V). In some cases, the decomposition process is more complicated; the products have not yet been identified.

We have found that in acidic medium strong oxidants, *e.g.* $K_2Cr_2O_7$ (couple $Cr_2O_7^{2-}/Cr^{3+}$, E^0 = 1.33 V, *vs.* standard hydrogen electrode) oxidizes immediately 2,10-disubstituted phenothiazines with the formation of colored oxidation products. These products are further oxidized by strong oxidizing agents to colorless sulfoxide.[21]

Some oxidizing agents, *e.g.* Fe(III), $[Fe(CN)_6]^{3-}$, which have relatively low oxidation potentials (couple Fe(III)/Fe(II), E^o = 0.77 V and couple $[Fe(CN)_6]^{3-}/[Fe(CN)_6]^{4-}$, E^o = 0.71 V, *vs.* standard hydrogen electrode) allow only the first step of the oxidation reaction of phenothiazines, and do not proceed to the second step.[20,21] This situation is illustrated on Fig. 1. It was impossible to obtain the spectrum of sulfoxide in the chlorpromazine–$FeCl_3$ system.

A reversible oxidation process of chlorpromazine was re-entered by the electrochemical method, cyclic voltammetry (CV). Figure 2 shows cyclic voltammograms of

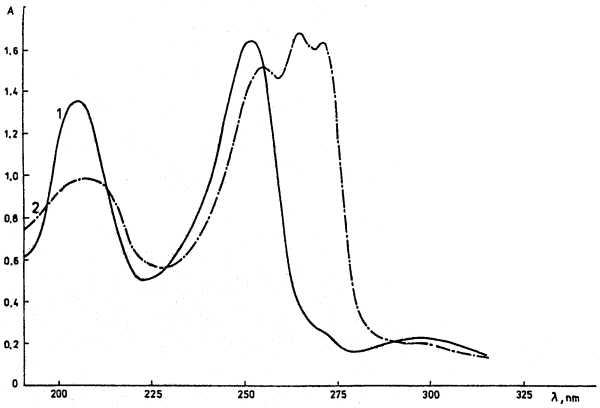


Fig. 1 Absorption spectra in the UV region of aqueous solutions of chlorpromazine hydrochloride (CPZ). 1, Non-oxidized form, $C = 5 \times 10^{-5}$ M; 2, colored oxidation product, $C_{CPZ} = C_{FeCl_3} = 5 \times 10^{-5}$ M.

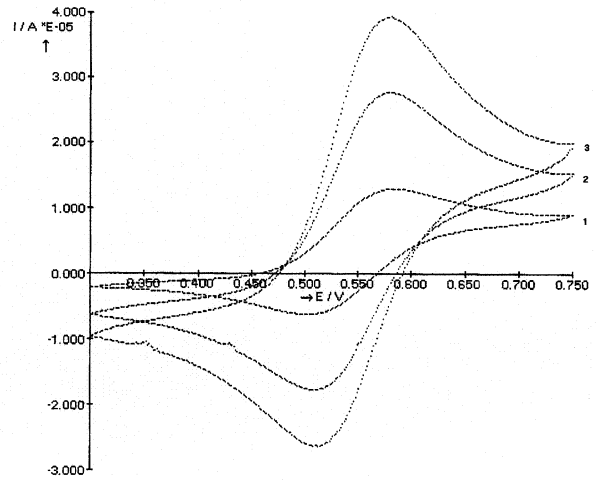


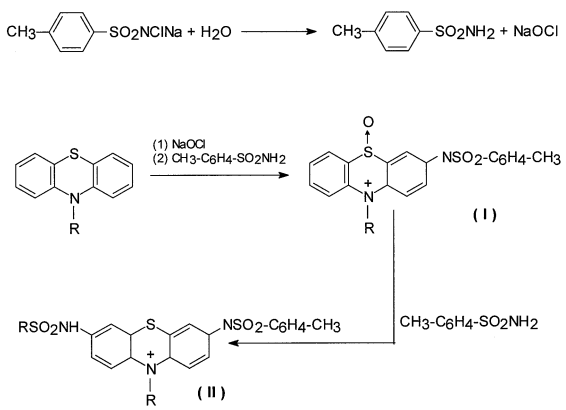
Fig. 2 Cyclic voltammograms of chlorpromazine (CPZ) at a Pt electrode; C_{CPZ}, 1.25×10^{-3} M, in 0.1 M HCl. Scan rate: (1) 10 mV/s; (2) 50 mV/s; (3) 100 mV/s.

chlorpromazine (CPZ) at a Pt electrode. Cyclic voltammograms of CPZ were recorded at various scan rates. As can be seen, the chlorpromazine exhibits oxidation and reduction peaks. At those scan rate equal to 50 mV/s, CPZ exhibits an oxidation peak (0.577 V) corresponding to the reduction peak (0.510 V), which appears when the signal is reversed (ΔE_p = 67 mV). The values of ΔE_p recorded at other scan rates are similar. This suggests that the electrode reaction is quasi-reversible.

Investigations in the UV region testify to the fact that the reaction of chlorpromazine and other 2,10-disubstituted phenothiazines (*e.g.* promazine, diethazine, levomepromazine, perazine, thioproperazine) with $FeCl_3$ or $K_3[Fe(CN)_6]$ proceeds only to the first step (Scheme 3). According to an electrochemical study, this reaction is reversible.

Pelizzetti and Mentasti[22] studied the kinetics of the oxidation of 2,10-disubstituted phenothiazines (PT) by $[Fe(H_2O)_6]^{3+}$ and $[Fe(CN)_6]^{3-}$ to their cation radicals.

It was found that colored radicals are stable under certain conditions.[13] These properties have been exploited for the spectrophotometric determination of 2,10-disubstituted phenothiazines. Various oxidants have been recommended: cerium(IV) sulfate,[23] ammonium metavanadate,[24-27] potassium



Scheme 4 The reaction of chloramine T with phenothiazines.

dichromate,[28] potassium iodate,[29] potassium periodate,[30] potassium bromate,[31,32] sodium nitrite,[33] iodine monochloride,[34] iron(III) chloride,[35-37] hexacyanoferrate(III),[20,38] nitrosoferricyanide,[39] potassium persulfate,[40] hydrogen peroxide,[41] sodium cobaltnitrite,[42] sulfuric acid,[43] chloramine T,[44] *p*-benzoquinone[45] and *N*-bromosuccinimide[46,47] for phenothiazines determination.

According to Puzanowska-Tarasiewicz and Karpińska,[20] potassium dichromate cannot be used for the spectrophotometric determination of 2,10-disubstituted phenothiazines. The system PT-$Cr_2O_7^{2-}$ appeared to be unsuitable due to the rate of the reaction and the instability of the colored product. The product of reaction appeared immediately, and than disappeared in a few minutes. This property causes a poor reproducibility and precision of determination.

Basavaiah *et al*.[48,49] proposed two indirect spectrophotometric methods for the determination of phenothiazines with $K_2Cr_2O_7$. The methods are based on the following:

• The oxidation of the 2,10-disubstituted drugs by a known excess of chromium(VI), and a subsequent determination of the unreacted oxidant by interacting with methanol and sulfanilic acid;

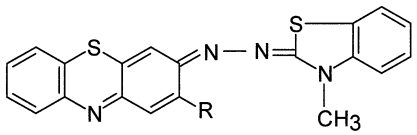
• The oxidation of phenothiazines by a know excess amount of potassium dichromate, followed by an estimation of the unreacted amount of $K_2Cr_2O_7$ by a reaction with an excess of iron(II), and measuring the iron(III) formed by complexing with thiocyanate.

Issa *et al*.[50] proposed chloramine T for the spectrophotometric determination of 2,10-disubstituted phenothiazines. The color is produced by heating the drug solution with chloramine T. The colored product is extracted into chloroform and the absorbance is measured.

The chemistry of the reaction is not clear, but it may involve the oxidation of the drug by chloramine T to give the sulfoxide; then, the latter interacts with the sulfonamido group of the hydrolyzed reagent and produces compound I or II (Scheme 4).[50]

In general, the presence of an acidic medium permits the oxidation reaction of phenothiazines, and in some cases stabilizes the color radical. However some methods are based on the formation of a color product in a neutral medium. Sometimes the colored product is extractable with organic solvents from an alkaline medium. These results are completely different from those obtained by oxidation in an acidic medium. The formed products in reactions with oxidizing agents, such as $KMnO_4$, $Ce(SO_4)_2$, KIO_3, $KBrO_3$, H_2O_2 are not extractable with organic solvents from an acid medium, and decompose if the pH of the medium increases.[50]

El-Kommos and Emara[51] described spectrophotometric methods for the determination of five 2,10-disubstituted phenothiazines. The methods are based on the development of colored products with 3-methylbenzothiazolin-2-one hydrazone (MBTH) in the presence of iron(III) salts. The reaction proceeds preliminary *via* the oxidation of drugs to a phenothiazinyl radical, followed by coupling of the reagent in the 3-position:[51]



The resulting colors are well developed within 5 min at 60°C, are stable for more than 24 h. MBTH was also used as a reagent for the simultaneous determination of three 2,10-disubstituted phenothiazines by Carreto *et al*.[52]

Spectrophotometric methods for the determination of 2,10-disubstituted phenothiazines also include: derivate-spectrophotometric methods,[53-55] as well as methods based on the formation charge transfer[56,57] and ion-association complexes.[20,22,58-60] The official methods include UV spectrophotometry[61] and non-aqueous titrimetry.[61,62]

3 Flow-injection Methods

In recent years flow-injection analysis (FIA) has found wide application in various fields of routine chemical analysis, including pharmaceuticals. The versatility and simplicity of the FIA technique allow it to adopt at relatively low cost to the different requirements of analytical problems.[63]

Most of the flow-injection procedures that were developed for the determination of 2,10-disubstituted phenothiazines in pharmaceuticals involved the use of chemical,[64-66] photochemical[67,68] or electrochemical oxidation[69] and various methods of detection.[70-72]

Perez-Ruiz *et al*.[73] described the flow-injection fluorometric determination of two phenothiazines. An automated flow-injection analysis for the determination of several 2,10-disubstituted phenothiazines is based on their oxidation with iron(III).[74] In another paper, Georgiou and Koupparis[75] described an automated flow-injection titrimetric determination of amines (*e.g*. chlorpromazine) and their hydrochlorides with perchloric acid.

The colored radicals formed in the first step of oxidation were the basis of many spectrophotometric FIA methods for the determination of phenothiazines. Some oxidizing agents, such as ammonium vanadate,[76] cerium(IV) sulfate[77-79] and molybdophosphoric acid,[80] were used in spectrophotometric flow-injection procedures.

Sultan[81] and Karpińska *et al*.[82] proposed flow-injection methods for the determination of chlorpromazine,[81] promethazine,[81] promazine[82] and thioridazine.[82] The proposed methods are based on the oxidation of the studied drugs with potassium dichromate in an acidic medium.

Many FIA methods utilized solid manganese dioxide, potassium hexacyanoferrate(III)[83,84] and lead dioxide[85] as oxidative columns (Fig. 3).[86]

Aqueous solutions of potassium hexacyanoferrate(III), iron(III) and iodine were used for the indirect FIA determination of phenothiazines using amperometric detection with two polarized platinum electrodes.[69] Phenothiazines can be easily oxidized in the anodic range of potentials; this

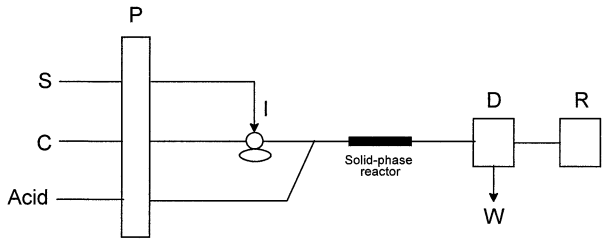


Fig. 3 Flow-injection manifold proposed for the determination of different phenothiazines. S, sample; C, carrier; I, injection; D, detector; W, waste; R, recorder.

characteristic was the basis for amperometric[72] and voltammetric[70,71] detection. Kojło *et al*.[85,86] have proposed the indirect potentiometric determination of chlorpromazine with an oxidative column using flow-injection systems. The procedure is based on the oxidation of analyte with lead dioxide and the determination of Pb(II) ions using a selective electrode.

There are many methods existing based on the phenomenon of emission of chemiluminescence or fluorescence by phenothiazines oxidation products. Kojło *et al.*[87] have utilized the chemiluminescence emitted by thioridazine oxidized by potassium permanganate in an acidic medium for determining the parent phenothiazine. The fluorometric determination of phenothiazines by photooxidation in a flow-injection system was also described by Laassis *et al*.[88]

Feher *et al*.[89] described two flow-techniques: flow-injection with UV spectrophotometric detection and the triangle-programmed flow titrimetric determination of phenothiazines.

Martinez Calatayud *et al*.[68] and Romero *et al*.[90] applied photochemical derivatization to the spectrofluorometric determination of chlorpromazine in the FIA system. Chen *et al*.[91] elaborated on the simultaneous determination of chlorpromazine and promethazine by photochemical reaction. Other FIA methods for the determination of phenothiazines were described by Sultan,[92] Martinez Calatayud[68,93] and Daniel.[94,95]

4 Conclusions

As mentioned previously, the official compendia[61,62] recommended for the determination of phenothiazines in bulk, or in pharmaceutical forms, involve measurements of the absorbance at selected wavelengths, or titration in a non-aqueous medium with potentiometric or visual indication at the end-point.

The proposed pharmacopoeial procedures required intensive isolation and purification steps in the case of the assay of phenothiazines in their pharmaceuticals form. The main disadvantage of direct UV-spectrophotometry is the sensitivity to excipients usually presented in pharmaceutical preparations.

The descriptions given in the presented review methods, based on their oxidation reaction, can be alternatives. The absorbance of colored phenothiazine radicals is less liable to spectral interferences from others ingredients of pharmaceuticals. The described methods offer advantages in their simplicity, rapidity and common access to instrumentation. There are only a few methods[96] based on the UV-absorption spectra of phenothiazines for their determination (*e.g*. on the absorption measurements in the methanol solution). Flow-injection analysis (FIA) has recently been the most important automated technique. Due to its speed, simplicity and use of small amounts of the sample, the technique has found application in various fields of routine chemical analysis, including of 2,10-disubstituted phenothiazines. The methods may be recommended as alternatives to the official methods.

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