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Indirect Polarographic Method for the Determination of Fluphenazine hydrochloride using Peroxomonosulphate

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Abstract:
A new analytical method for the quantitative determination of Fluphenazine hydrochloride in dosage form by indirect polarography of its sulfoxide form produced using potassium hydrogenperoxomonosulfate as an oxidant was developed. Calibration curve was linear in the concentration range of 0.1 to 2 μg.mL^{-1} and was approximated as I(nA) =(2.57±0.02)·10^{4}C (mg.mL^{-1})+(1.38±0.27)); r=0.999). Using calibration curve a limit of detection (LOD) and a limit of quantification (LOQ) were estimated to be 0.03 μg.mL^{-1} and 0.1 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 tablets Fluphenazine (HCl) - 5mg was 1.74-1.76%. The trueness/accuracy of the measurement method was investigated by comparing the accepted reference value (μ) with the level of the results given by the measurement method : |(X̄-μ)100% / μ | < RSD. Analytical recovery values were 100,2-101.2 %. The method is simple, sensitive and does not require expensive and relatively toxic solvents required for HPLC procedures.

Key Word*: Analytical Method; Assay; Derivitization; Fluphenazine; Polarography.*

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I. Introduction

Fluphenazine hydrochloride (FP), 2-[4-[3-(2-(trifluoromethyl)phenothiazine-10-yl)propyl]piperazine-1-yl]ethanol dihydrochloride (Fig. 1) belonging to the piperazine class of phenothiazines[1] , is a typical antipsychotic drug used for the treatment of psychoses such as schizophrenia, manic phases of bipolar disorder, agitation, and dementia[2]. In addition, as a serotonin antagonist, this agent may inhibit lymphocyte and myeloma cell proliferation[3]. Numerous analytical methods have been published in literature for the determination of FP, either in pure form or pharmaceutical preparations and biological fluids. These methods include spectrophotometry[4,5], spectrofluorimetry[6,7,8], voltammetry[9,10,11], High Performance Liquid Chromatography (HPLC)[12,-17], Densitometric High Performance Thin Layer Chromatography (HPTLC)[18], capillary electrophoresis[19] and chemiluminescence[20]. The British Pharmacopoeia (BP)[21] recommended a non-aqueous potentiometric method for the determination of FP using perchloric acid as a titrant; the LOQ was 6.3 mg mL-1. For analysis of its tablets, the British Pharmacopoeia (BP) un like the European Pharmacopoeia (Ph Eur) recommended a spectrophotometric method based on recording second-derivative ultraviolet absorption spectra of the working and reference solutions in the range 230 to 300 nm. For each solution measure the amplitude from the peak at about 266 nm to the through at about 258 nm[22]. The United States Pharmacopoeia (USP) on the other hand, described an HPLC method for the determination of FP in pure form, Fluphenazine Hydrochloride Injection and Fluphenazine Hydrochloride Tablets using UV detection at 254 nm, where the LOQ was 2.4 μg mL^{-1}[23]. Although chromatographic methods offer a high degree of specificity, sample clean-up and instrumental limitations preclude their use in routine clinical studies. Therefore, there is a need for an alternative substitute to the HPLC methods, and voltammetry by virtue of its high sensitivity was a promising substitute.

Electrochemical behaviour of these substances can be successfully employed for elaborate simple, rapid and sensitive procedures for the determination of these drugs in pharmaceutical preparations[24]. It is known that Phenothiazines are easily oxidized chemically and electrochemically. Electrochemical oxidation of some active substances for subsequent analysis using polarographic and voltammetric methods is being explored. Several electrochemical techniques have been applied for the determination of psychotropic substances in drugs preparations (including phenothiazine derivatives) and differential biological samples[25]. Fluphenazine and trifluoperazine were determined by differential pulse voltammetry after pre-concentration at a wax-impregnated

graphite electrode. For plasma, the electrode was covered with a membrane to prevent fouling by proteins[26]. The electrochemical behaviour of fluphenazine based on its oxidation at platinum and glassy carbon electrodes was investigated by linear sweep and cyclic voltammetry. The influence of pH, concentration, nature of the buffer and scan rate was carefully examined. At both electrodes, three anodic steps (representing an irreversible oxidation) were obtained. The method was applied to the determination of fluphenazine in sugar-coated tablet on 1 mg. RSD was 10% and 5% (n=10) for platinum and glassy carbon electrode respectively[27]. A novel multi-walled carbon nanotubes/(3-mercaptopropyl) trimethoxysilane (MPS) bilayer modified gold electrode was prepared and used to study the electrochemcial behavior of fluphenazine and determine it. Fluphenazine could effectively accumulate at this electrode and produce two anodic peaks at about 0.78V and 0.93V (versus SCE). This method was successfully applied to the determination of fluphenazine in drug samples and the recovery was 96.4-104.4% [28]. Derivatization polarography, i.e., the conversion of a polarographically inactive compound into an active one is brought about through chemical reactions can be use as alternative too. These reactions should occur selectively, rapidly and with a yield of nearly 100%[29]. Phenothiazines in pharmaceutical preparations have been determined by polarographic technique. The polarographic method is based on prior conversion of phenothiazines into polarographically active derivatives through nitration[30], followed by measuring the redox wave. After nitrosation they can be determined by Differential-pulse polarography (DPP) on dropping mercury electrode (DME) at submicromolar level. HPLC and DPP methods are both good, but polarography enables rapid analysis with simple apparatus, does not require a tedious clean-up step and provides better reproducibility and accuracy[31]. Differential-pulse polarographic determination of some N-substituted phenothiazine derivatives in dosage forms and urine through treatment with nitrous acid produced results that correspond with those found in the official methods[32]. Based on our previous successful derivatization of compounds using peroxy acid oxidation and subsequent deployment for pharmaceutical analysis[33,34], the purpose of this work was to develop a simple, accurate, precise and inexpensive method for the assay of some phenothiazine psychotropics in pharmaceutical formulations.

Peroxymonosulfuric acid (MPS) seemingly possesses several advantages over other reagents used in this field. In this paper, we report on its use in the oxidation of fluphenazine to polarography-active form, and the development of a simple and sensitive method for its determination.

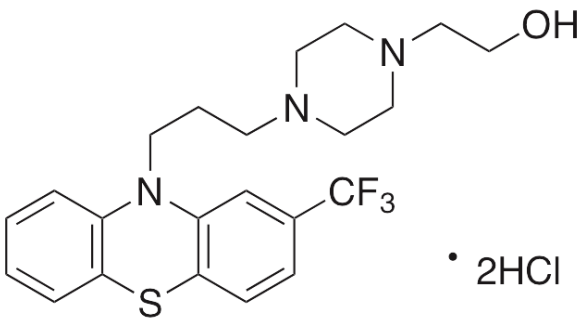

Fig. 1 The molecular structure of Fluphenazine hydrochloride

II. Material And Methods

Voltammetric measurements:

All voltammetric measurements were carried out using 797 VA Computrace System for voltammetric analysis (Metrohm, Switzerland). 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 solution of hydrochloric acid as supporting electrolyte.

Reagents:

Oxidation of a FP to a FP S-oxide using a potassium triple salt containing potassium peroxymonosulfate (KHSO5), potassium hydrogensulfate (KHSO4), and potassium sulfate (K2SO4) 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 as "green" oxidizing agent because it has not toxic effects.

Fluphenazine dihydrochloride (grade: pharmaceutical primary standard). European Pharmacopoeia (EP) Reference Standard (>98%, titr.). Synonym: 4-[3-[2-(Trifluoromethyl)-10H-phenothiazin-10-yl]propyl]-1-

piperazineethanol dihydrochloride. CAS Number 146-56-5, C22H26F3N3OS·2HCl , Molecular Weight 510.44 (Sigma-Aldrich).
The object of study were tablets Fluphenazine (HCl) - 5mg, production Mediphar Laboratories (Dbayeh - Lebanon), batch number 8273. The average weight of the tablet (n=15) was 0.3177 g.
All other reagents were of analytical grade.

Preparation of working solutions:
Fluphenazine:
Stock solutions were prepared daily by dissolving fluphenazine in double-distilled water. A working standard solution of FP (0.1 mg/ml) was prepared by mass/volume method. 10 mg equivalent of FP in the tablets was dissolved in 100 ml of 0.02 M solution of hydrochloric acid.
Alkaline media were avoided as fluphenazine undergoes a precipitation reaction in such media. Double-distilled water was used to prepare the solutions.
Potassium hydrogenperoxomonosulfate:
Preparation of 0.005 mol L^{-1} potassium hydrogen peroxymonosulfate solution:- About 0.15-0.2 g of Oxone® was dissolved in 100 mL of double-distilled water. The content of potassium hydrogen peroxymonosulfate was determined by iodometric titration.

Method for content determination of fluphenazine in tablets:
A precise amount of crushed tablets (0,64 g), corresponding to the average mass of two tablets was mixed with 20 ml of 0.1 M Hydrochloric acid and then with 20 – 30 ml of water. After shaking for 30 minutes, it was filtered and residue thoroughly rinsed with ultrapure water. The contents were quantitatively transferred into a 100 ml volumetric flask. The volume is made up to the mark with ultrapure water and mix thoroughly. 1 ml of the solution was transferred to a 100 ml volumetric flask to which 20 ml of 0.1 M HCl solution was added and made up with ultrapure water to 100 ml. 10 ml of the obtained solution was transferred to the electrochemical cell where it was degassed with nitrogen for 120 seconds. 120 µl of the stock Oxone® solution, mixed for 150 seconds and voltammograms of oxidized sulfoxide was recorded. The same procedure is carried out with the working standard solution. Content of Fluphenazine hydrochloride in mg is calculated by this formula:

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

where
I is current in the experiment with a test solution;
I_{st} is current in the experiment with the FP standard working solution;
C_{st} is a concentration of the FP 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 tablet content, g;
V is the volume of the flask used for test or standard solution preparation;
k is a dilution coefficient (200 or 100).

Preparation of Fluphenazine Sulfoxide: A Fluphenazine dihydrochloride, 500 mg (1 mmol), was transferred to an Erlenmeyer flask, and dissolved in 25 ml of water and a calculated amount of oxone was added (135 mg, 1 mmol KHSO5). The reaction mixture was stirred in a water bath at 20°C for 10 min. When conversion of fluphenazine to compound fluphenazine S-oxide was complete, 1 M sodium hydroxide was added until the solution became alkaline (pH 9,5) and extract with dichloromettlane twice (25 ml each). Dichloromettlane was separated in a vacuum evaporator. Fluphenazine sulfoxide in the residue was crystallized from methanol-acetone. Off-White to Pale Orange Solid, C22H26F3N3O2S; Melting Point (°C) 131-133.

III. Result And Discussion

The UV spectra of the isolated compounds in methanolic solution were recorded on Specord 200 «AnalitykJena» (Germany) scanning spectrophotometer. For Fluphenazine S-oxide (base) λmax(nm), (ε) in water : 216 (23165); 234 (28535); 273 (12372); 301 (8424); 347 (5897) . On IR spectra (cm-1): 1050, 1060.

All reports affirmed that oxidation of the phenothiazine ring S atom results in a bathochromic shift of the λ_{max} with respect to the parent phenothiazine, and that the spectra of the sulphoxides were characterised by the presence of three wavelengths of maximum absorption (at about 273, 301 and 347 nm). By comparing melting points and spectral characteristics, the product of oxidation was found to be a sulfoxide.

Excitation and fluorescence spectra of the isolated compounds in 0.1% methanolic hydrochloric acid were recorded on a Perkin-Elmer model 204 spectrofluorimeter. For Fluphenazine S-oxide (base) Fluorescence spectra: 300; 348 (Shoulder); Fluorescence, λmax (nm), Strong 393 (Exitation).

Fluphenazine, which exhibits a weak native fluorescence, was transformed to a strongly fluorescent sulphoxide by hydrogen peroxomonosulfate. In addition, the fluorescence λmax shifted to a shorter wavelength. The intense fluorescence is believed to result from the extended conjugation of the aromatic nucleus formed by substitution of oxygen at the phenothiazine ring S atom as seen in the scheme in Fig 2.

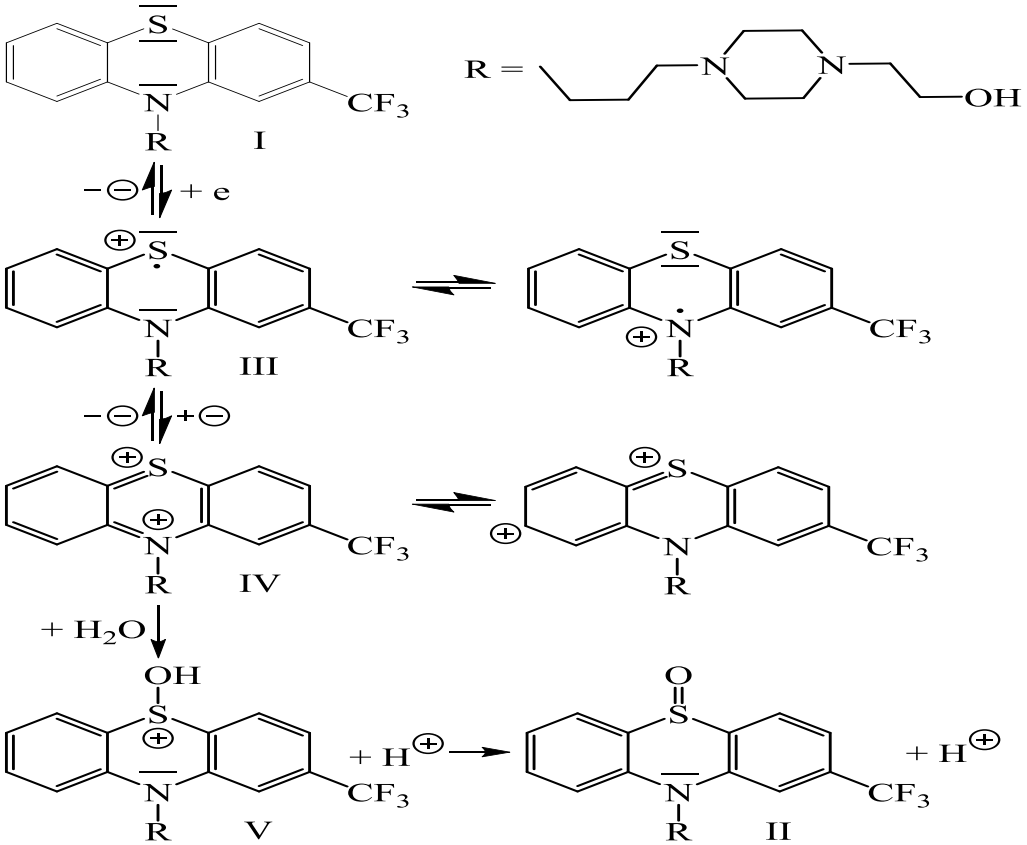

Fig 2. Scheme of S-oxidation reaction of Fluphenazine by hydrogen peroxymonosulfate in acidic medium

Voltammetric parameter optimization in differential pulse mode

Differential pulse mode was chosen for quantification of FP in pharmaceuticals due to its enhanced selectivity and sensitivity compared to cyclic voltammetry. Firstly, sweep parameters have to be optimized to obtain best signal/noise ratios. Parameter optimization was performed under the following conditions: a PRC concentration was 0,014 $mg{\cdot}mL^{-1}$, an Oxone® aliquot was 2 mL, a background electrolyte consisted of 10 mL of 0,02 mol L^{-1} HCl. Three parameters such as pulse amplitude, pulse time and sweep rate were studied. Two parameters were constant and the third one was 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).

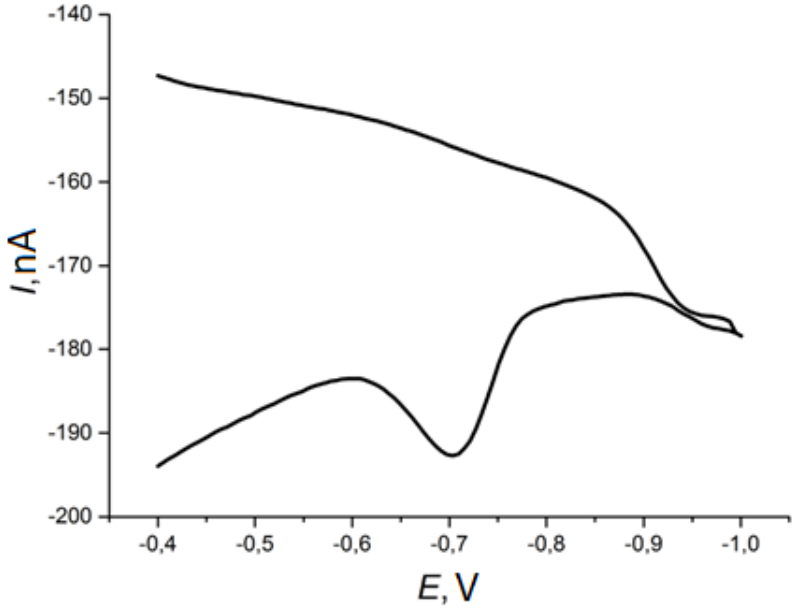

Fig.3 Cyclic voltammogram
c(FP) = 0,01 mg/ml, *c*(oxone) ≈ 0,2 mg/ml,
10 ml 0,02 M HCl, voltage sweep rate – 0,1 V/s, E_p = -0,72 V

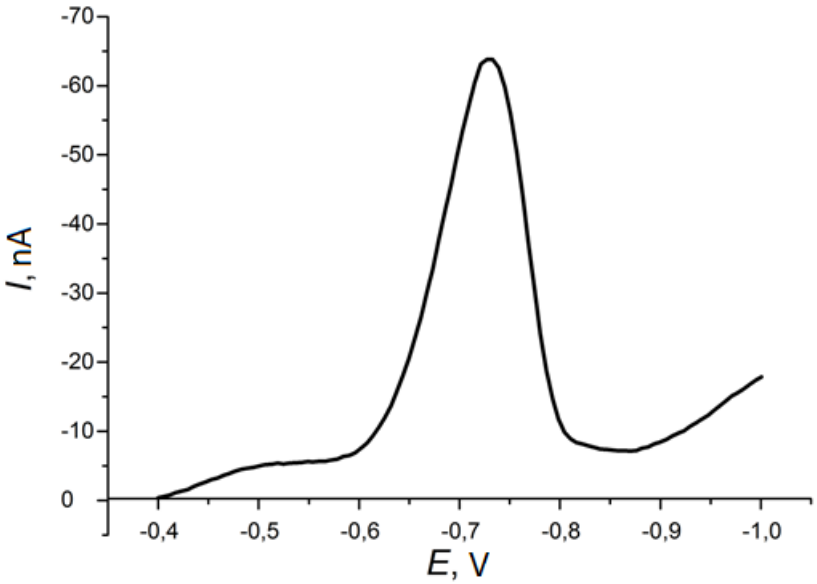

Fig. 4 Differential pulse voltammogram
10 ml 0,02 M HCl; *c*(Oxone) ≈ 0,02 мг/мл,
c(FP) = 2,3 mcg/ml, sweep rate: 0,1 V/s,
Pulse amplitude: 0,06 V, Pulse width: 0,007 s,
E_p = -0,73 V

Calibration curve for Fluphenazine

10 ml 0,02 M HCl and 120 µL of Oxone solution were added to the electrochemical cell. Nitrogen was applied for 120 seconds to degas the solution, after which aliquots of FP standard solution (20 – 30 µL) were added to the cell. For every addition of aliquot, the solution was stirred for 150 seconds and then recording was made of the voltammogram reading (Fig. 4). The resultant regression formula deduced from the calibration curve was Y= $(2.57\pm0.02)\cdot10^4+(1.38\pm0.27)$.

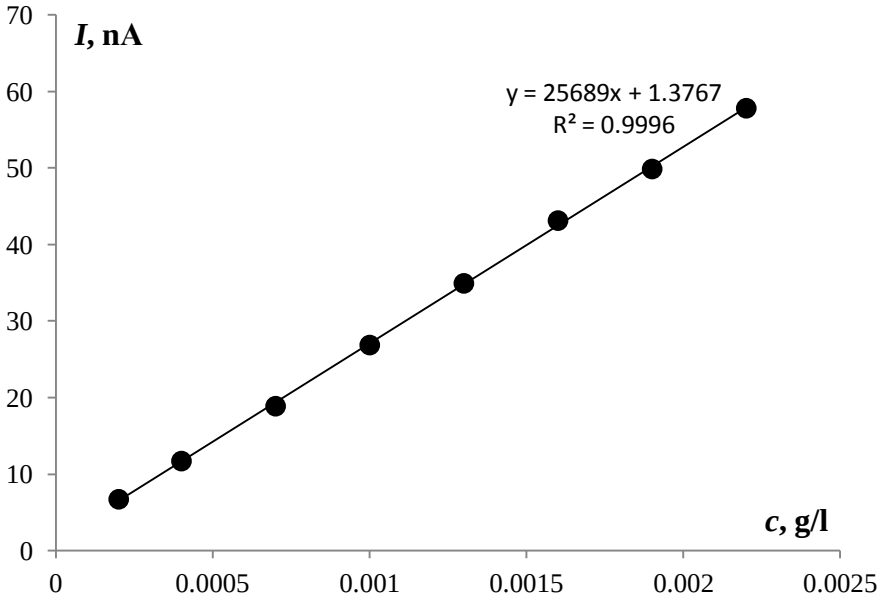

Fig. 5 Dependence of electrochemical reduction of products of fluphenazine oxidation on concentration of fluphenazine.

Calibration curve is linear in the concentration range of 0.1 to 2 $\mu g \cdot mL^{-1}$ and can be approximated as $I(nA) = (2.57\pm0.02)\cdot10^4 C$ $(mg \cdot mL^{-1})+(1.38\pm0.27)$); r=0.999). Using calibration curve a limit of detection (LOD) and a limit of quantification (LOQ) were estimated to be 0.03 $\mu g \cdot mL^{-1}$ and 0.1 $\mu g \cdot mL^{-1}$, respectively.

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. In general, good levels of precision were obtained for API with perfect values of 1.74-1.76% RSD, as shown in Table 1. The measured and accepted reference values obtained for the analysis of API by differential pulse polarographic method were highly comparative to certified values. Analytical recovery value is 100,2-101.2 %. for FP determined, as reported in Table 1.

Table 1: Shows the results of the quantitative determination of fluphenazine hydrochloride in tablets of 5 mg

Taken for analysis	Fluphenazine dihydrochloride content was found, mg/one tablet	Metrological characteristics, p=0,95
0,6405 g tablets powder Fluphenazine hydrochloride 5 mg, Mediphar Laboratories (Dbayeh - Lebanon) 200-Fold dilution	4,80 4,94 5,00 4,95 5,02	$\bar{X} \pm \Delta\bar{x}$= 4.94±0.107 RSD=1.74% δ=+0.2%
0,6405 g tablets powder Fluphenazine hydrochloride 5 mg, Mediphar Laboratories (Dbayeh - Lebanon) 100-Fold dilution	5,02 4,94 5,02 4,87 5,10	$\bar{X} \pm \Delta\bar{x}$= 4.99 ±0.109 RSD=1.76% δ=+1.2%

Note: The calculation is based on the average content found by the method of USP 39 (4.93 mg / tablet - 98.60 ± 10% (µ). $\delta = (\bar{x}-\mu)\ 100\% / \mu$

The work was performed within the project titled "Implementation of modern principles for synthesis and analysis of substances and material components used in pharmaceutical products", state registration no. 0119U100727 (Ukraine).

IV. Conclusion

A new analytical method for the quantitative determination of Fluphenazine hydrochloride in dosage form by indirect polarography of its sulfoxide form produced using potassium hydrogenperoxomonosulfate as an oxidant was developed. Calibration curve was linear in the concentration range of 0.1 to 2 $\mu g \cdot mL^{-1}$. A limit of detection (LOD) and a limit of quantification (LOQ) were estimated as 0.03 $\mu g \cdot mL^{-1}$ and 0.1 $\mu g \cdot mL^{-1}$, 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 tablets Fluphenazine (HCl) - 5mg was 1.74-1.76%. 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: $|(\bar{X}-\mu)100\% / \mu| < RSD$. Analytical recovery values were 100,2-101.2 %. The method is simple, sensitive and does not require expensive and relatively toxic solvents required for HPLC procedures.

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