The Oxidative Derivatization Method for the Spectrofluorimetric Determination of Periciazine in Pharmaceutical Preparations

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Recieved: April 13, 2019; Accepted: January 21, 2020
DOI: 10.17721/moca.2020.21-26

The oxidative derivatization method for the indirect spectrofluorimetric determination of Periciazine has been presented. Potassium hydrogenperoxymonosulfate (Oxone®) is proposed as a derivatizing agent for Periciazine, yielding the strongly fluorescent Periciazine sulfoxide. A highly sensitive, simple and rapid method for determination of the Periciazine by fluorescence of its oxidation product with Oxone® solution in 0.02 M hydrochloric acid solution (λ_{ex} = 364 nm; λ_{em} = 444 nm) has been developed. The calibration plot is linear in concentration range of 0.05–4.00 μg mL^{-1}. LOQ (10S) is 0.05 μg mL^{-1}. The possibility of quantitative determination of Periciazine in pharmaceutical preparations (Neuleptil®, 10 mg capsules and Neuleptil®, a 30 mL 4% oral (solution) drops) has been shown RSD < 2.2% (δ < RSD).

Keywords: spectrofluorimetry, Oxone, determination, periciazine, phenothiazine sulphoxide; pharmaceuticals

Метод оксидаційної дериватизації для спектрофлюориметричного визначення періціазину у фармацевтичних препаратах

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Надійшла: 13 квітня 2019 р; Прийнята: 21 січня 2020 р
DOI: 10.17721/moca.2020.21-26

Запропоновано метод оксидаційної дериватизації для непрямого спектрофлюориметричного визначення Періціазину. Калій гідрогенпероксомоносульфат (Оксон®) запропонований як дериватизуючий агент для перетворення Періціазину у сильно флюоресціюючий сульфоксид Періціазину. Розроблено чутливу, просту та швидку методику кількісного визначення Періціазину за флюоресценцією його продукту окиснення розчином Оксону® у кислому середовищі ($\lambda_{зб}$ = 364 нм; $\lambda_{випр}$ = 444 нм). Градуювальний графік лінійний в інтервалі концентрацій 0.05–4.00 мкг/мл. LOQ (10S) 0.05 мкг/мл. Розроблена методика апробована для кількісного визначення Періціазину у лікарських препаратах (капсули Neuleptil® по 10 мг та Neuleptil® 30 мл 4% пероральний розчин (краплі)) з RSD < 2.2% (δ < RSD).

Ключові слова: спектрофлюориметрія, Оксон®, визначення, періціазин, фентіазину сульфоксид; лікарські препарати

Periciazine (INN), also known as pericyazine (BAN) or Propericiazine, is active pharmaceutical ingredient (API), a member of the class of phenothiazines that is 10*H*-phenothiazine substituted by a 3-(4-hydroxypiperidin-1-yl) propyl group at the nitrogen atom and a carbonitrile group at position 2 (Figure 1). Periciazine is a first generation antipsychotic. It is commonly sold in Canada and Ukraine under the tradename Neuleptil and in the United Kingdom and Australia under the tradename Neulactil. The primary uses of pericyazine include the short-term treatment of severe anxiety or tension and in the maintenance treatment of psychotic disorders such as schizophrenia. Compared to chlorpromazine, pericyazine reportedly has more potent antiemetic, antiserotonin, and anticholinergic activity [1-3].

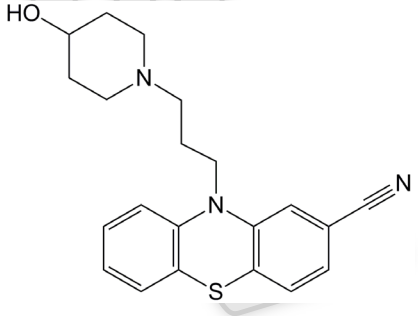

Fig. 1. Chemical structure of Periciazine base.

The importance of this drug prompted the development of many methods for its determination. The official methods (British Pharmacopoeia 2010 [4]; The United States Pharmacopeia 2016 [5]) for the assay of phenothiazines in bulk, or in pharmaceutical forms include measurements of the absorbance at selected wavelengths, titration in a non-aqueous medium with potentiometric or visual indication at the end-point for pure drugs, or high-performance liquid chromatography (for oral drops).

Other procedures for the determination of these substances in pharmaceuticals and biological fluids involve, for example, capillary gas chromatography and selected ion monitoring detection [6]. The described procedure is specific and provides between-assay variability of 4.8 % CV at 5 μg L^{-1} plasma concentration; the method enables quantification down to 1 μg L^{-1} and hence demonstrates sufficient sensitivity to permit pharmacokinetic or drug monitoring studies.

A HPLC method has been developed for the simultaneous analysis of the twelve phenothiazines in human serum with detection limits of 3.2–5.5 ng mL^{-1} [7]. The selectivity, accuracy and precision of this method are satisfactory for clinical and forensic purposes.

A robustness and highly sensitive liquid chromatography-tandem mass spectrometry (LC-MS/MS) method was developed and validated for the determination of pericyazine in human plasma [8]. The method exhibited great improvement in sensitivity (LOQ of 0.021 ng mL^{-1}) and good linearity over the concentration range of 0.021-9.90 ng mL^{-1}. Also, optimal conditions were proposed for a qualitative analysis of combined pharmaceutical forms of cinnarizine and psychotropic drugs using high performance liquid chromatography [9]. A strategy of chemical-toxicological analysis of psychoactive medical agents useable for combined poisonings via thin-layer chromatography method was developed [10]. The chromatographic behavior of phenothiazine derivatives was studied by the method thin-layer chromatography on plates with Sorbfil silica gel in a binary mixture solvents benzene-methanol. The conditions for their separation and identification was proposed [11].

Two voltammetric techniques (DPV and SWV) have been developed for the determination of phenothiazines in pharmaceutical dosage forms. The developed determination methods of phenothiazines are based on electrochemical oxidation of this substance to cation radical. Linearity range for Periciazine: 3.2 10^{-6} to $1.2 \cdot 10^{-3}$ mol L^{-1}. LOQ = $2.3 \cdot 10^{-6}$ mol L^{-1} (DPV method) and $1.2 \cdot 10^{-6}$ mol L^{-1} (SWV method). RSD for repeatability of peak current was 2.21 % (DPV method) and 1.68 (SWV method). The methods are simple, sensitive, and do not require the expensive grades of solutions that are needed for HPLC procedures [12].

Spectroscopic methods based on the oxidation behavior of phenothiazines have been recommend for their assay [13-17]. These methods have many disadvantages, including the use of alcoholic solutions and very acidic medium, heating in a boiling water bath and, above all, poor sensitivity [13].

Newly the oxidative derivatization method for the indirect spectrophotometric determination of Periciazine was presented [18]. The proposed method was simple, convenient, sensitive and free from many analytical problems like critical acid and reagent concentrations and instability of the coloured product. A potassium hydrogenperoxymonosulfate (Oxone) as a derivatizing agent for Periciazine, yielding the absorbative Periciazine sulfoxide at λ_{max} = 362 nm was proposed. This reaction product was successfully employed for spectrophotometric determination of the Periciazine. It has been shown that UV spectrophotometric determination of the Periciazine as its sulfoxide proved to be the more simple and selective method. Limit of quantification (LOQ = 10S) was 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 %.

Spectrofluorimetric techniques have been used for the determination of a wide range of drug compounds [19]. The techniques have been excellent for the determination of pharmaceutical compounds in different matrices. The selectivity of spectrofluorimetric methods is normally excellent because the analyte can be determined by maximum fluorescence of its sulphoxide. The described methods offer advantages in their simplicity, rapidity and common access to instrumentation. The methods may be recommended as alternatives to the official methods.

The aim of this study is to establish the experimental conditions needed to investigate the determinations of Periciazine in pharmaceutical preparations (capsules and oral drops) using spectrofluorimetric method.

Experimental part

Apparatus. Registration of spectra of solutions of Periciazine and products of its oxidation, as well as measurement of absorbance of solutions, has been carried out in a 1 cm thick quartz cuvette on a UV-2401 PC «Shimadzu» spectrophotometer (Japan) against a solution without the studied phenothiazine derivative or double-distilled water (compensation solution).

The excitation and fluorescence spectra have been recorded using a Cary Eclipse “Varian” spectrofluorometer (Australia) with a 150 W Xenon lamp. All measurements have been performed at room temperature (21-23 °C).

Periciazine, 10-[3-(4-Hydroxy-1-piperidinyl)propyl]-10H-phenothiazine-2-carbonitrile (RS); Formula: $C_{21}H_{23}N_3OS$, MW 365.49 g mol^{-1}, Active Pharmaceutical Ingredient (API). CAS No: 2622-26-6. Specification: *Assay*: 98 % (HPLC) (Capot chemical Co., Ltd, China). LGM Pharma (USA). Periciazine is a

yellow crystalline powder, almost without odour, non-hygroscopic and sensitive to light. It melts at about 115 °C. The molecular weight is 365.48. It is insoluble in water, slightly soluble in ether, fairly soluble in ethanol, acetone and benzene and freely soluble in chloroform.

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 gelatine 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***.** Oxone®, monopersulfate ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) (SIGMA-ALDRICH), CAS: 70693-62-8 (further as Oxone), Active oxygen (AO) 4.5 %.

Solution Oxone. 300 mg of Oxone was dissolved in a 200.0 mL volumetric flask, the volume of the solution is adjusted to the mark with double-distilled water and mixed. The content of potassium hydrogen peroxymonosulfate was determined by iodometric titration.

Standard solutions of phenothiazine drugs. 10.0 mg of RS periciazine is placed in a 50.0 mL volumetric flask, 30 mL of 0.02 M hydrochloric acid solution are added, and the mixture is stirred for 10 minutes, is adjusted the volume of the solution to the mark with the same solvent and mixed (periciazine working solution – 100.0 μg mL^{-1}).

Calibration graph. To construct the calibration curve, to a row of 50.0 mL volumetric flasks 0.025; 0.05; 0.1; 0.3; 0.5; 1.0 and 2.0 mL periciazine working solution (100.0 μg mL^{-1}) were added, 5 mL of 0.2 M hydrochloric acid solution and 20.0 mL of Oxone solution were added, the solution is adjusted to the mark with double-distilled water and mixed.

After 5 minutes, fluorescence intensity (*I*) was measured at λ_{em} = 444 nm (λ_{ex} = 364 nm). According to the data obtained, a calibration curve was constructed.

a) Procedures for capsules.

For a quantitative determination, we take a portion of the powder content 20 capsules.

Test solution. A weighed amount of 150.0 mg (exact weight) of the capsule contents powder, equivalent to 10.0 mg of Periciazine, is placed in a volumetric flask with a capacity of 100.0 mL, 70 mL of 0.02 M hydrochloric acid solution is added, and the mixture is stirred for 10 minutes, is adjusted the volume of the solution with the same solvent to the mark and mixed. The resulting solution is filtered through a membrane filter (0.20 μm; RC 25).

1.0 mL of the resulting solution is placed in a 50.0 mL volumetric flask, 5 mL of 0.2 M hydrochloric acid and 20.0 mL of Oxone solution are added, the volume of the solution is adjusted to the mark with double-distilled water and mixed.

Comparison solution. 10.0 mg of RS periciazine is placed in a 50.0 mL volumetric flask, 30 mL of 0.02 M hydrochloric acid solution are added, and the mixture is stirred for 10 minutes, is adjusted the volume of the solution to the mark with the same solvent and mixed (periciazine working solution – 100.0 μg mL^{-1}).

1.0 mL of the resulting solution is placed in a 50.0 mL volumetric flask, 5 mL of 0.2 M hydrochloric acid and 20.0 mL of Oxone solution are added, the volume of the solution is adjusted to the mark with double-distilled water and mixed. The solutions are used freshly prepared.

Measure the fluorescence intensity of the test solution and the reference solution after 5 min at a wavelength of 444 nm in a cuvette with a layer thickness of 1 cm (λ_{ex} = 364 nm).

The content of periciazine (X) in one capsule, in milligrams, is calculated by the formula:

$$X = \frac{I \cdot m_0 \cdot 1 \cdot 100 \cdot 50 \cdot b}{I_0 \cdot m \cdot 100 \cdot 50 \cdot 1} = \frac{I \cdot m_0 \cdot b}{I_0 \cdot m},$$

where: *I* is the fluorescence intensity of the test solution; I_0 is the fluorescence intensity of the reference solution; m_0 is the mass of Periciazine RS, in milligrams; *m* is the mass of the powder content of the capsule contents, in milligrams; b - the average weight of the contents of the capsules, in milligrams.

b) Procedures for oral solution.

Blank solution. 5 mL of 0.2 M hydrochloric acid solution and 20.0 mL of Oxone solution are placed in a 50.0 mL volumetric flask, the solution is adjusted to the mark with water and mixed.

Test solution. An aliquot of 0.5 mL of 4 % Neuleptil oral solution is placed in a volumetric flask with a capacity of 100.0 mL and adjusted to the mark with a 0.02 M solution of hydrochloric acid and mixed. 0.5 mL of the resulting solution is placed in a 50.0 mL volumetric flask, 5 mL of 0.2 M hydrochloric acid and 20.0 mL of Oxone solution are added, the volume of the solution is diluted with double-distilled water to the mark and mixed.

Comparison solution. 10.0 mg of RS periciazine is placed in a 50.0 mL volumetric flask, 30 mL of 0.02 M hydrochloric acid solution are added, and the mixture is stirred for 10 minutes, is adjusted the volume of the solution to the mark with the same solvent and mixed (periciazine working solution – 100.0 μg mL^{-1}).

1.0 mL of the resulting solution is placed in a 50.0 mL volumetric flask, 5 mL of 0.2 M hydrochloric acid and 20.0 mL of Oxone solution are added, the volume of the solution is adjusted to the mark with double-distilled water and mixed. The solutions are used freshly prepared.

Measure the fluorescence intensity of the test solution and the reference solution after 5 min at a wavelength of 444 nm in a cuvette with a layer thickness of 1 cm (λ_{ex} = 364 nm).

The content of periciazine (X) in 1 mL of solution, in milligrams, is calculated by the formula:

$$X = \frac{I \cdot m_0 \cdot 1 \cdot 100 \cdot 50}{I_0 \cdot 100 \cdot 50 \cdot 0.5 \cdot 0.5} = \frac{I \cdot m_0}{I_0 \cdot 0.25},$$

where: I is the fluorescence intensity of the test solution; I_0 is the fluorescence intensity of the reference solution; m_0 is the mass of the RS periciazine, in milligrams.

Results and Discussion

The absorption (Fig. 2) and fluorescence excitation (Fig. 3) spectrums of Periciazine solution after oxidation with Oxone are presented. The absorption spectrum of periciazine in a 0.02 M solution of hydrochloric acid is characterized by the presence of bands in the UV region of the spectrum with maxima at λ = 307 nm and at λ = 364 nm.

As can be seen from Fig. 3, the fluorescence excitation spectrum of a solution of periciazine after oxidation with oxone in the region of 250-400 nm is similar to its absorption spectrum. We first proposed to determine Periciazine by fluorescence of its oxidation product (Fig. 4) in a 0.02 M hydrochloric acid medium. There is a linear increase of fluorescence (Fig. 5) in the range from 0.05 μg mL^{-1} to 4.0 μg mL^{-1}.

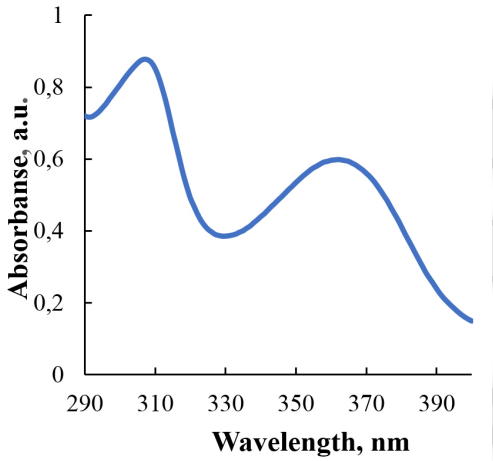

Fig. 2. Absorption spectra of Periciazine solution after oxidation with Oxone (C = 40.0 μg mL^{-1}).

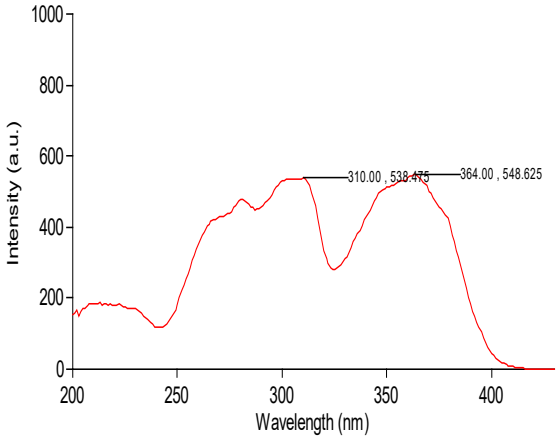

Fig. 3. Fluorescence excitation spectra of Periciazine solution after oxidation with Oxone (C = 40.0 μg mL^{-1}, slits 5-5; λ_{em} = 444 nm, gain 560).

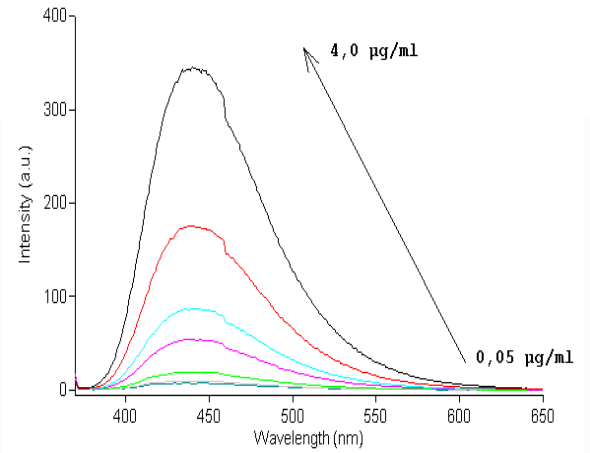

Fig. 4. Fluorescence spectra of Periciazine solutions after oxidation with Oxone (λ_{ex} = 364 nm; gain 560, slits 5-5).

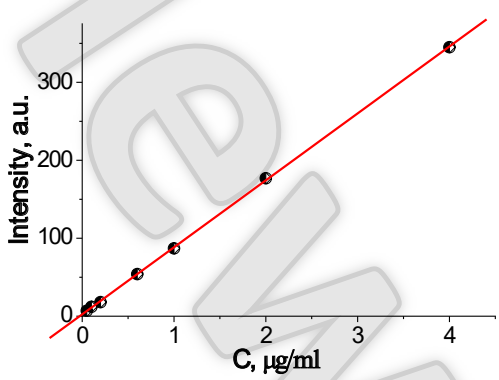

Fig. 5. Calibration plot for the determination of Periciazine.

The dependence of *I* on concentrations of periciazine is described by the equation: $I = (2.4604 \pm 0.8335) + (85.88 \pm 0.4777) \cdot C$; (R = 0.9999) and is linear in the concentration range of 0.05–4.00 μg mL^{-1} (Fig. 5). The detection limit is 0.015 μg mL^{-1}.

Table 1 show the results of the determination of Periciazine in capsules of 10 mg, as well as 4 % solution (drops) (40 mg mL^{-1}) of Periciazine obtained from the newly developed method. They show that our proposed method of performing the analysis allows us to determine the Periciazine in ready-made dosage forms with satisfactory accuracy. The relative standard deviation (RSD) does not exceed ±2.5 %. The results are in good agreement with the findings of the study of Periciazine in capsules of 10 mg and 40 mg mL^{-1} (drops) in accordance with the recommended European Pharmacopoeia.

Table 1. Results of Quantitative Determination of Periciazine in real samples.

Pharmaceutical preparation	Taken	Founded	Metrological characteristics (P = 0.95)
		mg/capsule	
Neuleptil® 10 mg Capsules - № 5, (SANOFI Famarella Chea Services Madrid)	0.1500 g (10.07 mg/ capsule)*	9.78 10.07 10.43 10.08 10.33 10.00 9.99	$\overline{X} \pm \Delta\overline{X}$ = 10.10±0.20 *RSD* = ±2.2 % δ* = +0.30 %
		mg/mL	
Neuleptil® oral solution 4%, 30 mL (SANOFI - AVENTIS FRANCE (France)	0.50 mL (3.96 %)*	41.04 40.84 39.40 40.43 39.62 39.51 40.85	$\overline{X} \pm \Delta\overline{X}$ = 40.24±0.657 *RSD* = ±1.8% δ* = +1.6%

Notes: *The calculation is based on the average content found by the method of EP 9.0 [19]. Limits: 9.50-10.50 mg Periciazine / 1 caps (95.0-105.0 %); **Calculation done according to the certificate of analysis, HPLC (Ph Eur 9) [20].

As mentioned previously, the official compendia 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. Spectrofluorimetric determination of Periciazine in capsules of 10 mg, as well as 4 % oral solution in the presence of a number of auxiliary substances with the corresponding sulfoxide obtained with potassium hydrogen peroxomonosulphate, more sensitive, faster and less time-consuming compared to methods based on the formation of free radicals, as well as a simpler HPLC technique recommended by Ph Eur. The limit of quantification LOQ is 0.05 μg/mL, which is one and a half orders of magnitude lower than in spectrophotometric determination.

Conclusions

A highly sensitive, simple and rapid method for determining Periciazine by fluorescence of its oxidation product with Oxone solution in 0.02 M hydrochloric acid solution (λ_{ex} = 364 nm; λ_{em} = 444 nm) has been developed. The calibration graph is linear in its concentration range of 0.05–4.0 μg mL^{-1}. The limit of quantification LOQ (10S) is 0.05 μg mL^{-1}. The possibility of quantitative determination of Periciazine in pharmaceutical preparations, namely Neuleptil® capsules of 10 mg and Neuleptil® 4 % oral solution (drop) has been shown, RSD < 2.5 % (δ < RSD).

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