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Differential-Pulse Polarographic Determination of Periciazine by Hydrogenperoxymonofulfate Treatment

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Abstract: A new analytical method for quantitatively determining Periciazine in dosage forms by indirect polarography in the form of a respective sulfoxide produced with potassium hydrogenperoxomonosulfate as an oxidant was developed. The calibration curve is linear in the concentration range of 0.2 to 2μg.mL^{-1} and can be approximated as I(nA) =(4.80±0.08)·104C (mg.mL^{-1})+(1.43±0.90)); r=0.999). Using a calibration curve, a limit of detection (LOD) and a limit of quantification (LOQ) were estimated to be 0.06μg.mL^{-1} and 0.2 μg.mL^{-1}, respectively. The levels of precision and accuracy for the measurement method were confirmed by calculation of the relative standard deviation (%RSD), and percentage recoveries (%R) using five replicate measurements of a drug sample: RSD for Neuleptil® oral drop solution 4 % and Neuleptil capsules 10mg were 1.2-1.8% and 1.3-1.6%, respectively. Measured the accepted reference values obtained for the analysis of API by differential pulse polarographic method were highly comparative to certified values. Analytical recoveries' values were 99-100.5%. The methods are simple, sensitive, and do not require expensive and relatively toxic solvents for HPLC procedures.

Keywords: peroxymonosulfate; periciazine; electrochemical sensing; differential-pulse polarography; voltammetric analysis.

1. Introduction

Periciazine (synonyms: Pericyazine, Propericiazine, Neuleptil, Neulactil), chemically 10-[3-(4-Hydroxypiperidin-1-yl)propyl]-10H-phenothiazine-2-carbonitrile (Figure 1), is usually given as the base but the tartrate and mesylate 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 [1-10].

Its application in therapy requires methods for determining pharmaceutical dosage forms and body fluids. Several methods for its analysis have been reported in the literature.

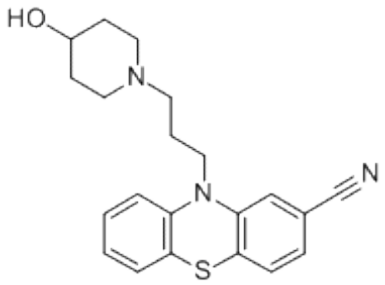

Figure 1. Chemical structure of Periciazine base.

A high-performance liquid chromatographic method (HPLC) has been developed for the simultaneous analysis of Periciazine (PRC) and another phenothiazine in human serum using spectrophotometric detection [11]. A highly sensitive liquid chromatography–tandem mass spectrometry method was developed to determine PRC in the presence of 7-hydroxy and sulphoxide metabolites of PRC in human plasma after liquid-liquid extraction with ethyl acetate [12]. The chromatographic behavior of phenothiazine derivatives was studied by thin-layer chromatography using Sorbfil silica gel plates in a binary benzene-methanol mixture of solvents. Chromatographic conditions were optimized, and a thin-layer chromatography method for determining phenothiazine derivatives was described. Chromatographic systems with different polarity eluents in the wide composition range for screening of phenothiazine derived was studied [13]. The official compendia USP-39 and Ph Eur. 9 for the determination of phenothiazines in bulk or pharmaceutical formulations involves potentiometric titration in a non-aqueous medium, measurements of the absorbance at selected wavelengths, and also HPLC method for estimation of API content in pharmaceutical preparations.

Among the methods, electrochemical ones are very useful for determining the drugs. Voltammetric methods based on the oxidation behavior of phenothiazines have been recommended for their assay. Two voltammetric techniques—differential pulse voltammetry (DPV) and square-wave voltammetry (SWV)—have been developed to determine PRC. The developed determination methods of PRC are based on the electrochemical oxidation of this substance to cation radical. The direct oxidation of phenothiazine derivatives at a bare glassy carbon electrode is simple, and the electrode does not foul the oxidation product; therefore, using a modified electrode is unnecessary. The linearity range was 3.2 10^{-6} to $1.2 \cdot 10^{-3}$molL^{-1}. LOQ was $2.3 \cdot 10^{-6}$molL^{-1} (DPV method) and $1.2 \cdot 10^{-6}$molL^{-1} (SWV method). RSD for reproducibility of peak current was 3.63% (DPV method) and 2.88 (SWV method). The methods are simple, sensitive, and do not require the expensive grades of solutions needed for HPLC procedures [14–21].

Based on their oxidation reaction, the descriptions given in the presented review methods can be a suitable alternative. The work aimed to develop a new analytical method for the quantitative determination of PRC in dosage forms in the presence of inactive ingredients by indirect polarography in the form of a respective sulfoxide produced with potassium hydrogen peroxomonosulfate as an oxidant.

2. Materials and Methods

2.1. Experimental.

2.1.1. Voltammetry.

All voltammetric measurements were carried out using 797VA 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 a platinum electrode was used as an auxiliary electrode. Voltammogramms were obtained in cyclic and differential pulse modes. The voltammetric experiments were carried out at room temperature using 0.02 mol L^{-1} hydrochloric acid solution as a supporting electrolyte.

2.1.2. Reagents.

In this experiment, the oxidation of a PRC to a PRC S-oxide 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 a "green" oxidizing agent because it has no toxic effects.

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, series number 17N0020. One capsule of Neuleptil contains 10mg of PRC active ingredient, as well as inactive ingredients such as magnesium stearate (3mg) and calcium hydrogen phosphate dihydrate (137mg). As part of the capsule, there are such chemicals as gelatin and titanium dioxide. According to the analysis certificate, the average content of the drug (PRC base) was 10.07mg in one capsule (limits - not less than 9.50 and not more than 10.50mg in one capsule, that is 95-105%).

The second subject was Neuleptil, a 30mL 4% oral (solution) drop containing 4g of the PRC active ingredient, and also inactive ingredients such as purified water (100mL), glycerol (15g), ascorbic acid (0.8g), ether oil, peppermint leaf extract (0.04g), saccharose (sucrose) (25g) and E150d (caramel, 0.2g), tartaric acid (1.65g) and 96% ethanol (9.74g); 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 (PRC active substance) was 3.96% (limits of not less than 3.8 and not more than 4.2%, that is 95-105%).

2.1.3. Solution preparation.

Stock solution of potassium hydrogenperoxomonosulfate. Preparation of 0.005molL^{-1} potassium hydrogen peroxymonosulfate solution. About 0.15-0.2g 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 PRC. The working standard PRC solution, 0.10mgmL^{-1}, was prepared using the volume-weight method. A weighted amount of substance powder with a known content of the active substance containing 10.0mg of PRC, recalculation on the PRC base ($C_{21}H_{23}N_3OS$), was dissolved in 100.0mL of a 0.02mol L^{-1}hydrochloric acid solution at +20°C.

All solutions were prepared with ultrapure water purified by a P.Nix Power II water purification system. IKA Pette (IKA, Germany, 20-200µl) and MicroPette pipette (DragoLab, China, 100-1000µl) were used for aliquoting of solutions.

3. Results and Discussion

3.1. Cyclic voltammetry.

10mL of 0.02molL^{-1} hydrochloric acid solution and 2mL of the stock Oxone® solution were placed in the electrochemical cell. Nitrogen was bubbled through the cell for 120s and a cyclic voltammogram was recorded. In another experiment, an aliquot of the working standard solution of PRC was added to 10mL of 0.02molL^{-1} hydrochloric acid solution, and a cyclic voltammogram was recorded after bubbling with nitrogen. Furthermore, 10mL of 0.02molL^{-1} hydrochloric acid, 2mL of the stock Oxone® solution and an aliquot of the working standard solution of PRC were mixed in the electrochemical cell, and a cyclic voltammogram was recorded after bubbling with nitrogen. The obtained curves in the first two cases have no peaks, indicating electrochemical processes. A cyclic voltammogram obtained in the third case is shown in Figure 2. The shape of the voltammogram reveals that the reduction of S-oxide is an irreversible process.

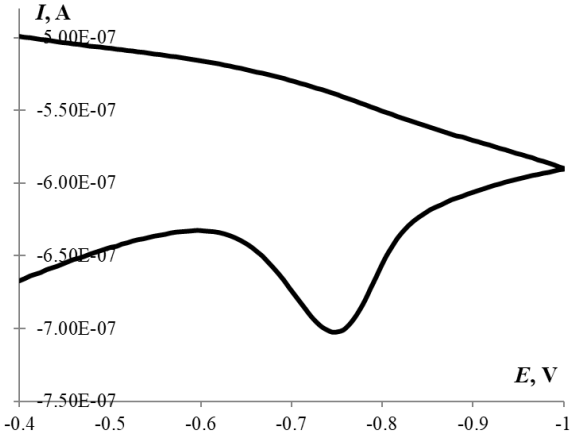

Figure 2. Cyclic voltammogram of PRC sulfoxide, PRC concentration in the cell was 0,014mg/mL.

3.2. Voltammetric parameter optimization in the differential pulse mode.

Differential pulse mode was chosen to quantify PRC in pharmaceuticals due to its enhanced selectivity and sensitivity compared to cyclic voltammetry. First, sweep parameters must be optimized to obtain the best signal/noise ratios.

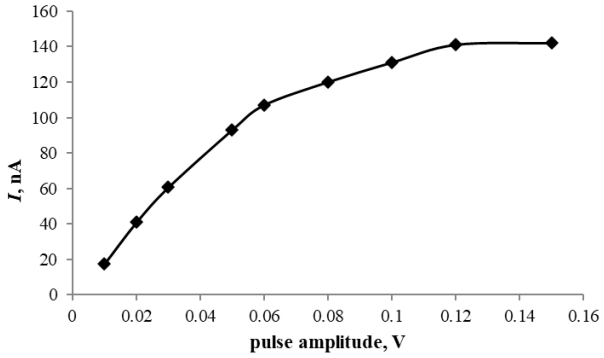

Figure 3. Peak current *vs.* pulse amplitude conditions: PRC concentration was 0,014mgmL^{-1}, Oxone® concentration was about 0.001molL^{-1}, background electrolyte was 0,02molL^{-1} HCl; pulse time and sweep rate have default values of 0.04s and 0.1Vs^{-1}, respectively.

Parameter optimization was performed under the following conditions: a PRC concentration was 0,014mgmL^{-1}, an Oxone® aliquot was 2mL, and a background electrolyte consisted of 10mL of 0,02molL^{-1} HCl. Three parameters, pulse amplitude, pulse time, and sweep rate, were studied. Two parameters were constant, and the third one varied in an acceptable range. An optimal value between a background current and a Faradaic peak height was chosen for each parameter (Figures 3, 4, 5).

An optimal value for pulse amplitude was found to be 0,06V.

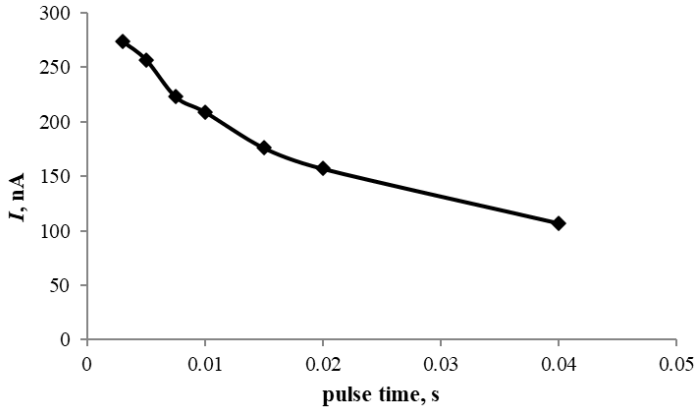

Figure 4. Peak current *vs.* pulse time: PRC concentration was 0,014mgmL^{-1}, Oxone® concentration was about 0.001molL^{-1}, background electrolyte was 0,02molL^{-1} HCl; pulse amplitude was 0,06V, sweep rate has a default value of 0.1Vs^{-1}.

An optimal value for pulse time was found to be 0,008s.

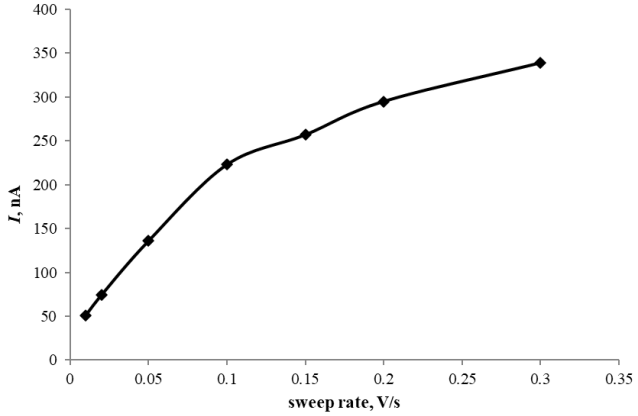

Figure 5. Peak current *vs.* sweep rate: PRC concentration was 0,014mgmL^{-1}, Oxone® concentration was about 0.001molL^{-1}, background electrolyte was 0,02molL^{-1} HCl; pulse amplitude and pulse time were 0,06V and 0,008s, respectively.

An optimal value for sweep rate was found to be 0.1V/s

Table 1. Working parameters for differential pulse determination of PRC.

Parameter	Optimized value
Electrode	HMDE
Voltage step[1]	0.006 V
Pulse amplitude	0.06 V
Pulse time	0.008 s
Voltage step time[1]	0.06 s
Equilibrium time[2]	10 s
Drop size[2]	4

[1]The ratio voltage step/voltage step time gives the sweep rate

[2] Equilibrium time and drop size values were used by default

The working parameters chosen are summarized in Table 1 and used for all subsequent measurements.

3.3. Oxone® concentration selection.

10mL of 0.02molL^{-1} hydrochloric acid solution, an aliquot of the working standard solution of PRC, and varying aliquots of the stock Oxone® solution (in the range of 20 to 160µL) were placed in the electrochemical cell. Nitrogen was bubbled each time for 120s and voltammograms of sulfoxide reduction were recorded. Figure 6 shows the dependence of the current for sulfoxide reduction on the volume of Oxone® solution added.

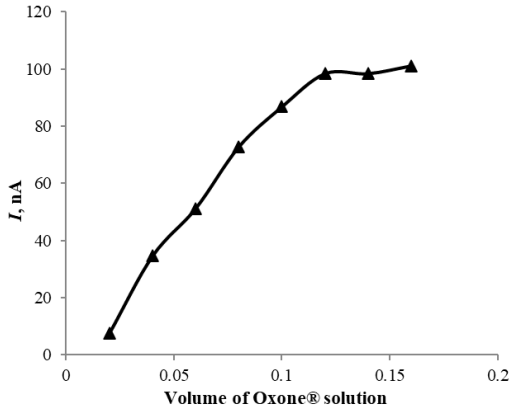

Figure 6. Sulfoxide reduction current vs. volume of Oxone® solution added (c(PRC) = 1,9·10^{-3} gL^{-1}).

A peak height for sulfoxide reduction increases with an increasing amount of Oxone® added until the volume of 120µl corresponds to Oxone® concentration of about 0.01gL^{-1}. Accordingly, all PRC transforms into sulfoxide.

3.4. Reaction time.

10mL of 0.02molL^{-1} hydrochloric acid solution, an aliquot of the working standard solution of PRC (200µL), and an aliquot of the stock Oxone® solution were placed in the electrochemical cell. Voltammograms of sulfoxide reduction were recorded every 10s and then every 30s (Figure 7). An optimal reaction time was chosen to be 150s.

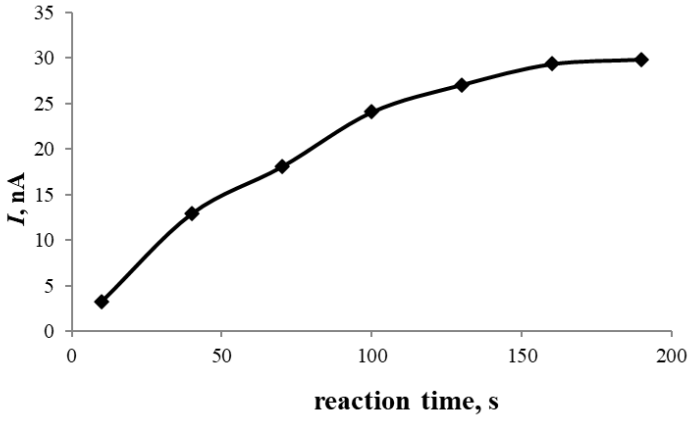

Figure 7. Peak current vs. time of reaction between Oxone® and PRC.

3.5. Calibration curve for PRC.

10mL of 0.02molL^{-1} hydrochloric acid solution and 120µL of the stock Oxone® solution were placed in the electrochemical cell. Nitrogen was bubbled through the solution for

120s. Aliquots of the working standard solution of PRC (20-30µL) were then added to the cell. After each addition of an aliquot, the solution was mixed for 150s, and voltammograms were recodered (Figure 8).

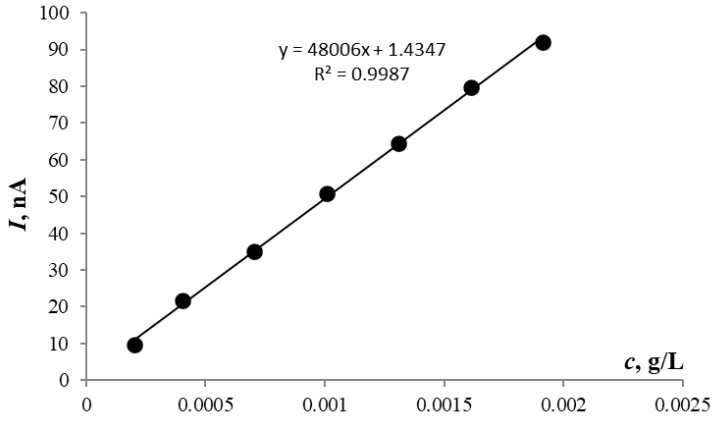

Figure 8. Peak current for PRC sulfoxide reduction vs. PRC concentration.

The calibration curve is linear in the concentration range of 0.2 to 2µgmL^{-1} and can be approximated as *I (nA)* =(4.80±0.08)·10^4*C* (mgmL^{-1}) +(1.43±0.90); r=0.999).

Using a calibration curve a limit of detection (LOD) and a limit of quantification (LOQ) were estimated to be 0.06µg·mL^{-1} and 0.2µg·mL^{-1}, respectively.

Based on the data obtained from these experiments, methods for PRC content determination in Neuleptil®, 4 % solution, and Neuleptil®, 10mg capsules were proposed below.

3.5.1. Method for PRC content determination in the solution in mg for 1mL (Neuleptil, 4 % solution).

Transfer a precise aliquot (0.5mL) of the solution to a 200mL volumetric flask and complete to 200mL with 50% ethanol solution. Cap the flask and vigorously mix the solution. Pipette 0.5mL or 0.75mL of the solution into a 100mL volumetric flask, add 20mL of 0.1molL^{-1} hydrochloric acid solution and make the volume with ultrapure water. Cap the flask and vigorously mix the solution. Transfer 10mL of the resulting solution to the electrochemical cell, degassed with nitrogen for 120s. Add 120µL of the stock Oxone® solution, mix for 150 s, and record voltammograms for sulfoxide reduction. Transfer 10mL of the resulting solution to the electrochemical cell, degassed with nitrogen for 120s. Add 120µL of the stock Oxone® solution and an aliquot of the standard working PRC solution (50µL or 75µL), mix for 150s, and record voltammograms of sulfoxide reduction.

PRC content based on PRC base in mg/mL can be calculated using formula (1):

$$X = \frac{k \times I \times C_{add}}{(I_{add} - I)} \quad (1)$$

Herein

I_{add} is current after the addition of PRC; I is current in a test solution without the addition of PRC; C_{add} is an added amount of PRC base recalculated for the cell volume, mg/mL; k is a dilution coefficient of 4 % formulation solution (80000 or 53333).

3.5.2. Precision and accuracy.

The levels of precision and accuracy for the measurement method were confirmed by calculation of the relative standard deviation (%RSD), and percentage recoveries (%R) using five replicate measurements of a drug sample; the trueness of the measurement method was investigated by comparing the accepted reference value (according to the certificate of analysis) with the level of the results given by the measurement method. Generally, good levels of precision were obtained for API with perfect values of 1.2-1.8% RSD, as shown in Table 2 and Table 3. Measured the accepted reference values obtained for the analysis of API by differential pulse polarographic method were highly comparative to certified values. The analytical recovery value is 99-100.5 % for API determined, as reported in Tables 2 and 3.

Table 2. The results of the analysis of 4% oral drops Neuleptil by differential pulse polarography method.

Taken for analysis	Found, % of PRC	Statistics, p=0.95
0,50 mL (3,96 %*) of drop solution SANOFI-AVENTIS FRANCE produced by A.NATTERMANN and Cie., GmbH, Germany, serial № 6K0331 **80000-fold dilution**	3.87 3.97 3.90 3.97 3.96	$\bar{X}$ =3.93 (R=99.24%) $\Delta\bar{x}$=0.06 RSD=1.17% $(\bar{X}-\mu)100\%/\mu$ = -0.76%
0,50 mL (3,96 %) of drop solution SANOFI-AVENTIS FRANCE produced by A.NATTERMANN and Cie., GmbH, Germany, serial № 6K0331 **53333-fold dilution**	4.02 4.08 3.97 3.95 3.89	$\bar{X}$ =3.98 (R=100.50%) $\Delta\bar{x}$=0.089 RSD=1.81% $(\bar{X}-\mu)100\%/\mu$=+0.56%

*According to the Certificate of Analysis the average content of the drug (PRC active substance) was 3.96% (μ).

3.5.3. Method for PRC content determination in 10mg capsules.

Mix a precise amount (about 0.150g) of capsule content powder, corresponding to the average capsule weight, with 20mL of 0.1molL^{-1} hydrochloric acid and around 20-30mL of water. Shake for 30min, filtrate using filter paper, and rinse a filter cake with ultrapure water. Quantitatively transfer the combined filtrate to a 100mL volumetric flask. Make volume with ultrapure water and mix thoroughly. Pipette 0.5mL or 0.75mL of the resulting solution and transfer to a 100mL volumetric flask. Add 20mL of 0.1molL^{-1} hydrochloric acid solution and dilute to 100mL with ultrapure water. Cap the flask and mix thoroughly. Transfer 10mL of the resulting solution to the electrochemical cell and degas with nitrogen for 120s. Then add 120μl of the stock Oxone® solution, mix, and record voltammograms of sulfoxide reduction. Carry out the same procedure with the working standard solution. Pipette 0.5mL or 0.75mL of the standard solution and 20mL of 0.1molL^{-1} hydrochloric acid into a 100mL volumetric flask, make a volume with ultrapure water, cap the flask, and mix thoroughly. Transfer 10mL of the resulting solution to the electrochemical cell, degas for 120s. Then add 120μL of the stock Oxone® solution, mix for 150 s, and record voltammograms of sulfoxide reduction.

PRC content based on PRC base in mg for a capsule can be calculated using formula (2):

$$X = \frac{C_{st} \times I \times k \times V \times m'}{I_{st} \times m} \quad (2)$$

in which:

I is current in the experiment with a test solution; I_{st} is current in the experiment with the PRC standard working solution; C_{st} is a concentration of the PRC base in the standard solution in the cell, mg/mL; *m* is a weight of the capsule content powder, g; *m*' is an average weight of the capsule content, g; *V* is the volume of the flask used for test or standard solution preparation; *k* is a dilution coefficient (200 or 133).

Table 3. The results of the analysis of 10 mg capsules of Neuleptil by differential pulse polarography method.

Taken for analysis	Found, % of PRC	Statistics, p=0.95
0,1502 g (10,07* mg for 1 capsule ± 5 %) Neuleptil®, 10 mg capsules- № 5, produced by «SANOFI» Famar Health Care Services, Madrid, S.A.U., Spain. Serial № 17N0020 **200-fold dilution**	10.09 9.96 10.24 10.23 9.86	$\bar{X}$ =10.08 (R=100.10%) $\Delta\bar{x}$=0.203 RSD=1.62% $(\bar{X}-\mu)100\%/\mu$ =+0.1%
0,1502 g (10,07*mg for a capsule ± 5 %) Neuleptil®, 10 mg capsules- № 5, produced by «SANOFI» Famar Health Care Services, Madrid, S.A.U., Spain. Serial №17N0020 **133-fold dilution**	10.05 10.06 9.75 9.97 9.87	$\bar{X}$ =9.94 (R=98.71%) $\Delta\bar{x}$=0.163 RSD=1.32% $(\bar{X}-\mu)100\%/\mu$ =-1.29%

*According to the analysis certificate, the average content of the drug (PRC base) was 10.07 mg in one capsule (μ).

4. Conclusions

A new analytical method for quantitatively determining Periciazine in dosage forms by indirect polarography in the form of a respective sulfoxide produced with potassium hydrogenperoxomonosulfate as an oxidant was developed. A calibration curve is linear in the concentration range of 0.2 to 2μg.mL^{-1} and can be approximated as I (nA) =(4.80±0.08)·104C (mg.mL^{-1}) +(1.43±0.90)); r=0.999). Using a calibration curve, a limit of detection (LOD) and a limit of quantification (LOQ) were estimated to be 0.06μg.mL^{-1} and 0.2μg.mL^{-1}, respectively. RSD for Neuleptil® oral drop solution 4% and Neuleptil capsules 10mg were 1.2-1.8% and 1.3-1.6%, respectively. 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: $(\bar{X}-\mu)100\%/\mu$ < RSD. The methods are simple, sensitive, and do not require expensive and relatively toxic solvents for HPLC procedures.

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Conflicts of Interest

The authors declare no conflict of interest.

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