A new oxidative derivatization method for spectrophotometric determination of Periciazine in pharmaceutical preparations

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A new the oxidative derivatization method by means of peroxoacid for the indirect spectrophotometric determination of *Periciazine* is presented. A potassium hydrogenperoxymonosulfateas a derivatizing agent for *Periciazine*, yielding the absorbative *Periciazine* sulfoxide at λ_{max}=362 nm is proposed. This reaction product was successfully employed for spectrophotometric determination of the *Periciazine*. The UV spectrophotometric determination of the *Periciazine* as its sulfoxide proved to be the more simple and selective method. Limit of quantification (LOQ=10S) is 2.8 μg·mL^{-1}. The common excipients employed do not interfere in the determination of phenothiazine drug. Results of analysis of the drug dosage forms by the proposed method are in good agreement with those of the official method. RSD=1.76 % (δ <RSD).

Introduction

Periciazine (Synonyms: Pericyazine, Pro*Periciazine* (PCZ), Neuleptil, Neulactil,) chemically, 3-cyano-10 (3-4'-hydroxy piperidinopropyl) phenothiazine or 10-[3-(4-Hydroxypiperidino)propyl]phenothiazine-2-carbonitrile; 1-[3-(2-Cyanophenothiazin-10-yl)propyl]piperidin-4-ol; (Figure 1)is usually given as the base but the mesilate and tartrate have also been used; a synthetic piperidine phenothiazine derivative with general properties similar to those of chlorpromazine. It is used in the treatment of psychoses including schizophrenia and disturbed behavior, and in the short-term management of severe anxiety [1,2]. *Periciazine* is a phenothiazine derivative used for the treatment of people with schizophrenia and is reputed to have a low level of extrapyramidal adverse effects.

Very few analytical methods have been reported with *Periciazine* individually and along with other drugs. Among that there is

spectrophotometric method based on the development of red colored products by the interaction of phenothiazines with diazotisedanthranilic acid in hydrochloric acid medium.

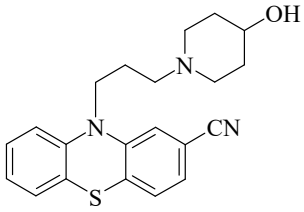

Figure 1. Chemical structure of *Periciazine* base

The reaction proceeds via the oxidation of the phenothiazine nucleus into a semiquinonoid radical [3].Flow-injection procedure of the spectrophotometric determination of *Periciazine* based on its the oxidation reaction by means of Fe(III) and $K_3[Fe(CN)_6$ [4], differential pulse and square wave voltammetric methods [5] and refractometry [6] have beenalready reported. Several chromatographic methods have been published for the determination of *Periciazine* in bulk or in different pharmaceutical formulations as in biological fluids as well. A high-performance liquidchromatographic method (HPLC) has been developed for the simultaneous analysis of the *Periciazine* and another phenothiazines in human serum using spectrophotometric detection [7]. A highly sensitive liquid chromatography–tandem mass spectrometry method was developed for the determination of *Periciazine* in the presence of 7-hydroxy and sulphoxide metabolites of *Periciazine* in human plasma after liquid-liquid extraction with ethyl acetate [8]. The chromatographic behavior of phenothiazine derivatives was studied by thin-layer chromatography with the use of Sorbfil silica gel plates in a binary benzene-methanol mixture of solvents [9]. A chromatographic conditionswere optimized and thin-layer chromatography method for determination of phenothiazine derivatives was described. Chromatographic systems with different polarity eluents in the wide composition range for screening of phenothiazine derived was studied [10].

The official compendia USP-39 [11] and Ph Eur. 9 [12] for the determination of phenothiazines in bulk, or in pharmaceutical formulations involves measurements of the absorbance at selected wavelengths, potentiometric titration in a non-aqueous medium and also HPLC method for estimation of API content in pharmaceutical preparations.

HPLC technique, though selective and sensitive, is relatively expensive involving costly instruments and solvents.

The main disadvantage of direct spectrophotometry in UV region 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 phenothiazine sulphoxides is less liable to spectral interferences from others ingredients of pharmaceuticals [13]. The described methods offer advantages in their simplicity, rapidity and common access to

instrumentation. There are only a few methods based on the UV-absorption spectra of phenothiazines for their determination (e.g. on the absorption measurements in the methanol solution). The methods may be recommended as alternatives to the official methods.

The purpose of the work was to develop a new analytical method for the quantitative determination of *Periciazine* in dosage forms in the presence of inactive ingredients by indirect absorption optical spectrophotometry in the form of a respective sulfoxide produced with potassium hydrogen peroxymonosulfate as an oxidant.

Based on the results of the comparative study of the electron spectra of light absorption of solutions of *Periciazine* and its S-oxidation product with hydrogen peroxymonosulfate in acidic media, we proposed a selective method for spectrophotometric determination of *Periciazine* in 10 mg capsules and in a 4% solution (drops) for intravenous use.

Experimental part

Apparatus

Registration of spectra of *Periciazine* solutions and products of its chemical oxidation, as well as measurement of absorbance of solutions, were carried out in a 1 cm thick quartz cuvette on an Evolution 60S UV-Visible Thermo-Scientific Spectrophotometer (USA) against a solution without the studied phenothiazine derivative or double-distilled water (compensation solution).

The subject of the test was the finished form of the well-known drug Neuleptil®, 10 mg capsules No. 5, manufactured by SANOFI Famarella Chea Services Madrid S.A.U., Spain, number 17N0020 series. One capsule of Neuleptil contains 10 mg of *Periciazine* active ingredient, as well as inactive ingredients such as magnesium stearate (3 mg) and calcium hydrogen phosphate dihydrate (137 mg). As part of the capsule itself, there are such chemicals as gelatin and titanium dioxide. According to the analysis certificate, the average content of the drug (*Periciazine* base) was 10.07 mg in one capsule (limits - not less than 9.50 and not more than 10.50 mg to one capsule, that is 95-105%).

Neuleptil, a 30 mL 4% oral (solution) drops containing 4 g of the *Periciazine* active ingredient, and also inactive ingredients such as purified water (100 mL), glycerol (15 g), ascorbic acid (0.8 g), ether oil, peppermint leaf extract (0.04 g), saccharose (sucrose) (25 g) and E150d (caramel, 0.2 g), tartaric acid (1.65 g) and 96% ethanol (9.74 g). SANOFI - AVENTIS FRANCE (France), produced by A. Hutterman&Sie, GmbH, Germany.

According to the Certificate of Analysis (series No. 6K0331), the average content of the drug (*Periciazine* active substance) was 3.96% in one capsule (limits of not less than 3.8 and not more than 4.2%, that is 95-105%).

Reagents

In this experiment, the oxidation of a *Periciazine* to a S-oxide *Periciazine* using a potassium triple salt containing potassium peroxymonosulfate ($KHSO_5$), potassium hydrogensulfate ($KHSO_4$), and potassium sulfate (K_2SO_4) in a 2:1:1 molar ratio was realized. This product is sold under the trade name Oxone®Its formula weight is 614.8. Moreover, it is considered as "green" oxidizing agent because it has not toxic effects.

Preparation of 0.005 mol L^{-1} potassium hydrogen peroxymonosulfate solution. About 0.15-0.2 g of Oxone® was dissolved in 100 mL of double-distilled water. The content of potassium hydrogen peroxymonosulfate was determined by iodometric titration.

Working Standard solution (WSS) of *Periciazine*

The working standard *Periciazine* solution, 0.10 $mgmL^{-1}$, is prepared by volume-weight method. A weighted amount of substance powder with a known content of the active substance containing 10.0 mg of *Periciazine*, recalculation on the *Periciazine* base ($C_{21}H_{23}N_3OS$), is dissolved in 100.0 mL of a 0.02 mol L^{-1}hydrochloric acid solution at +20°C.

Procedures

Preparation of calibration graph

An accurately measured by means of microburette, aliquot volumes of 2.5; 5; 10; 15; 20 mL of *Periciazine* WSS are transfered in 50 mL volumetric flasks. After that, 5 mL of 0.2 mol L^{-1}hydrochloric acid and 20 mL of a 0.005 mol L^{-1} potassium hydrogen peroxymonosulfate solution were successively added. Then, it was necessary to shake thoroughly and bring the volume of the solution to the mark with double-distilled water and close the flask and mix thoroughly. The solutions are measured at an analytical wavelength of 362 nm. Double-distilled water as a compensating solution was used.

Procedure for Pharmaceutical Preparations

Method for *Periciazine content* determination in 10 mg capsules. An accurately weighed amount of about 0.150 g of powder containing capsules (10 mg) corresponding to the average weight of the capsule is mixed with 50 mL of a 0.2 mol L^{-1} solution of hydrochloric acid and shaken thoroughly for 30 min, filtered through a "yellow tape" filter, the residue is thoroughly rinsed on filter (3 times, 10 mL) with double-distilled water. Combine the filtrate, quantitatively transfer the solution to a 100 mL volumetric flask. The volume of the solution to the mark is adjusted with double-distilled water and mixed thoroughly. Take 20 mL of the *Periciazine* solution obtained by pipette and transfer to a 50 mL volumetric flask, add 5 mL of a 0.2 mol L^{-1} solution of hydrochloric acid and 20.0 mL of 0.005 mol L^{-1} potassium hydrogen peroxymonosulfate solution, carefully shake and bring the solution to the mark with double-distilled water, close the flask and mix thoroughly

Similar procedures wereperformed with a standard solution was carried out.In this case, a volume of 20 mL of *Periciazine* solution were taken with pipette and transferred to a 50 mL volumetric flask together with 5 mL of 0.2 mol L^{-1} solution of hydrochloric acid and 20.0 mL of a 0.005 mol L^{-1}potassium hydrogen peroxymonosulfate solution.Resulting solution was carefully shaked and the volume of the solution was filled to the mark with double-distilled water. Finally, the flask was closedand mixed thoroughly. The solution was measured at an analytical wavelength of 362 nm in a 1 cm thick quartz cuvette against the double-distilled water as a compensating solution.

The content of *Periciazine*, in calculation on *Periciazine* base ($C_{21}H_{23}N_3OS$), in mg in one capsule, (X) is calculated by the equation 1:

$$X = \frac{C_{st} \times A_x \times 100 \times \overline{m}}{Ast \times m} \quad (1)$$

where $A_x$isoptical density in an experiment with a solution of capsules,

Ast–represents an optical density of the solution in the experiment with the *Periciazine WSS*; C_{st}iscontent of *Periciazine* active substance in WSS, $mgmL^{-1}$; *m*is weight of the powder contained in the capsules, g; 100 – volume of the volumetric flask, taken for the WSS or drug preparation;

$\overline{m}$ represents average weight of the capsule content, g.

Method of determining the content of Periciazine in a solution

An accurately measured volume of 0.5 mL of solution was transferred to a 200 mL volumetric flask. The solution was diluted to 200 mL with 50% solution of ethanol. The flask was closed and mixed thoroughly.

Using a pipette, a volume of 5.00 mL of resulting *Periciazine* solution was transferred into 50 mL volumetric flask with 5 mL of 0.1 mol L^{-1} solution of sulfuric acid and 10.0 mL of 0.005 mol L^{-1} potassium hydrogen peroxymonosulfate solution. Finally, the volume of the solution was filled to the mark using double-distilled water, closed and mixed thoroughly. The solution was measured at wavelength 362 nm.

Into another 50 mL volumetric flask, successively 5.00 mL of pre-diluted (1:400) 4% (40 mg to 1.00 mL) Neuleptil solution, 5.00 mL of 0.10 mg mL^{-1} of *Periciazine* WSS, 5 mL of 0.1 mol L^{-1} solution of sulfuric acid and 20 mL of 0.005 mol L^{-1} potassium hydrogen peroxymonosulfate solution were mixed, bring the volume of the solution to the mark with double-distilled water, close and mix thoroughly. The solution was measured at wavelength 362 nm.

The content of *Periciazine*, in calculation on *Periciazine* base ($C_{21}H_{23}N_3OS$) in mg in one capsule (X) is calculated by theequation 2:

$$X = \frac{C_a \times A_x \times 400}{(A_{x+a} - A_x)} \quad (2)$$

where A_{x+a} is optical density in the test with the test solution and with the solution of the *Periciazine* additive, A_x - optical density in an

experiment with *Periciazine* test solution, C_a – content of the *Periciazine* base in the solution of the additive mg/mL, 400 - dilution of 4% (40 mg/mL) solution of the preparation.

Results and discussion

A study of the kinetics of the reaction by the method of iodometric titration of an oxidizing agent showed that in an acidic medium (0.001-0.01 mol L^{-1} HCl or H_2SO_4) at a temperature of 15-25°C, *Periciazine* is oxidized almost instantly (observation time 1 min). One mole of *Periciazine* consumes one mole of oxidizing agent, which indicates the formation of sulfoxide. Fig. 2 shows the UV absorption spectra of S-oxidation products of *Periciazine* in a solution of 0.02 mol L^{-1} HCl at a change in its concentration from 5 to 40 μgmL^{-1}, obtained with $1 \cdot 10^{-3}$ mol L^{-1} $KHSO_5$.As can be seen, an oxidation product is observed, characterized by a band with a maximum at 362 nm. Proceeding from the literature, the chemistry of the process can be represented by the scheme (Fig. 3)

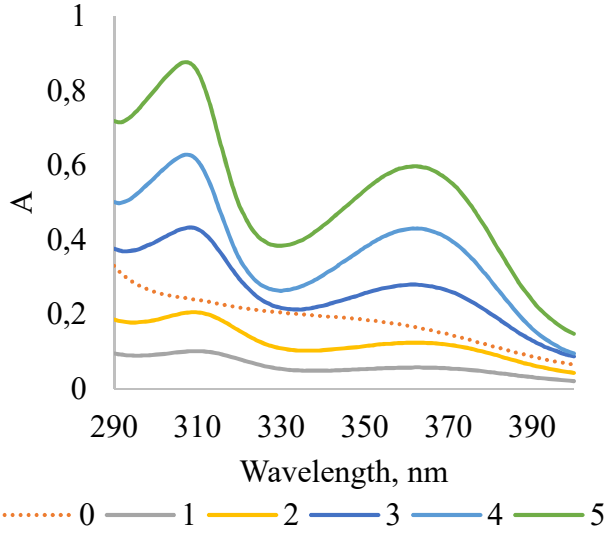

Figure 2. UV spectra of light absorption of S-oxidation product of *Periciazine*. 0.02 mol L^{-1} HCl. C, μgmL^{-1}:*1*-5; *2* - 10; *3* - 20; *4* to 30; *5*–40; UV absorption spectra of unoxidized *Periciazine, 0* - 20,μgmL^{-1}

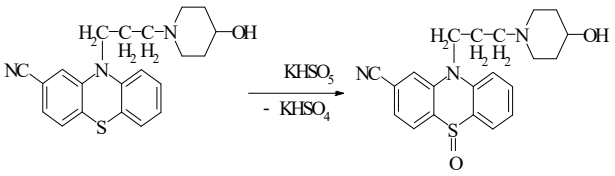

Figure 3. Scheme of S-oxidation reaction of potassium *Periciazine* with hydrogen peroxymonosulfate in acidic medium

The reaction product – the corresponding sulfoxide – is stable over time (the optical density at a given acidity did not change with the observation time 2 hours). The optical density of solutions at the maximum of light absorption is a linear function of the concentration of the derivative phenothiazine (the equation has the form $A=(0.015\pm0.0005)\cdot C$ characterized with correlation coefficient of 0.999) (Fig. 4).

According to the calibration graph, the limit of detection (LOD) and the limit of quantification (LOQ) were calculated to be 0.9 μgmL^{-1} and 2.8μgmL^{-1}, respectively.

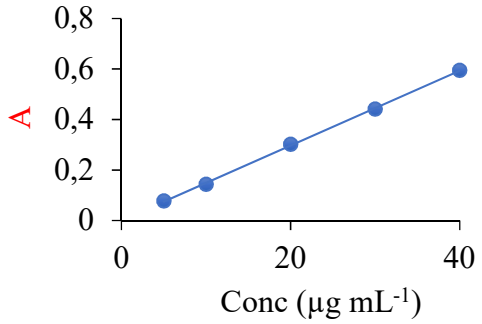

Figure 4. Concentration dependence of light absorption of oxidation product (calibration graph for quantitative determination) of *Periciazine*

Tables 1 and 2 show results obtained from determination of *Periciazine* in 10 mg capsules, as well as 4% solution (drops) (40 mgmL^{-1}) of *Periciazine* using the novel methods. They testified that proposed method of analysis performance allows to determine the *Periciazine* in finished dosage forms with reliable accuracy. The RSD lower than 1.76% was calculated. The results are in good correspondence with the findings of the study of phenothiazine derivative in 10 mg capsules and 40 mg mL^{-1} solutions (drops) in accordance with the recommended in European Pharmacopoeia (δ=<RSD).

Determination of *Periciazine* in 10 mg capsules, as well as 4% solution for intravenous use in the presence of a number of inactive ingredients with a corresponding sulfoxide, obtained with potassium hydrogen peroxymonosulfate, is more sensitive, faster and less laboriousness compared to methods based on the formation of free radicals of phenothiazine, as well as a simpler than a HPLC techniquementioned in introduction. It should be noted that the technique developed by our scientific group allows to determine *Periciazine* in the presence of ascorbic acid without their prior separation.

Table 1. Results of Quantitative Determination of *Periciazine* in Neuleptil® 10 mg capsules

Taken for analysis of the drug	Found contents mg/capsule	Metrological characteristics P=0.95
0.1500 g (10.07 mg in one capsule)*Neuleptil® 10 mg Capsules- № 5, SANOFI FamarellaChea Services Madrid S.A.U., Spain	10.23 10.40 9.88 10.06 9.95 10.15 10.01	$\bar{x}$=10.10 S=0.1779 $S_{\bar{x}}$=0.0673 $\Delta\bar{x}$=0.1648 *RSD*=1.76 % δ*=+ 0.27 %

Notes: * Calculated according to the certificate of analysis; δ=($\bar{x}$-a)100/a; a - the content specified on the certificate.. Limits: 9.5 - 10.5 mg *Periciazine* / 1 caps. (95 - 105%).

Thus, for the first time, in the practice of pharmaceutical analysis the method for indirect spectrophotometric determination of 10-piperidyl alkyl derivatives of phenothiazine on the example of Neuleptil in pharmaceutical preparations based on reactions of peroxyacid S-oxidation was proposed.

Table 2. Results of Quantitative Determination of *Periciazine*in 30 mL of 4% Neuleptilsolution

Taken for analysis of the solution	Found contents %	Metrological characteristics P=0.95
0.50 ml (3.96%)* drops solution SANOFI - AVENTIS FRANCE (France), produced by A. Hutterman&Sie, GmbH, Germany.; № 6K0331 series	3.91 3.84 3.92 3.88 3.82 3.99 4.00	$\bar{x}$=3.91 S=0.069 $S_{\bar{x}}$=0.026 $\Delta\bar{x}$=0.0638 *RSD*=1.76 % δ*=-1.13 %

Notes: * Calculated according to data on certificate (HPLC). δ=($\bar{x}$-a)100/a; a - the content specified on the certificate.

Conclusions

A completely new spectrophotometric procedures were developed for quantitative determination of *Periciazine* in pharmaceutical preparations. The common excipients employed do not interfere in the determination of phenothiazine drug. Results of analysis of the drug dosage forms by the proposed method are in good agreement with those of the official method.

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