A New Oxidative Derivatization Method for the Indirect Spectrofluorimetric Determination of Prochlorperazine Maleate in Pharmaceutical Preparations

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A new oxidative derivatization method for the indirect spectrofluorimetric determination of Prochlorperazine maleate has been presented. Potassium hydrogenperoxomonosulphate is proposed as a derivatizing agent for Prochlorperazine, yielding the strongly fluorescent sulfoxide. This reaction product was successfully employed for the spectrofluorimetric determination of the Prochlorperazine maleate. A highly sensitive, simple and rapid method has been developed for determining prochlorperazine maleate in tablets by fluorescence of its oxidation product with Oxone solution in 0.01 M sulfuric acid solution (λ_{ex} = 340 nm; λ_{em} = 380 nm). The calibration curve is linear in its concentration range of 0.8–10.0 μg/ml. Limit of quantification (LOQ = 10S) is 0.8 μg/ml. The possibility of quantitative determination of Prochlorperazine maleate in Vertinex® tablets 5 mg has been shown, RSD < 2.3% (δ < RSD).

Keywords: spectrofluorimetry, oxone, derivatization, prochlorperazine maleate, prochlorperazine sulphoxide, tablets

Новий спосіб оксидаційної дериватизації для непрямого спектрофлюориметричного визначення прохлорперазину малеату у лікарських препаратах

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Розроблено новий метод оксидаційної дериватизації, придатний для непрямого спектрофлюориметричного визначення прохлорперазину малеату. Як дериватизуючий агент для Прохлорперазину запропоновано Калій гідропероксомоносульфат, котрий перетворює його у флюоресціюючу сполуку - сульфоксид Прохлорперазину. Продукт дериватизації успішно був застосований для спектрофлюориметричного визначення Прохлорперазину малеату. Розроблено високочутливий, простий та швидкий метод визначення Прохлорперазину малеату у пігулках за флюоресценцією його продукту окиснення, добутого за допомогою розчину Оксону у середовищі 0.01 М розчину сульфатної кислоти ($\lambda_{зб}$ = 340 нм; $\lambda_{випр}$ = 380 нм). Градуювальний графік лінійний в інтервалі концентрацій 0.8–10.0 мкг/мл. Межа кількісного визначення (LOQ = 10S) становить 0.8 мкг/мл. Показана можливість здійснення кількісного визначення Прохлорперазину малеату у у пігулках Vertinex® по 5 мг, RSD < 2.3% (δ < RSD).

Ключові слова: спектрофлюориметрія, оксон, дериватизація, прохлорперазину малеат, прохлорперазину сульфоксид, пігулки

Prochlorperazine maleate, a member of the piperazine subclass of phenothiazines, is chemically the dihydrogen maleate of 2-chloro-10-[3-(4-methyl piperazine-1-yl) propyl] phenothiazine (Fig. 1), well known antipsychotic and antiemetic with weak sedative activity [1]. It is official in European Pharmacopoeia (EP) and United States Pharmacopoeia (USP). In which, USP [2] describe liquid chromatographic method for the estimation of Prochlorperazine in tablet. While BP [3] and EP [4] describe potentiometric method for assay.

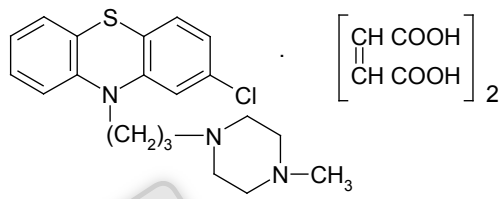

Fig. 1. Chemical structure of Prochlorperazine maleate.

Several methods have been published for the determination of Prochlorperazine in bulk or in different pharmaceutical formulations as well as in biological fluids. These methods include titrimetric [5-7], spectrophotometric [8-20], kinetic [21], fluorimetric [22-26], electrochemical [27, 28], liquid chromatographic with liquid-liquid or solid-phase extraction and different detectors [29-39] methods. The proposed procedures required intensive isolation and purification steps in the case of the assay of phenothiazines in their pharmaceutical formulations.

A powerful hyphenated technique for the determination of phenothiazines based on the combination of HPLC, electrochemical on-line oxidation, and different detection methods of the formed oxidation products has been developed. The oxidation of phenothiazine leads to the formation of a radical cation and other oxidized products that can be detected by means of spectroscopy. The basic phenothiazine derivatives are transferred into strongly fluorescent sulfoxides. This offers possibilities to quantify phenothiazines at very low limits of detection in the nanomolar range using fluorescence detection with simple, robust, and readily available instrumentation and avoiding laborous derivatization procedures [40]. A fluorescence of phenothiazine sulphoxides is less liable to spectral interferences from others ingredients of pharmaceuticals [41]. The described methods offer advantages in their simplicity, rapidity and common access to instrumentation. There are only a few methods based on the fluorescent spectra of phenothiazines for their determination. The methods may be recommended as alternatives to the official methods. The oxidation of Prochlorperazine maleate to its corresponding fluorescent sulphoxide by means of potassium hydrogen peroxymonosulfate was used to develop a new method for spectrofluorimetric determination of the drug.

Experimental part

Apparatus. 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). Electronic absorption spectra have been recorded on a UV-2401 PC Shimadzu spectrophotometer (Japan) using a quartz cuvette (l = 1 cm).

Pharmaceutical Formulation. The subject of the test was a dosage form of the well-known drug - Vertinex® tablets. Active substance: Prochlorperazine maleate; 1 tablet contains 5 mg of Prochlorperazine maleate; Excipients: Lactose monohydrate, Microcrystalline Cellulose, Maize Starch, Croscarmellose sodium, Sodium lauryl Sulphate, Magnesium Stearate, Colloidal anhydrous Silica; manufactured by KUSUM HEALTHCARE PVT LTD. (Alwar (Rajasthan), India.), serial number VE7003. According to the Certificate of Quality A.R. FG / 1054/17, the content of the drug was 4.92 mg per pill (98.40 %) (limit of not less than 95.0 and not more than 105.0 % per tablet of Prochlorperazine maleate).

Reagents. Solution Oxone. 150 mg of Oxone is placed in a volumetric flask with a capacity of 100.0 mL, the volume of the solution is adjusted to the mark with double-distilled water and mixed.

Procedure for Pharmaceutical Preparations.

Comparison solution. 5.0 mg of RS prochlorperazine maleate is placed in a 50.0 mL measuring flask, 30 mL of a 0.01 M solution of sulfuric acid are added, and the mixture is stirred for 10 minutes, is adjusted to the mark with the same solvent and mixed. 2.0 mL of the resulting solution is placed in a volumetric flask with a capacity of 25.0 mL, add 2.5 mL of 0.1 M solution of sulfuric acid and 2.0 mL of Oxone solution, is adjusted to the mark with double-distilled water and mixed. The solutions are used freshly prepared.

Blank solution. 2.5 mL of a 0.1 M solution of sulfuric acid and 2.0 mL of a solution of Oxon are placed in a volumetric flask with a capacity of 25.0 mL, the volume of the solution is adjusted to the mark with double-distilled water and mixed. For quantitative determination, we take a portion of the powder of 20 tablets.

Test solution. A accurately weighed portion of 150.0 mg of powdered tablets, equivalent to 5.0 mg of prochlorperazine maleate, is placed in a 50.0 mL volumetric flask, 30 mL of 0.01 M sulfuric acid solution is added, and the mixture is stirred for 10 minutes, is adjusted to the mark with the same solvent and mixed. The resulting solution is filtered through a membrane filter (0.20 μm; RC 25). 2.0 mL of the resulting solution is placed in a volumetric flask with a capacity of 25.0 mL, add 2.5 mL of 0.1 M solution of sulfuric acid and 2.0 mL of Oxone solution, is adjusted to the mark with double-distilled water and mixed.

Measure the fluorescence intensity of the test solution and the reference solution at a wavelength of 380 nm in a cuvette with a layer thickness of 1 cm (λ_{ex} = 340 nm).

The content of prochlorperazine maleate (X) in one tablet, in milligrams, is calculated by the formula:

$$X = \frac{(I - I_{blank}) \cdot m_0 \cdot 2 \cdot 50 \cdot 25 \cdot b}{(I_0 - I_{blank}) \cdot m \cdot 50 \cdot 25 \cdot 2} = \frac{(I - I_{blank}) \cdot m_0 \cdot b}{(I_0 - I_{blank}) \cdot m},$$

where: I is the fluorescence intensity of the test solution; I_0 is the fluorescence intensity of the

reference solution; I_{blank} - fluorescence intensity of the blank solution; m_0 is the mass of the sample of RS prochlorperazine maleate, in mg; m is the mass of the powder of powdered tablets, in milligrams; b is the average tablet weight, in mg.

Calibration curve. To construct the calibration curve, to a row of 25.0 mL volumetric flasks 0.2; 0.5; 1.0; 1.5; 2.0; 2.5; 3.5 and 5.0 mL of the working solution of prochlorperazine maleate (100.0 μg/mL) were added, 2.5 mL of 0.1 M solution of sulfuric acid and 2.0 mL of Oxone solution were added, the solution was is adjusted to the mark with double-distilled water and mixed.

Blank solution. 2.5 mL of a 0.1 M solution of sulfuric acid and 2.0 mL of a solution of Oxon are placed in a volumetric flask with a capacity of 25.0 mL, the volume of the solution is adjusted to the mark with double-distilled water and mixed. Fluorescence intensity (I) was measured at λ_{em} = 380 nm (λ_{ex} = 340 nm). According to the data obtained, a calibration curve was constructed.

Results and discussion

The scheme of the oxidation process of prochlorperazine with potassium hydrogen peroxomonosulphate into the corresponding sulfoxide has the form (Fig. 2).

Spectral characteristics of prochlorperazine maleate. The absorption spectrum of prochlorperazine maleate in a 0.01 M solution of sulfuric acid is characterized by the presence of bands in the UV spectral region with maxima at λ = 238 nm, λ = 273 nm, λ = 298 nm, and λ = 340 nm (Fig. 3).

The fluorescence excitation spectrum of a Prochlorperazine maleate solution after oxidation with Oxone is similar to its absorption spectrum (Fig. 3). We first proposed to determine prochlorperazine maleate by fluorescence of its oxidation product (Fig. 3) in a 0.01 M solution of sulfuric acid. There is a linear increase in fluorescence (Fig. 4) in the range from 0.8 μg/mL to 10.0 μg/mL.

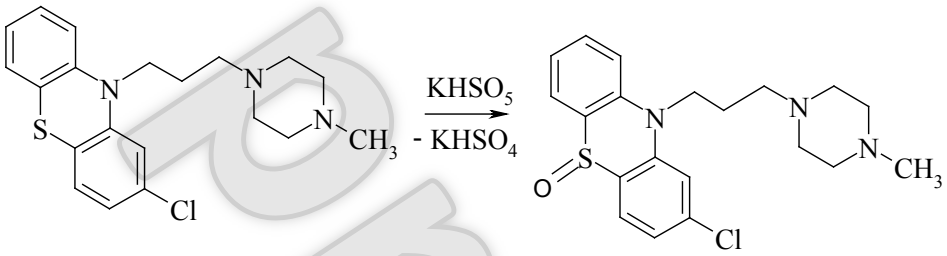

Fig. 2. Scheme of the oxidation reaction of prochloroperazine with potassium hydrogen peroxomonosulphate to S-oxide Prochlorperazine.

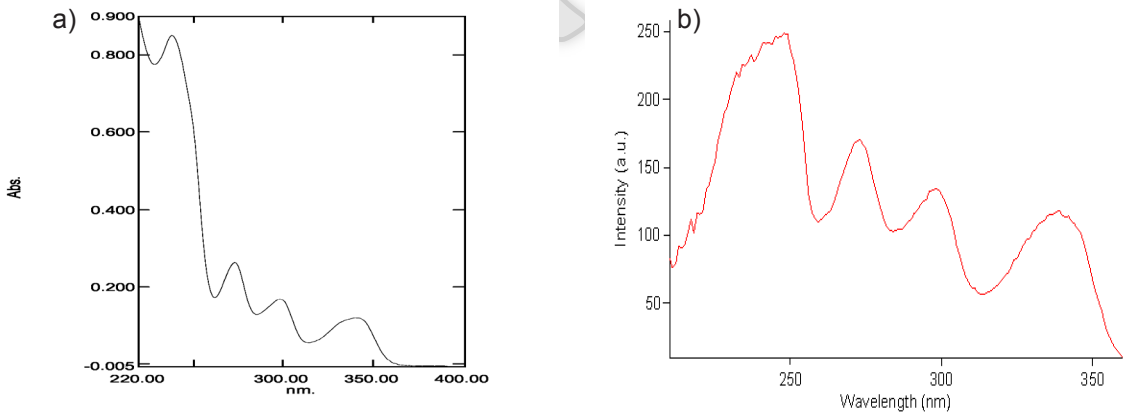

Fig. 3. Absorption(a) and excitation(b) fluorescence spectra of Prochlorperazine maleate solution of after oxidation with Oxone (C = 10.0 μg/ml, slits 5–5; λ_{em} = 380 nm, gain 740).

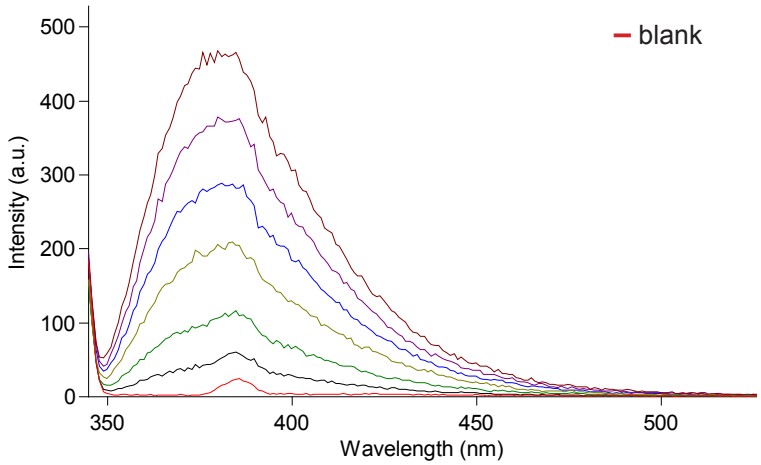

Fig. 4. Fluorescence spectra of Prochlorperazine maleate solutions (from 0.8 μg/ml to 10.0 μg/ml) after oxidation with Oxone (λ_{ex} = 340 nm; gain 740, slits 5-5).

The dependence of the concentration of Prochlorperazine maleate is described by the equation $I = (3.2179 \pm 2.3096) + (44.0159 \pm 0.33809) \cdot C$ (μg/mL) ($R^2 = 0.9996$). The calibration curve is linear fitting in the concentration range 0.8–10.0 μg/mL (Fig. 5). The limit of detection is 0.17 μg/mL.

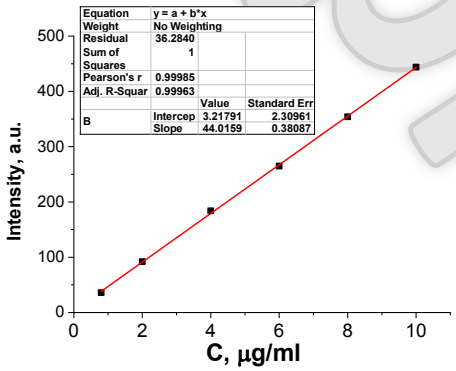

Fig. 5. Calibration curve for the determining the Prochlorperazine maleate.

Table 1 shows the results of the determination of prochlorperazine maleate in tablets of 5 mg obtained by the newly developed spectrofluorometric method. They show that the proposed method of performing the analysis allows us to quantify the substituted derivative of phenothiazine - Prochlorperazine maleate - in the pharmaceutical dosage forms with an acceptable accuracy. Relative standard deviation does not exceed ±2.3 %. The obtained results are in good agreement with the data of the determination of prochlorperazine maleate by the recommended Pharmacopoeial liquid chromatography.

Consequently, the determination of prochlorperazine maleate in Vertinex® tablets 5 mg by the corresponding sulfoxide obtained with potassium hydrogen peroxomonosulphate by spectrofluorometric method is more sensitive, faster and less labour-intensive in comparison with methods based on the formation of free radicals, and also simpler than the chromatographic technique recommended by the Pharmacopoeia USP 39.

Table 1. The results of determination of Prochlorperazine maleate in Vertinex® tablets 5 mg.

Taken	Found, mg/tablet	Metrological characteristics (P = 0.95)
0.1500 g (4.92 mg in one Vertinex® tablet 5 mg)*	4.98 4.88 5.03 4.98 4.75	4.92 ± 0.14 *RSD* = ±2.26 % δ* = +0 %

Notes: * The calculation is based on the average content found by the method of EP 9 [19]. Limits: not less than 95.0 and not more than 105.0 % per tablet of Prochlorperazine maleate.

Conclusions

Potassium hydrogenperoxomonosulphate is introduced as a derivatizing agent for Prochlorperazine maleate, yielding the strongly fluorescent sulfoxide. This reaction product has been successfully employed for the determination of the Prochlorperazine maleate. A highly sensitive, simple and rapid method has been developed for determining prochlorperazine maleate by fluorescence of its oxidation product with Oxone solution in 0.01 M sulfuric acid solution (λ_{ex} = 340 nm; λ_{em} = 380 nm) in tablets. The calibration curve is linear in concentration range of 0.8–10.0 μg/mL. LOD = 0.17 μg/mL; LOQ = 0.8 μg/mL. The possibility of quantitative determination of Prochlorperazine maleate in Vertinex® tablets, 5 mg has been shown, RSD < 2.3 % (δ < RSD).

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