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The Oxidative Derivatization Method for the Indirect Spectrophotometric Determination of Prochlorperazine in Tablets

M.Ye. Blazheyevskiy*, V.P. Moroz

National University of Pharmacy, 53 Pushkinska Str., Kharkiv, 61002, Ukraine; *e-mail: blazejowski@ukr.net

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The oxidative derivatization method by means of peroxoacid for the indirect spectrophotometric determination of Prochlorperazine Maleate is presented. Potassium hydrogen peroxymonosulfate as a derivatizing agent, yielding the Prochlorperazine sulfoxide with λ_{max}=338 nm is proposed. This reaction product was successfully employed for the spectrophotometric determination of the Prochlorperazine Maleate. The UV spectrophotometric determination of Prochlorperazine as its sulfoxide proved to be the more robust and selective method. Concentration dependence of the oxidation product remains linear in the range of concentrations from 2 to 40 μg·mL^{-1}. Limit of quantification (LOQ) is 1.7 μg·mL^{-1}. A new spectrophotometric technique was developed and the possibility of quantitative determination of Prochlorperazine Maleate in 5 mg Vetrinex tablets was demonstrated. The present method is precise and accurate. The common excipients employed do not interfere in the determination. Results of analysis of the tablet dosage form by the proposed method are in good agreement with those of the official method. RSD = 1.34% (δ = + 0.57%).

Keywords: prochlorperazine maleate, spectrophotometry, oxone, phenothiazine sulphoxide, tablets

Метод оксидаційної дериватизації для непрямого спектрофотометричного визначення прохлорперазину у пігулках

М.Є. Блажеєвський*, В.П. Мороз

Національний фармацевтичний університет, вул. Пушкінська, 53, Харків, 61002, Україна; *e-mail: blazejowski@ukr.net

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Представлений метод окиснювальної дериватизації з використанням пероксокислоти для непрямого спектрофотометричного визначення Прохлорперазину малеату. Калій гідрогенпероксомоносульфат запропонований як дериватизуючий агент для добування сульфоксиду Прохлорперазину з λ_{max} = 338 нм. Цей продукт реакції успішно використаний для спектрофотометричного визначення Прохлорперазину. УФ-спектрофотометричне визначення Прохлорперазину у вигляді його сульфоксиду виявилося більш надійним і вибірковим методом. Розроблена нова спектрофотометрична методика та продемонстрована можливість здійснення кількісного визначення Прохлорперазину малеату у таблетованій формі Вертинекс по 5 мг. Даний метод дає правильні результати і є точним. Загальновживані допоміжні речовини не заважають аналізу. Результати визначення АФІ у пігулках запропонованим способом добре узгоджуються з результатами офіційного методу, RSD = 1.34% (δ = + 0.57%).

Ключові слова: прохлорперазин малеат, спектрофотометрія, оксон, фентіазину сульфоксид, пігулки

Prochlorperazine Maleate (PCM), is the dihydrogen maleate of 2-chloro-10-[3-(4-methyl piperazine-1-yl) propyl] phenothiazine (Figure 1), a synthetic, piperazine phenothiazine derivative with antiemetic, antipsychotic, antihistaminic, and anticholinergic activities [1].

Prochlorperazine (brand names: Vertinex®), Stemetil®) comes in the form of tablets, syrup, mouth dissolving tablets, injectables, and suppositories.

The literature shows a wide variety of employed analytical techniques for determination of piperazine phenothiazine derivatives in particular Prochlorperazine Maleate. These include titrimetric [2-4], spectrophotometric [5-17], kinetic [18], fluorimetric [19-23], electrochemical [24, 25], liquid chromatographic with liquid-liquid or solid-phase extraction and different detectors [26-35] methods.

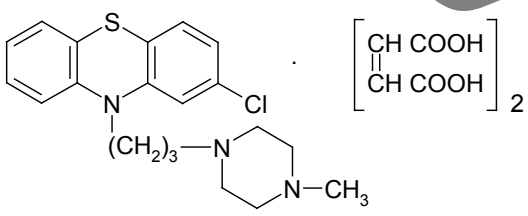


Fig. 1. Chemical structure of Prochlorperazine Maleate.

The official compendia USP-39 [36] for the determination of phenothiazines in bulk, or in pharmaceutical forms, involve measurements of the absorbance at selected wavelengths, potentiometric titration in a non-aqueous medium or liquid chromatographic method for estimation of content Prochlorperazine maleate in tablets. 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 phenothiazine sulphoxides is less liable to spectral interferences from others ingredients of pharmaceutical preparations [37, 38]. 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.

Determination of active pharmaceutical ingredient (API) in tablets at the presence of excipients without previous chemical separation is a basic analytical problem. The presence of a number of inactive ingredients in the drug troubles the performance of the analysis and requires the preceding separation of the components of the mixture. Thus, the recommended Ph Eur method of HPLC using the appropriate standard samples requires large time spent on calibration and analysis along with long-term sampling. In this case, the quality control performance is very low, and the cost is relatively high.

In this connection, the development of swift and universal analytical methods for the quantitative determination of active pharmaceutical ingredients content by indirect spectrophotometry is considered relevant. An express method is the latest in research pharmaceutical practice, due to the high accuracy, relatively low laboriousness and swiftness.

In the present study, based on the results of a comparative study of light absorption electron spectrum of PCM solutions and of its S-oxidation product with potassium hydrogen peroxymonosulfate (in form the triple salt $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) in an acidic medium, we proposed a selective method for spectrometric determination of PCM in the final dosage form, namely 5 mg tablets.

Experimental part

Apparatus. Registration of spectrum of Prochlorperazine Maleate solutions and products of its oxidation, as well as measurement of absorbance of solutions, was performed in a 1 cm quartz cuvette on an Evolution 60S UV-Visible Thermo-Scientific Spectrophotometer (USA) against a solution without the analyzed Phenothiazine derivative or double-distilled water (compensation solution).

The subject of the test was a final 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 tablet (98.40 %) (not less than 95.0 and not more than 105.0 % per tablet of Prochlorperazine Maleate calculated on the Prochlorperazine base).

Reagents. The triple salt $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$ (Sigma-Aldrich), CAS: 70693-62-8 (known as Oxone®), Active oxygen (AO) 4.5 %.

The 0.005 mol·L^{-1} potassium hydrogen peroxymonosulfate solution was trepared with double-distilled water. The exact content of potassium hydrogen peroxymonosulfate was determined by iodometric titration.

Working standard Prochlorperazine Maleate solution (WSS), 0.10 mg·mL^{-1}, is prepared by volume-weight method. A weighted substance with a known content of the active substance containing 10.0 mg of Prochlorperazine Maleate, calculated on Prochlorperazine ($C_{20}H_{24}ClN_3S$), is dissolved in 100.0 mL of 0.01 M solution of sulfuric acid at +20 °C.

Procedure of *Prochlorperazine Maleate* determination. *Graduation curves:* An accurately measured aliquot volumes of 2.00; 3.00; 5.00; 10.00; 15.00 and 20.00 mL of the WSS of Prochlorperazine Maleate were successively transferred to 50 mL volumetric flasks, each with 5 mL of a 0.1 M solution of sulfuric acid and 4.0 mL of 0.005 M potassium hydrogen peroxymonosulfate solution, carefully shaken, volumes of solutions were adjusted to the mark by adding double-distilled water, then the flasks were closed and mixed thoroughly by shaking 7-10 times. The solutions were measured at an analytical wavelength of 338 nm in a 1 cm thick quartz cuvette against double-distilled water as a compensating solution.

Determination of Prochlorperazine Maleate in tablets. An accurately weighed amount of powdered tablets of about 0.3 g, corresponding to the average weight of two tablets of Prochlorperazine Maleate, is mixed with 50 mL of a 0.1 M solution of sulfuric acid and shaken thoroughly for 30 minutes, filtered through the “yellow tape” filter, the residue is thoroughly rinsed on a filter (3 times in 10 mL) with double-distilled water and, by combining the filtrate, the solution was quantitatively transferred to a 100 mL volumetric flask. The volume of the solution was adjusted to the mark with double-distilled water and mixed thoroughly. 20 mL of Prochlorperazine Maleate solution was pipetted and transferred to a 50 mL volumetric flask, 5 mL of a 0.1 M sulfuric acid solution and 4.0 mL of

0.005 M potassium hydrogen peroxymonosulfate solution were added, carefully shaken, the volume was adjusted to the mark by the double-distilled water, the flask was closed and mixed thoroughly by shaking 7-10 times. The solution is measured at an analytical wavelength of 338 nm in a 1 cm thick quartz cuvette against the double-distilled water as a compensating solution. Similar procedures are carried out with a standard solution: with help of a pipette, 20 mL of Prochlorperazine Maleate WSS are taken and transferred to a 50 mL volumetric flask, 5 mL of a 0.1 M solution of sulfuric acid and 4.0 mL of 0.005 M potassium hydrogen peroxymonosulfate, shaken thoroughly, the volume of the solution is adjusted to the mark with double-distilled water, the flask is closed and mixed thoroughly by shaking 7-10 times. The solution is measured at an analytical wavelength of 338 nm in a 1 cm thick quartz cuvette against double-distilled water as a compensating solution.

The content of Prochlorperazine Maleate, in recalculation on Prochlorperazine base ($C_{20}N_{24}ClN_3S$) (X), in mg to one tablet, is calculated by the formula:

$$X = \frac{C_{st} \times A_x \times 100 \times \bar{m}}{A \times m}$$

where A_x - optical density of the test solution of tablets; A - optical density of the solution in the test with WSS; C_{st} - the content of the drug in the WSS mg·mL^{-1}; m – weight of powder tablets, g; 100 - volume of a volumetric flask, mL; - average weight of a tablet, g.

Results and Discussion

In Fig. 2 the electronic spectra of the oxidation product of Prochlorperazine with potassium hydrogen peroxymonosulfate in an aqueous solution are presented.

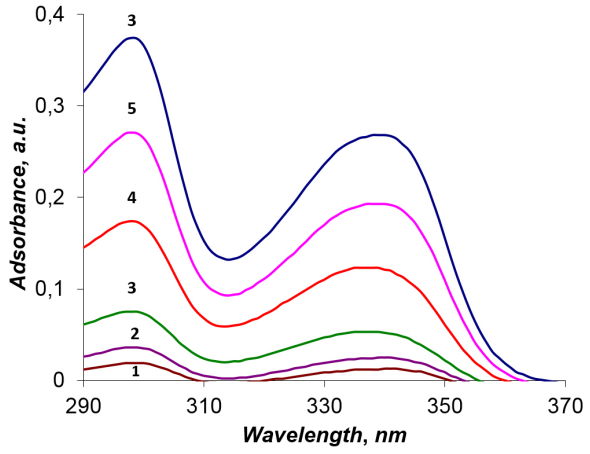
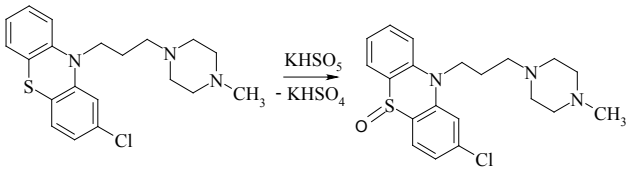


Fig. 2. UV-vis absorbance spectrum of Prochloroperazine sulfoxide 0.01 mol·L^{-1} H_2SO_4. c, 10^{-5} mol·L^{-1}: ***1*** - 1.07; ***2*** - 1.6; ***3*** - 2.67; ***4*** - 5.34; ***5*** - 8.01; ***6*** - 10.68.

As can be seen, a product with a characteristic light-collecting band with a maximum of 338 ± 2 nm occurs as a result of oxidation. The time of formation of this product does not exceed several minutes (the observation time is 5-30 minutes). According to literature, this band belongs to Procloroperazine sulfoxide [19].

The oxidation process of potassium Prochlorperazine with hydrogen peroxymonosulfate to S-oxide Prochlorperazine is presented by following scheme:



Concentration dependence of the oxidation product remains linear in the range of concentrations from 2 to 40 μg/mL (A = 0.0072·C, r^2=0.999).

Table 1 shows the results of the determination of Prochlorperazine Maleate in 5 mg tablets obtained by the novel spectrophotometric method. They show that the proposed method of performing the analysis allows us to quantify the substituted derivative of Phenothiazine - Prochlorperazine Maleate in the finished dosage forms with an acceptable accuracy. The relative standard deviation does not exceed ± 1.34 %. The obtained results are corresponding well with the data of the studied phenothiazine derivative determination in the tablet formulation by the recommended pharmacopoeial liquid chromatography method (accuracy δ = + 0.57 %).

Determination of Prochlorperazine Maleate in 5 mg tablets by the corresponding sulfoxide obtained with potassium hydrogen peroxymonosulfate is more sensitive, faster and less laboriousness than the methods based on the formation of free Phenothiazine radicals, as well as simpler than the chromatographic technique recommended by USP 39 Pharmacopoeia.

Table 1. Results of quantitative determination of Prochlorperazine Maleate in Vertinex® tablets.

Sample	C, mg/tabl	Metrological parametrs (P=0.95)
0.3000 g of Vertinex® tablets, Kusum Healthcare PVT LTD. (Alwar (Rajasthan), India), serial number VE7003	4.90 4.88 4.95 5.05 4.96	$\bar{x}$ = 4.95 S = 0.0661 $S_{\bar{x}}$ = 0.0296 $\Delta\bar{x}$ = 0.0822 RSD = 1.34 % δ* =+0.57 %

Notes: *Calculated based on the average content obtained by the USP 39 method [36] (4.92 mg/tablet - 98.40 % with a tolerance of ± 5 %).

Thus, for the first time, it is proposed to apply in the practice of pharmaceutical analysis the method of indirect spectrophotometric determination of Phenothiazine derivatives with Piperazine cycles

in side chains at position 10 on the example of Prochlorperazine Maleate in dosage forms based on the reaction of peroxyacidic S-oxidation. The feature of the novel method, which distinguishes it favorably from the known ones, is the possibility of monitoring the homogeneity of dosage of Prochlorperazine drugs without the employment of additional separation manipulations. The limit of quantification (LOQ) is 1.67 $\mu g \cdot mL^{-1}$.

A new spectrophotometric technique was developed and the possibility of quantitative determination of Prochlorperazine in 5 mg tablets (Vetrinex) was demonstrated after its oxidation to the corresponding S-oxide with potassium hydrogen peroxymonosulfate was demonstrated. The proposed method is characterized by high selectivity and satisfactory accuracy: RSD = 1.34 % (δ = + 0.57 %). The developed method can be used during chemical and toxicological analysis of biological fluids for the content of phenothiazine derivatives in particular prochlorperazine maleate, as well as their metabolites - the corresponding sulfoxides.

Conclusions

For the first time the method was developed and the possibility of quantitative determination of Prochlorperazine Maleate in tablets by the indirect spectrophotometry method in the form of a corresponding sulfoxide obtained with potassium hydrogen peroxymonosulfate, which makes it more sensitive, faster and easier compared to methods based on the formation of free radicals of Phenothiazine was demonstrated. It is also less laboriousness and faster than the recommended USP HPLC method to quantitatively determine the active pharmaceutical ingredients in dosage form, and therefore expands the functional possibilities of optical absorption spectrophotometry method in pharmaceutical analysis practice. The developed method can be used during chemical and toxicological analysis of biological fluids for the content of phenothiazine derivatives in particular prochlorperazine maleate, as well as their metabolites - the corresponding sulfoxides.

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