Differential Pulse Cathodic Voltammetric Determination of Metopimazine in Dosage Forms through Treatment with Oxone

Victoria Varchenko[a], Olena Mozgova[b*], Mykola Blazheyevskiy[c], Valeriy Moroz[c]

[a] *State Scientific Institution "Institute for Single Crystals" of National Academy of Sciences of Ukraine, Nauky ave. 60, Kharkiv, 61072, Ukraine*

[b] *Institute of Physical Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland*

[c] *Department of General Chemistry, National University of Pharmacy, Skovorody 53, Kharkiv 61168, Ukraine*

elena.mozgovaya25@gmail.com

Keywords: *Metopimazine, Potassium caroate, Metopimazine sulfoxide, Differential-pulse, Voltammetry, HMDE.*

A simple, rapid and sensitive voltammetric method for determining Metopimazine (MPZ) as its sulfoxide was developed. The Metopimazine sulfoxide derivative (MPZO) is formed quickly and quantitatively at room temperature by adding potassium caroate solution. Well-defined cathodic waves were obtained for MPZO in 0.02 mol/L HCl using the differential-pulse mode at the hanging mercury drop electrode (HMDE). It is shown that the limiting stage of the MPZO reduction process is the adsorption of MPZO on the electrode surface. Factors affecting the peak current were studied and optimised. The current–concentration relationship was linear over the 0.4-2.7 μg/mL ranges for MPZ, respectively. The technique has been developed and the possibility of quantitative determination of Metopimazine in Vogalene Lyoc 7.5 mg tablets by an indirect voltammetric method using potassium caroate (Oxone) as an oxidising agent has been shown. RSD was ≤1.63% (δ = –0.40…..–1.07%), where δ = (x̄-μ)·100%/μ, and μ is the average value of the quantitative determination by reference spectrophotometric method. According to the data of the linear part of the calibration graph, the limit of detection (LOD) and the limit of quantification (LOQ) were calculated, which are 0.1 μg/mL and 0.4 μg/mL, respectively. The method is specific for an intact drug in the presence of oxidative and photochemical decomposition products and excipients.

Introduction

Metopimazine (MPZ; 1-[3-[2-(methylsulfonyl)-10H-phenothiazin-10-yl]propyl]-4-piperidine carboxamide) is a phenothiazine dopamine antagonist with an antiemetic action [1,2] (**Figure 1**). It is used in the treatment of nausea and vomiting, including that associated with cancer chemotherapy [3]. It has various brand names, such as Nortrip, Vogalen, and Vogalene. Significantly, it does not penetrate the blood-brain barrier, resulting in the absence of central side effects.

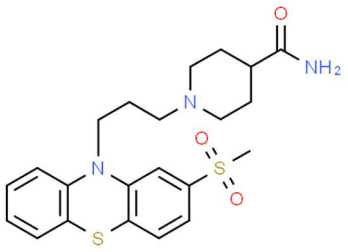


Figure 1. Structural formula of Metopimazine

The literature review revealed a few methods reported for quantitative estimation of MPZ, including the pharmacopoeial non-aqueous titrimetric method [4], HPTLC analytical method for determination of MPZ in the presence of its degradation products (DP) in dosage form and human plasma [5], spectrofluorimetric method which measures the native fluorescence of MPZ in the presence of its DP, second derivative D_2 spectrophotometric method, which allows determination of MPZ without the interference of its DP, spectrodensitometric method, in which MPZ is separated from DP, followed by its UV detection, which were applied to the analysis of the pharmaceutical formulation [6], and stability indicating spectrofluorimetric analysis by signal enhanced – partial least squares chemometric models [7]. MPZ in Vogalene® syrup was assayed using a difference spectrophotometric technique based on measuring the ΔA at 358 nm after adding a mixture of hydrogen peroxide and glacial acetic acid [8].

Finally, only a single analytical procedure is available in the literature to analyse MPZ by differential pulse voltammetric method [9]. MPZ reduction peak at −1.85V was explained by the reductive cleavage of the C–S bond in the methylsulfone group. No attempts have yet been made to determine either MPZ by any other electrochemical method.

In this article, we report on the use of potassium caroate ($KHSO_5$) to obtain a new polarographically active form of MPZ, namely the corresponding MPZ sulfoxide derivative (MPZO), which is the main product of the oxidative decomposition of the drug, and the development of a simple and sensitive method for their determination based on the differential-pulse cathodic voltammetric measurement on the hanging mercury drop electrode (HMDE). The use of $KHSO_5$ in the Oxone form has several advantages over other reagents used in the field.

Experimental part

Pure substance. Metopimazine (LGC GmbH, Luckenwalde, Germany), 99.41% purity (HPLC, Certificate of Analysis). Melting point 188-189 °C.

Pharmaceutical formulation. Vogalene Lyoc 7.5 mg Metopimazine Oral sugar-free-lyophilizate № B/16 (Teva Sante, France); PC: 3400933316259; SN 10081870059548. Composition of lyophilizate for preparation of oral solution: micronised MPZ (active ingredient) 7.5 mg; excipients: xanthan gum (Rodigel 23), aspartame (each lyophilizate contains 5.0 mg of aspartame), sodium docusate, dextran 70, and mannitol.

In our experiments, we used Oxone® for MPZ oxidation to its S-oxide. The active ingredient of Oxone® is potassium peroxomonosulphate ($KHSO_5$, potassium caroate, potassium monopersulphate; CAS 10058-23-8), which is a component of a highly stable triple salt $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$ (potassium hydrogen peroxomonosulphate sulphate (5:3:2:2); CAS 70693-62-8; formula weight is 614.8 g/mol). Oxone® is highly and easily soluble in water (at 20°C, the solubility is >250 g/L. Furthermore, this process is considered a "green" oxidation as it has no toxic effects.

Stock solution of Oxone. About 0.1 g of Oxone® was dissolved in 100 mL of ultra-clean water. The $KHSO_5$ content was determined by iodometric titration [10].

Stock solution of HCl with a concentration of 0.1 mol/L was prepared from a standard titre ("Alpharus") by diluting the contents of the tube to 1 litre according to the manufacturer's instructions.

Working solutions of HCl with concentrations of 0.01, 0.02, 0.04, and 0.06 mol/L were prepared by diluting the corresponding aliquot of the stock HCl solution.

Working standard solution of MPZ, 150 mg/L, is made by the volume-weight method. A suspension of MPZ substance powder with a known content of the main substance containing 7.5 mg of MPZ is dissolved in 50 mL of 0.01 M HCl solution.

Preparation of MPZ oxidation product (MPZO). 0.45g (≈0.001 mol) of pure MPZ was dissolved in 50 mL 0.1 M HCl, and 0.4 g of Oxone powder was added. An orange colour is produced, which fades after about 10 min. The solution was neutralised with 2 M NaOH solution till pH 7.5, and then MPZO (oxidation product) was extracted with multiple fractions of chloroform (4×30 mL). The extract was evaporated at room temperature, and the pale yellowish-white residue was collected and identified with UV- and IR-spectroscopy.

Voltammetry. All voltammetric measurements were carried out using a 797 VA Computrace System for voltammetric analysis (Metrohm, Switzerland). A hanging mercury drop electrode (HDME) was used as a working electrode. All potentials were recorded against an Ag/AgCl-reference electrode and an auxiliary platinum electrode. Voltammograms were obtained in cyclic and differential pulse modes. The voltammetric experiments were carried out at room temperature using a 0.02 mol/L HCl solution as a supporting electrolyte.

Method for registration of UV spectra. A double-beam Shimadzu UV-visible spectrophotometer, with a spectral bandwidth of 1 nm wavelength accuracy ±0.5 nm, Model – UV 1800 (Japan), Software UV-Probe 2.62, and a pair of 1 cm matched quartz cells, was used to measure the absorbance of the resulting solution. The ultraviolet absorbance spectrum for the MPZO sample showed an absorbance at 278±1

nm, 308±1 nm and 356±1, while the absorbance of MPZ at that wavelength was negligible. The extinction coefficient for MPZO (ε =4.5×10^3 L/mol cm) was calculated at 356 nm.

Method for registration of IR spectra. IR spectra were recorded at 400-4000 cm^{-1} on a SPECORD M-80 spectrometer manufactured by Zeiss, Jena, Germany. Tablets were prepared by mixing 200 mg of potassium bromide and 2 mg of the test compound (1% concentration), followed by compression in the standard manner. The IR spectrum of MPZ shows two characteristic bands at about 1657.5 and 3429.1 cm^{-1}, indicating the presence of the carbonyl group and the –NH_2 of the peripheral amide group, respectively. The IR spectrum of MPZO shows the same bands of MPZ, indicating that no changes had occurred to the peripheral amide link, besides the appearance of a new band at about 1017 cm^{-1} showing the formation of a new sulfoxide group due to oxidation.

Other instruments used were Analytical Balance RAD WAG AS 200/C, pH–meter I-160MI and IKA orbital shaker KS4000i.

The procedure for obtaining results of the calibration graph. 10 ml of 0.02 M HCl solution, an aliquot of MPZ standard solution and a corresponding aliquot of Oxone stock solution to create the required excess were placed in the electrochemical cell. The solution was stirred for 300 s, and then voltammograms were recorded using the parameters specified above.

Procedure for the determination of the MPZ content of Vogalene Lyoc tablets (7.5 mg). A precise amount of 1.38 g of crushed Vogalene Lyoc tablets is dissolved in a small volume of 0.02 M HCl and transferred to a 100 mL volumetric flask using the same HCl solution. The flask is corked and mixed thoroughly. Using a pipette, 1 mL or 2 mL of the resulting solution is withdrawn and transferred to a 250 mL volumetric flask and brought to the mark with 0.02 M HCl solution, corked and mixed thoroughly. 10 mL of the obtained solution is added to the electrochemical cell and degassed for 120 s. Then 180 µL of the stock Oxone solution is added, stirred for 300 s and recorded three times the voltammogram of MPZO reduction. To this solution, an MPZ working standard solution (40 µL or 80 µL) aliquot is added and stirred for 150 s, and the voltammogram of MPZO oxidation is also recorded.

MPZ content in mg/tablet is calculated according to the formula:

$$X = (C_a \times I_x \times k \times V \times m')/((I_{x+a} - I_x) \times m),$$

where I_{x+a} – current after addition of MPZ aliquot;

I_x – current in the tested solution without the addition of MPZ aliquot;

C_a – MPZ content in solution of an aliquot in terms of cell volume, mg/L;

k – dilution factor (250 or 125);

V – measuring flask volume taken for tested solution preparation, L;

m' – average tablet weight, g;

m – mass of tablet powder weight, g.

Results and discussion

MPZ is oxidised to the corresponding sulphoxide when treated with Oxone solution through the formation of an unstable red intermediate, which is converted into the stable colourless sulphoxide. Earlier, we established that sulfoxide derivative (MPZO) is formed quickly and quantitatively at room temperature by adding Oxone solution [11]. The scheme of the oxidation process of MPZ with $KHSO_5$ is presented in **Figure 2**.

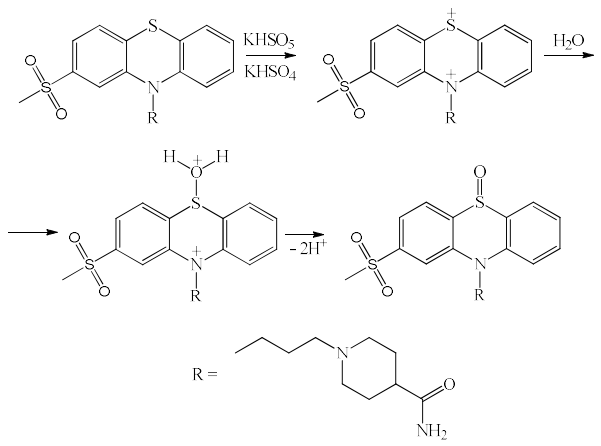


Figure 2. The scheme of the MPZ oxidation process with $KHSO_5$

The product formed by the reaction of MPZ with the oxidising agent under the analysis conditions was confirmed as MPZO through a comparison of its ultraviolet absorbance spectrum with that of an authentic MPZO sample obtained via an independent synthesis [5] and also through preparative chemistry methods employing IR-spectroscopy (see of *Experimental part*).

Well-defined cathodic waves were obtained for MPZO in 0.02 mol/L HCl using the differential-pulse mode at the hanging mercury drop electrode (HMDE).

Voltammetric parameter optimisation in the differential pulse mode

Dependence of voltammetric signal on the HCl concentration using cyclic voltammetry. 0.5 mL of MPZ working standard solution and excess (0.12 mL) of the Oxone stock solution were added to the electrochemical cell with 10 mL of HCl solution with appropriate concentration. The MPZ concentration was 7.5 mg/L.

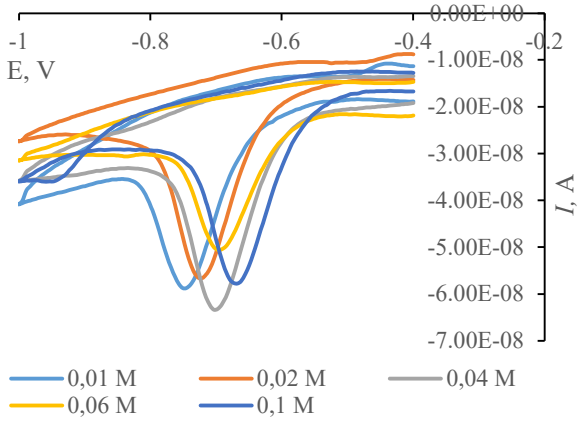


Figure 3. Cyclic voltammograms of MPZ oxidation product reduction at different concentrations of HCl

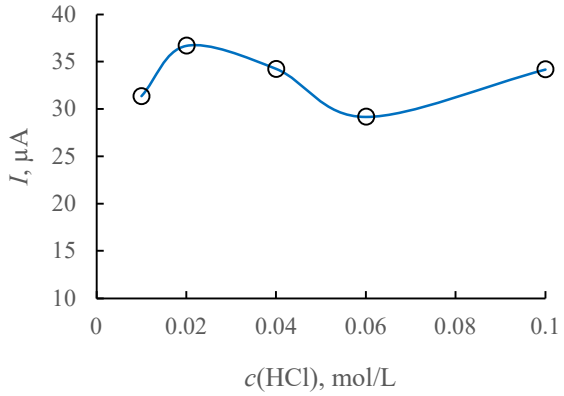


Figure 4. Dependence of current on the HCl concentration

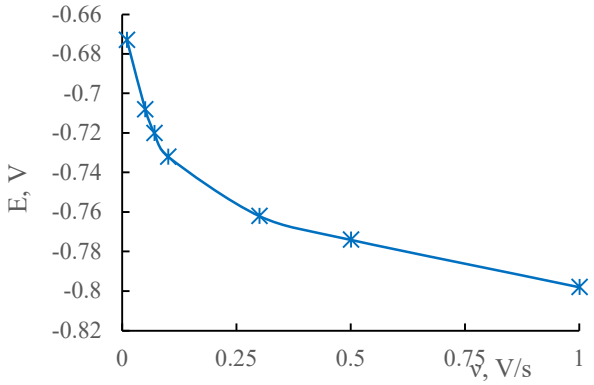


Figure 5. Peak potential dependence on the scan rate

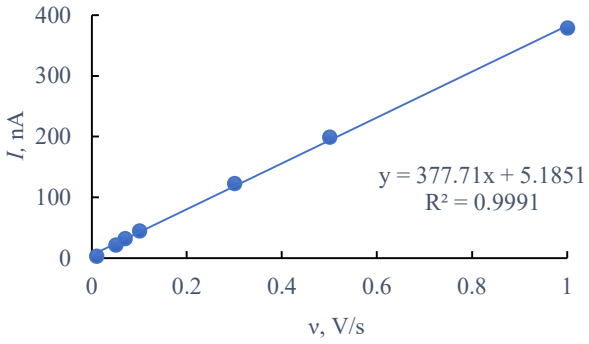


Figure 6. Dependence of current on scan rate

Consequently, the MPZO reduction at the mercury electrode is practically independent of the HCl concentration.

Differential pulse mode was chosen for quantification of MPZ in pharmaceuticals due to its enhanced selectivity and sensitivity compared to cyclic voltammetry. Firstly, the scan parameters must be optimised to achieve the best signal-to-noise ratio.

Effect of scanning rate. 0.5 mL of MPZ working standard solution and excess (0.12 mL) of the Oxone stock solution were added to the electrochemical cell with 10 mL of 0.2 mol/L HCl solution. The MPZ concentration was 7.5 mg/L. An optimal value for the scan rate was found to be 0.1 V/s (**Figure 5**).

Because the current depends linearly on the scan rate (**Figure 6**), it can be concluded that the limiting stage of the MPZO reduction process is the adsorption of sulfoxide on the electrode surface.

Determination of the optimum Oxone content. 10 ml of 0.02 M HCl, an aliquot of MPZ standard solution (3 mg/L) and various additions of Oxone stock solution (20-220 μL) were placed in the electrochemical cell. The voltammograms of sulfoxide reduction in differential-pulse mode were recorded at the following parameters: blowing time – 120 s, pulse amplitude – 0.06 V, pulse time – 0.008 V, scan rate – 0.1 V/s.

The sulfoxide reduction signal increases with the increasing amount of added Oxone up to V(Oxone) = 180 μL (**Figure 7**), which corresponds

to a total Oxone concentration of 0.018 g/L. Hence, all MPZ is converted to sulphoxide at this amount.

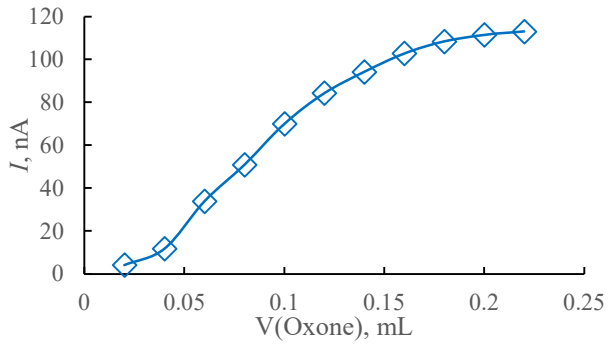


Figure 7. Dependence of the MPZO reduction current on the volume of added Oxone solution

Kinetics of the reaction. 10 mL of 0.02 M HCl, an aliquot of MPZ standard working solution (200 µL, 3 mg/L and an aliquot of Oxone stock solution (180 µL) were placed into the cell. The voltammograms of sulfoxide reduction were recorded at certain time intervals. The optimal reaction time is 300 s (**Figure 8**).

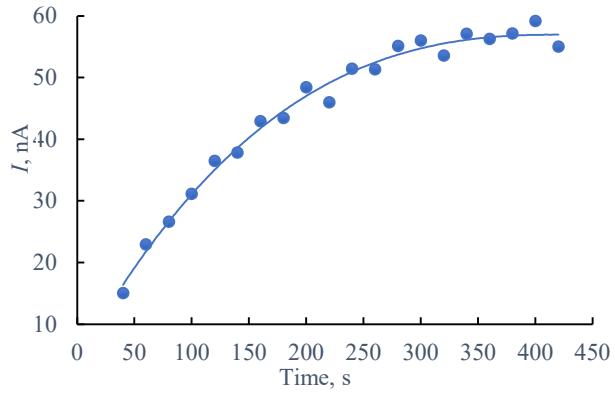


Figure 8. Dependence of the MPZO reduction current on the time of Oxone with MPZ interaction.

Mechanism of electrode reaction. For electron number determination, the following relationship can be used:

$|E_p - E_{p/2}| = (1.857RT)/(\alpha nF) = 47.7/\alpha n$ (at 298 K).

From this equation:

$$\alpha n = -47.7/(E_p - E_{p/2}),$$

where α − charge transfer coefficient;

n − number of electrons transferred in a stage of an electrode process;

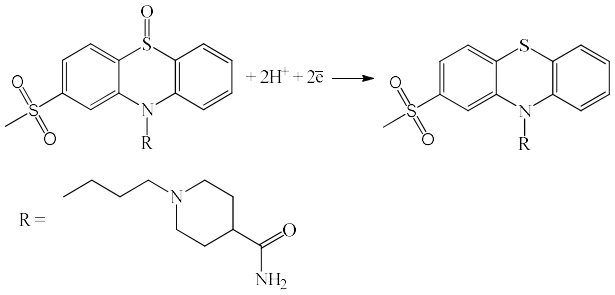
E_p − potential of reduction peak, mV;

$E_{p/2}$ − potential of reduction half-peak, mV.

For c(HCl) = 0.01÷1 mol/L, αn = 0.8÷1.01 was obtained. α-Value should be about 0.5, and so far as the number of electrons should be an integer, we can assume that n = 2.

The number of protons (m) was calculated using the relationship of E_p *vs* −log[c(HCl)]. The experimental value of the slope is equal to 71.5 mV. Therefore, we can conclude that m = 2 and two protons take part in the Metopimazine sulfoxide reduction.

So, the produced sulfoxide is reduced at the dropping mercury electrode (DME) with the consumption of two electrons:



According to the obtained data, the graduation relationship is linear in the MPZ concentration range of 0.0003-0.0027 mg/mL (R^2 = 0.998) (**Figure 9**). From the data of the calibration graph linear part, the limit of detection (LOD) and limit of quantification (LOQ) were calculated, which are 0.1 µg/mL and 0.4 µg/mL, respectively (**Table 1**).

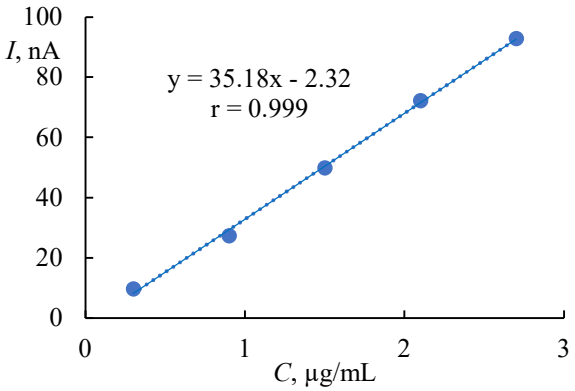


Figure 9. Dependence of MPZO reduction current on MPZ concentration

Table 1. Analytical characteristics of the calibration graph of MPZO reduction current dependence on MPZ concentration

Characteristics	*Parameters*
y=bx+a	y = 35.18 x – 2.32
Correlation coefficient (r)	0.999
Linear regression equation	$I = 35.18\ C$
Slope (b±Δb)	35.18±2.59
Intercept (a±Δa)	–2.32±4.46
S.D. of slope (S_b)	0.81×10^3
S.D. of intercept (S_a)	1.40
LOD, µg/mL	0.12
LOQ, µg/mL	0.40

Assay of pharmaceutical preparations. The proposed differential pulse voltammetric method was applied to the determination of MPZ in its dosage form (tablets Vogalene Lyoc (7.5 mg). For the determination of the MPZ content in tablets, a difference spectrophotometric technique based on measuring ΔA at 358 nm after the addition of Oxone solution was used as a reference method [12].

To study the accuracy, reproducibility and precision of the proposed method, recovery studies were conducted by adding a known amount (aliquot) of a model drug solution to a test tablet solution and then analysing the mixture using the proposed method. The results of the quantitative determination of MPZ in tablets of 7.5 mg by the newly developed and reference method are shown in **Table 2** and were found to be satisfactory.

Table 2. Results of MPZ quantitative determination in tablets Vogalene Lyoc (7.5 mg)

Taken	Found, mg/tablet	Statistical characteristics, p=0.95
1.3816 g of Vogalene Lyoc tablets, 7.5 mg, dilution 125	7.38 7.36 7.45 7.60 7.42 7.56 7.50	$\bar{x}$ = 7.47 mg $S\bar{x}$ = 0.0903 $\Delta\bar{x}$ = 0.08363 RSD = 1.21% δ* = –0.40 %
1.3821 g Vogalene Lyoc tablets, 7.5 mg, dilution 250	7.29 7.31 7.40 7.52 7.61 7.34 7.50	$\bar{x}$ = 7.42 mg $S\bar{x}$ = 0.1212 $\Delta\bar{x}$ = 0.1123 RSD = 1.63% δ* = –1.07 %

Notes. *$\delta = (\bar{x} - \mu)\ 100\%/\mu$; where µ is found MPZ content in tablets using the reference method.

In all cases, the inequality $\delta < t_\alpha(0.95, n=7)\times RSD/\sqrt{n}$ is satisfied, indicating the absence of systematic error, and therefore the analysis results are correct.

Such impurity in the drug as Metopimazine sulfoxide can interfere. However, its interfering effect is easy to compensate for by conducting a blank experiment. The manufacturer does not always indicate the amount of excipients in the drug; sometimes, it is a trade secret. Experimentally established that such excipients of tablets as xanthan gum (Rodigel 23) (5.0 mg), aspartame (5.0 mg), sodium docusate (0.4 mg), dextran 70 (35 mg), mannitol (630 mg) do not interfere with the determination. We didn't investigate the influence of other substances because they are not contained in the drug.

Conclusions

A new analytical method for the quantitative determination of MPZ in dosage forms by indirect differential pulse voltammetric method in the form of the corresponding sulfoxide produced with Oxone as an oxidant was developed. The calibration graph is linear in the concentration range of 0.4 to 2.7 μg/mL and can be approximated as I (nA) = (35.18±2.59)×C (μg/mL) – (2.32±4.46)); r = 0.999). Using a calibration graph, a limit of detection (LOD) and a limit of quantification (LOQ) were estimated to be 0.12 μg/mL and 0.40 μg/mL, respectively. RSD for Vogalene Lyoc tablets, 7.5 mg, was ≤1.63%. The trueness of the measurement method was investigated by comparing the accepted reference value (μ) with the level of the results given by the measurement method: $|(\bar{x} - \mu)100\% / \mu| < t_{\alpha}(0.95, n=7) \times RSD / \sqrt{n}$. The method is simple, sensitive and doesn't require expensive and relatively toxic solvents.

References

[1] Budavaried S. The Merck index, an encyclopedia of chemicals, drugs and biologicals. NJ, USA: Inc Whitehouse Station; 2006.

[2] Sweetman S. Martindale: The complete drug reference, 34th ed. London: Royal Pharmaceutical Society of Great Britain. 34 ed. Sweetman S, editor. London: Royal Pharmaceutical Society of Great Britain; 2005.

[3] Sweetman SC. Martindale : the complete drug reference. 33 ed. Sweetman SC, editor. London: Pharmaceutical Press; 2002.

[4] Pharmacopee Francaise. X-eme. Paris: L'ADRAPHARM; 1985.

[5] Naguib I, Abdelrahman M. Stability indicating HPTLC method for determination of Metopimazine in pharmaceutical formulation and human plasma. Beni-Suef University Journal of Basic and Applied Sciences 2014;3(1):52-62.

[6] Metwally FH, Abdelkawy M, Naguib IA. Development and validation of three stability indicating analytical methods for determination of metopimazine in pharmaceutical preparation. Bull Fac Pharm Cairo Univ. 2006;44(3):1–15.

[7] Darwish HW, Naguib IA, Bakheit AH. Stability Indicating Spectrofluorimetric Analysis of Metopimazine by Signal Enhanced - Partial Least Squares Chemometric Models: A Comparative Study. Current Pharmaceutical Analysis 2016;12(3):234-243.

[8] Davidson A. The determination of phenothiazine drugs in pharmaceutical preparations by a difference spectrophotometric method. Journal of Pharmacy and Pharmacology 1976;28(11):795-800.

[9] Gazy A, Hassan E, Abdel-Hay M, Belal T. Differential pulse cathodic voltammetric determination of floctafenine and metopimazine. Journal of Pharmaceutical and Biomedical Analysis 2007;43(4):1535-1539.

[10] Karpova SP, Mozgova OO, Krutskikh AA, Ivashura MM. Development and Validation of the Spectrophotometric Method for the Quantitative Determination of Azlocillin in Pure Substance and Medical Preparation. Asian J Pharm. 2018;12(4):1428–34.

[11] Blazheyevskiy MYe, Bouhlal M, Mozgova OO. Stability indicating spectrophotometric method for determination of metopimazine in pharmaceutical formulation. In: Kyiv Conference on Analytical Chemistry: Modern Trends. Kyiv: Interservis; 2022. p. 10–1.

[12] Mozgova O, Blazheyevskiy M, Kryskiw L, Kucher T, Shliusar O, Moroz V. Determination of prothipendyl by difference spectrophotometric method based on the absorption of its sulfoxide. Chemical Papers 2024;78(4):2613-2619.