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ARTICLE

Polarographic Determination of Prothipendyl in Dosage Forms using Differential Pulse Mode after Oxidation with Oxone

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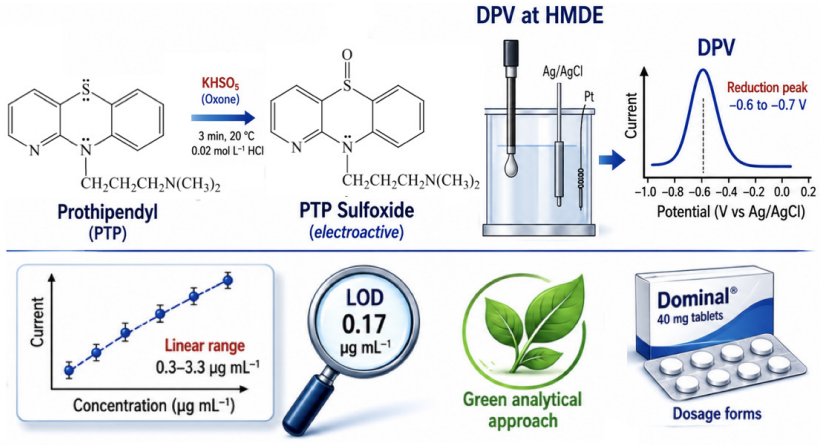

Indirect polarography was used to develop a novel analytical approach for prothipendyl quantification in dosage forms, using oxone as an oxidative agent. Prothipendyl is not reducible at a mercury electrode, but it can be determined by differential pulse voltammetry as its initial S-oxidation product, which is obtained by oxidation with $KHSO_5$ in 0.02 mol L^{-1} HCl solution at 20 °C for 3 min (reduction peak at 0.02 mol L^{-1} HCl, about -0.6 – -0.7 V *vs* Ag/AgCl-reference electrode). Using differential pulse voltammetry at a hanging mercury drop electrode, a linear calibration curve was established for prothipendyl over the concentration range of 0.3 to 3.3 µg mL^{-1} in 0.02 mol L^{-1} HCl, with a detection limit of 0.17 µg mL^{-1}. The feasibility of quantitatively determining prothipendyl hydrochloride in 40 mg Dominal® tablets was confirmed. A percentage recovery (%Re) of 100.425 and a relative standard deviation of 1.70% (n = 7) were obtained. The validity of the measurement method was examined by determining how closely the mean measured value ($\bar{x}$) aligned with the established reference value (µ), based on the condition $\left|(\bar{x} - \mu) \times 100\%/\mu\right| < t_{\alpha} \times RSD / \sqrt{n}$, with n = 7 and a 95% confidence level (P = 0.95).

Keywords: differential pulse polarography, assay, azaphenothiazine, prothipendyl, S-oxidation, potassium caroate

INTRODUCTION

Prothipendyl (PTP) is a tricyclic antipsychotic medication of the azaphenothiazine group.[1–4] Chemical

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name is N,N-Dimethyl-3-(10H-pyrido[3,2-b][1,4]benzothiazin-10-yl)propan-1-amine) (Figure 1). Due to its sedative and psychomotor-dampening effects, PTP is used to treat psychomotor agitation, as well as sleep disorders and anxiety. Recently, PTP was found to exhibit anticancer activity.[5,6]

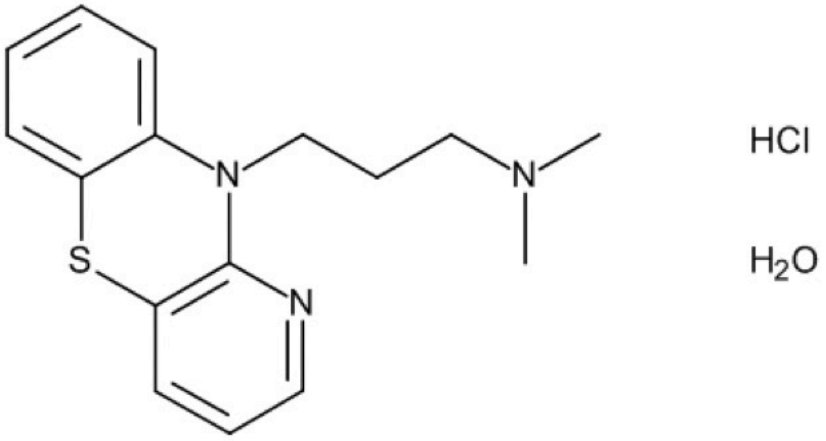


Figure 1. Chemical structure of PTP hydrochloride-1-water salt.

The therapeutic application of PTP necessitates the development of reliable methods for its determination in pharmaceutical dosage forms and biological fluids. Owing to its distinctive molecular structure, PTP exhibits several noteworthy analytical properties.

Various analytical methods for PTP have been documented in the literature. In a strongly acidic medium, PTP hydrochloride undergoes a reaction with ammonium peroxidisulfate and ammonium metavanadate, resulting in the formation of colored oxidation products with maximum absorbance at 372 nm and 374 nm, respectively. The absorbance reaches a stable value within two minutes after mixing PTP with the oxidizing agents. Optimal reaction conditions have been established, and it has been determined that Beer's law is followed within the concentration ranges of 3–95 μg mL^{-1} for the PTP-peroxidisulfate system and 3–90 μg mL^{-1} for the PTP-metavanadate system. PTP is primarily available in pharmaceutical dosage forms, including tablets and injections.[7]

Two spectrophotometric techniques – difference spectrophotometry at 340 nm (Method 1)[8] and at 278 nm (Method 2)[9] – have been developed for PTP determination. The proposed analytical procedures rely on the oxidation of PTP in a 0.01 mol L^{-1} sulfuric acid medium using potassium peroxomonosulfate ($KHSO_5$, oxone) to produce the corresponding sulfoxide. The molar absorptivity of the sulfoxide was determined to be (5.83 ± 0.07) × 10^3 L mol^{-1} cm^{-1} at 340 nm and (13.69 ± 0.01) × 10^3 L mol^{-1} cm^{-1} at 278 nm. The methods involve measuring the absorbance of the oxidized solution at 340 nm (Method 1) or 278 nm (Method 2) and comparing it to the absorbance of the unoxidized drug solution at an equivalent concentration. The oxidation of PTP by $KHSO_5$ is simple and rapid, and the oxidation product is stable. The linearity range was from 1.5 to 70 μg mL^{-1}; LOQ was 4.9 μg mL^{-1} (Method 1) and from 3.2 to 60 μg mL^{-1}; LOQ was 3.2 μg mL^{-1} (Method 2). RSDs were ≤ 1.3% (Method 1) and 1.4% (Method 2), respectively. The feasibility of quantitatively determining PTP hydrochloride in 40 mg Dominal® tablets was successfully demonstrated. The proposed methods, characterized by their simplicity and high sensitivity, do not require the use of costly reagents typically used in high-performance liquid chromatography (HPLC) procedures.

In a clinical serum analysis, PTP and its primary metabolite, PTP sulfoxides, were quantified using high-performance liquid chromatography coupled with triple quadrupole mass spectrometry (LC-QQQ-MS).[10,11] Additionally, a sensitive liquid chromatography-tandem mass spectrometry (LC-MS/MS) technique was established for the simultaneous determination of multiple antipsychotic drugs in plasma, achieving detection limits in the parts-per-billion (ppb) to low ppb range following solid-phase extraction.[12]

Chromatographic techniques offer sufficient sensitivity to detect the characteristically low therapeutic concentrations of PTP in biological fluids.[13–17] Their capability to handle complex sample matrices makes them especially suitable for such analyses, particularly at trace levels. In contrast, pharmaceutical analysis, where analyte concentrations are typically higher, prioritizes the development of analytical methods that are rapid, straightforward, reproducible, and economically viable for routine application in quality control and analytical laboratories.

Among the methods mentioned above, electrochemical ones are beneficial for drug determination. However, the number of publications on electrochemical methods for the determination of azaphenothiazine derivatives is significantly lower than for other methods. The significant tranquilizers, e.g., phenothiazines and their analogs, lack a reducible electroactive group. Voltammetric techniques that exploit the oxidation characteristics of phenothiazine have been proposed as suitable methods for its assay.

Electrochemical methods with high sensitivity and rapidity were developed for the analysis of phenothiazine and azaphenothiazine derivatives. A boron-doped diamond (BDD) electrode was used for the electrochemical oxidation of PTP. A reversible oxidation peak in the potential range 0.55-0.75 V *vs*. Ag/AgCl reference electrode was observed during the electrooxidation of these substances. An analysis of the influence of the scanning rate confirmed that the recorded currents exhibit characteristics typical of a diffusion-controlled process. The analyte was determined using square wave voltammetry (SWV) and differential pulse voltammetry (DPV). The concentration range of 4.95×10^{-7} to 4.54×10^{-5} mol L^{-1} was determined to be linear for PTP when analyzed by SWV using a BDD electrode.[18] However, the method requires polishing the BDD electrode with alumina for 2 minutes. In addition, the electrode was electrochemically cleaned by repeatedly cycling in the appropriate potential range at a certain scan rate. A small amount of the test substances absorbed on the surface of the BDD electrode were removed by soaking it in ethanol solution.

The literature describes polarographic methods involving the preliminary oxidation of phenothiazine derivatives to the corresponding sulfoxides, followed by their reduction on a dropping mercury electrode.[19] Chlorpromazine and related compounds are oxidizable at the sulfur atom quantitatively and selectively using nitrous acid. After standing for two minutes, an ammonium sulfamate solution is added to destroy the unreacted oxidant. The resulting sulphoxide is reducible at the DME, consuming $2e^-$ and $2H^+$ in acidic buffers. In more than 20 formulations, such as tablets, drops, ampoules, and suppositories, the API content (levomepromazine, perazine, thioridazine, and PTP) could be assayed with acceptable standard deviations.[20,21] Thus, the disadvantages of the known polarographic method for determining PTP in the form of a previously obtained sulfoxide using hydrogen peroxide as a derivatizer[20] include: the use of a concentrated oxidant solution (30% hydrogen peroxide solution) as a reagent, its complexity, associated with the presence of a heating operation, as well as the need to perform an additional procedure to destroy excess hydrogen peroxide after the reaction is completed, and the lengthy analysis time, with at least 40–45 min required to analyze a single sample.

Functionalization polarography involves transforming an electroinactive compound into an electroactive one by chemically introducing an electroactive group. This transformation requires highly selective, rapid reactions and can achieve yields close to 100%.

Following previous work in the field of phenothiazine and tricyclic azaphenothiazine derivative drugs,[22–24] this study aimed to investigate the feasibility of quantifying PTP by its oxidation with $KHSO_5$ using an indirect polarographic method. A hanging mercury drop electrode (HMDE) was used because it provides a wide cathodic potential range and a self-renewing smooth surface. Less toxic alternatives often have narrower potential windows and lower sensitivity. Controlled small-scale use minimizes mercury's toxicity while retaining high analytical performance. Compared to other oxidation reagents used in this field, $KHSO_5$ has several advantages. Unlike traditional oxidants such as m-chloroperbenzoic acid, H_2O_2, $NaIO_4$, peracetic acid, or nitrous acid, oxone combines high selectivity, mild ambient-temperature conditions, and broad functional group tolerance, minimizing over-oxidation to sulfones and preserving sensitive substituents. As a stable, non-volatile solid, it offers operational simplicity and improved safety, while decomposing to benign byproducts (potassium sulfate and bisulfate) and avoiding halogenated waste, aligning with green chemistry principles.

These attributes make $KHSO_5$ an environmentally friendly, reproducible, and sustainable alternative for sulfoxidation in both analytical laboratory of quality control and industrial applications.

The aim of this study was to develop a new, simple, selective, and rapid differential pulse voltammetry method for the determination of prothipendyl in dosage forms by oxidation with oxone using a hanging mercury drop electrode.

MATERIALS AND METHODS

Reagents

Prothipendyl hydrochloride (purity 98%) was obtained from Toronto Research Chemicals (Ontario, Canada). Dominal® 40 mg film-coated tablets (TEVA GmbH; Product Code: 600093498; E 307829.01-Z03; PZL Identifier: 14179534; Batch No.: 0602521) contain prothipendyl hydrochloride monohydrate as the active pharmaceutical ingredient, with each tablet delivering 40 mg of the compound. The formulation also comprises several excipients, including microcrystalline cellulose, corn starch, lactose monohydrate, sucrose, magnesium stearate, talc, and colloidal silica. The excipient composition also includes color additives (quinoline yellow aluminum lake combined with indigo carmine aluminum lake in a 7:3 ratio), as well as macrogol 35000, polysorbate 20, TiO_2, sodium carmellose, $CaCO_3$, povidone K25, and mountain glycol wax. An average mass of each tablet is 0.29979 g.

Potassium caroate ($KHSO_5$, potassium hydrogen peroxomonosulfate or potassium monopersulphate) was employed as the oxidizing agent in this study. It is a chlorine-free, white crystalline powder with strong oxidative properties. For enhanced stability and ease of handling, the reagent was used in its commercially available triple salt form – $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$ – marketed under the trade name Oxone® «extra pure» (Acros Organics), in which $KHSO_5$ functions as the principal active component.

All other used chemicals were analytical grade. All excipients were of pharmacopoeial purity.

Solutions were prepared using ultrapure water purified by a P.NIX Power system. Aliquoting was performed using an IKA Pette (20-200 µL; IKA, Germany) and a MicroPette pipette (100-1000 µL; DragoLab, China).

A 400 mg L^{-1} PTP working standard solution was prepared by dissolving an accurately weighed amount of PTP and diluting to volume. A powder suspension containing 40 mg of PTP hydrochloride was dissolved in 100 mL of 0.01 mol L^{-1} HCl solution.

Stock solution of HCl, 0.1 mol L^{-1} was prepared using a standard titer (NPP Alpharus LLC). The tube content was diluted to 1 L.

Working solutions of HCl 0.01, 0.02, 0.04, and 0.06 mol L^{-1}, were prepared by diluting the corresponding aliquot of the HCl stock solution with water.

Oxone stock solution was prepared by dissolving 0.1 g of oxone in 100 mL of ultrapure water. The exact concentration of $KHSO_5$ was controlled through iodometric titration.[25-26]

Apparatus

Voltammetric measurements were conducted using a 797VA Computrace System (Metrohm, Switzerland). A three-electrode electrochemical system was employed, comprising a hanging mercury drop electrode (HMDE) as the working electrode, an Ag/AgCl (3 mol L^{-1} KCl) reference electrode, and a platinum auxiliary electrode. Electrochemical responses were recorded under both cyclic voltammetry (CV) and differential pulse voltammetry (DPV) modes to evaluate redox behavior. All experimental procedures were conducted at ambient temperature. An HCl solution (c = 0.02 mol L^{-1}) was used as the supporting electrolyte, providing a stable ionic environment for accurate signal acquisition.

Procedures

Calibration graph construction

In the electrochemical cell were placed 10 mL of 0.02 mol L^{-1} HCl solution, an aliquot of PTP standard solution, and a corresponding aliquot of oxone stock solution to create the required excess. Before each measurement, the test solution was deoxidized with argon for 10 min. After stirring obtained solution continuously for 120 seconds, a series of voltammograms using the optimized parameters were recorded.

Procedure for determination of PTP content in Dominal (40 mg) tablets

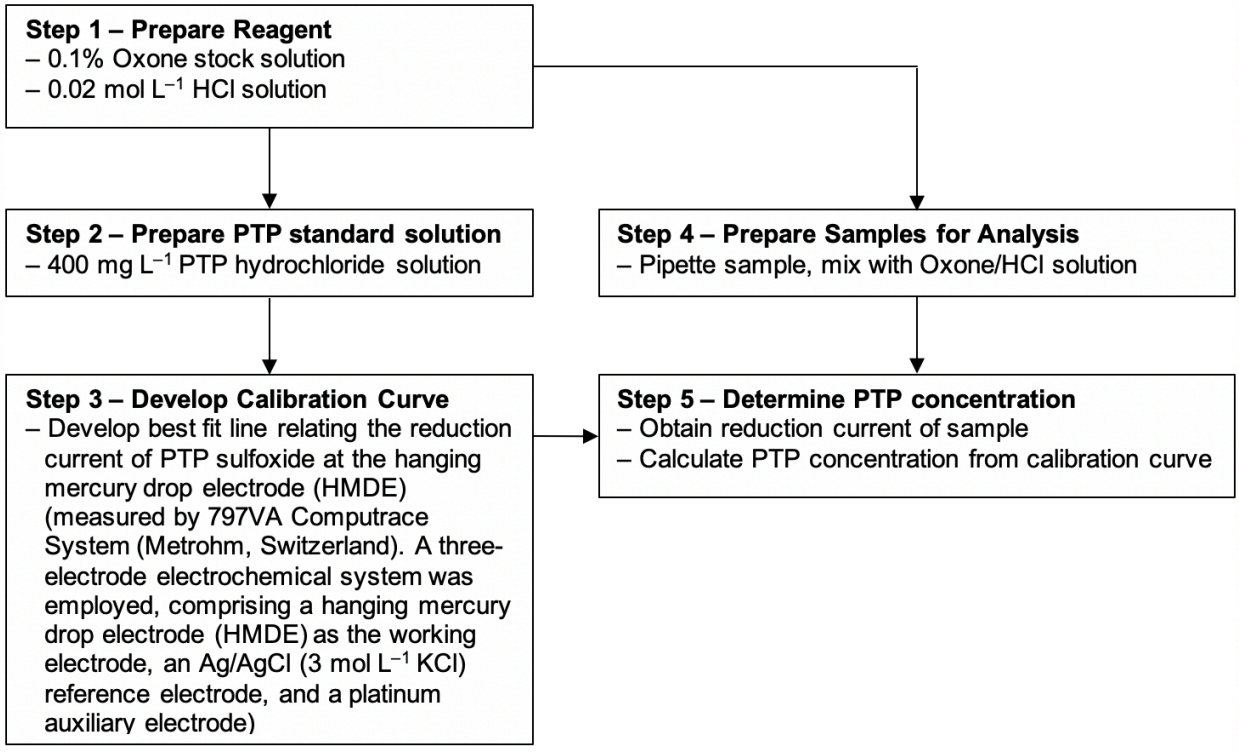
1.5 g of powdered Dominal tablets (exact weight) was dissolved in 300 mL of 0.02 mol L^{-1} hydrochloric acid on a shaker until a homogeneous suspension was formed, then filtered by washing the precipitate on the filter with the same acid solution and brought to a volume of 500 mL with the same acid solution. The prepared solution was sealed with a cork and thoroughly mixed to ensure uniformity. A 0.02 mL aliquot was then accurately pipetted into a 100 mL volumetric flask, and the volume was made up to the mark with 0.02 mol L^{-1} hydrochloric acid solution. After sealing, the solution was mixed again to achieve homogeneity. A 10 mL portion of this diluted solution was transferred into the electrochemical cell and degassed for 120 seconds to remove dissolved gases that could interfere with measurements. Subsequently, 180 µL of the stock oxone oxidizing solution was added, and the mixture was stirred for 30 seconds to facilitate oxidation. Voltammetric measurements of the reduction peak corresponding to PTP sulfoxide were recorded three times for reproducibility. The concentration of PTP in the test sample was determined by comparison with a calibration curve constructed under identical conditions.

Equation (1) was used to determine the PTP content in mg per tablet.

$$X = \frac{C_x \times k \times V \times m'}{m} \qquad \text{Equation (1)}$$

C_x – PTP concentration calculated according to the calibration graph, mg L^{-1};
k – dilution factor (500);
V – volume of measuring flask, L;
m' – average weight of tablet, g
m – tablet powder mass, g.

Summarizing of developed PTP determination procedure was described on Scheme 1.



Scheme 1. Main steps of the PTP determination procedure.

RESULTS AND DISCUSSION

Dependence of the voltammetric signal on the concentration of the supporting electrolyte using cyclic voltammetry

A volume of 0.5 mL of the PTP working standard solution, along with an excess amount (0.18 mL) of oxone stock solution, was introduced into 10 mL of hydrochloric acid solution of varying concentrations within the electrochemical cell. The PTP concentration was maintained at 19 mg L^{-1}. Cyclic voltammograms illustrating the reduction of the PTP oxidation product at different hydrochloric acid concentrations are presented in Figure 2. The voltammograms consistently indicate an irreversible electrochemical process, as demonstrated by the absence of a peak on the reverse scan.

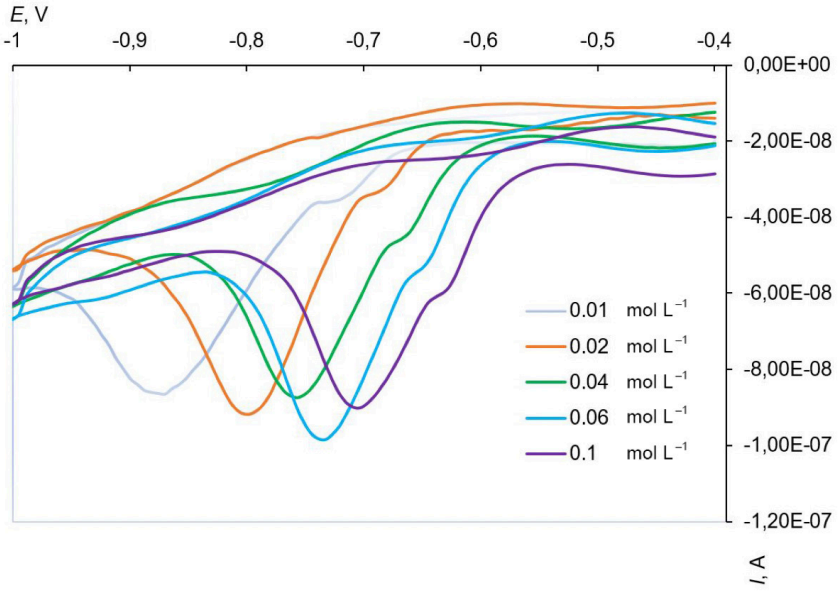


Figure 2. Cyclic voltammograms showing the reduction of the PTP oxidation product at varying hydrochloric acid concentrations; PTP concentration is 19 mg L^{-1}, sweep rate is 0.1 V s^{-1}.

Experimental data further reveal that the reduction current of PTP sulfoxide at the hanging mercury drop electrode (HMDE) remained largely unaffected by changes in the supporting electrolyte concentration. However, the reduction potential shifted in the positive direction (toward less negative values) with increasing acid concentration, as depicted in Figure 3. The shift of the PTP reduction peak towards more negative potentials when the HCl concentration decreases indicates the participation of H^+ ions in the electrochemical process.

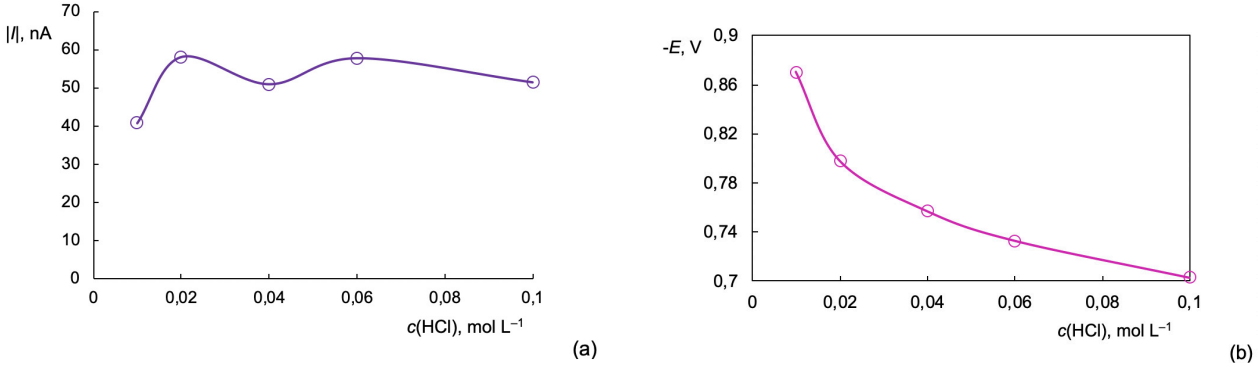


Figure 3. Current (a) and reduction potential (b) dependence on the concentration of hydrochloric acid.

Effect of scan rate

10 mL of 0.02 mol L^{-1} HCl solution, 0.5 mL of PTP working standard solution and 0.18 mL of oxone stock solution (an excess) were added to the electrochemical cell. The PTP concentration in the cell was 19 mg L^{-1}. Cyclic voltammetry was recorded at different scan rates (a). The dependence of the peak potential (b) and current (c) on the scan rate is shown in Figure 4.

The dependence of the peak potential on the scanning rate (Figure 4b) confirms the irreversibility of the reduction process at the electrode.

The slope of the $\log|I|$ vs. $\log\nu$ curve is greater than 0.5, indicating that the electroreduction process is limited by adsorption (d).

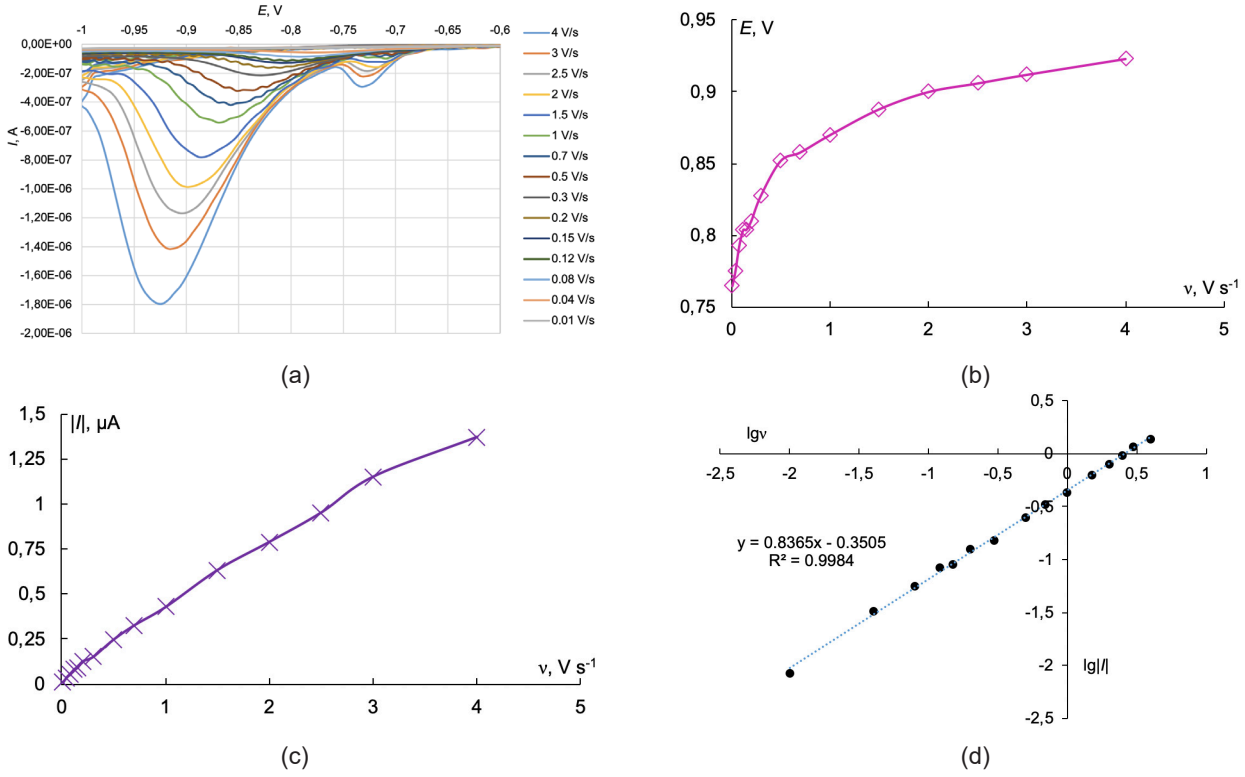


Figure 4. Relationship between: (a) Cyclic voltammograms showing the reduction of the PTP oxidation product at different sweep rates; (b) peak potential and scan rate; (c) dependence of peak current on scan rate; (d) logarithmic relationship between current ($\lg|I|$) and scan rate ($\lg\nu$).

Optimization of differential pulse voltammetry parameters

To optimize the conditions for differential pulse voltammetric determination of PTP sulfoxide, the electrochemical cell was prepared by adding 10 mL of 0.02 mol L^{-1} HCl as the supporting electrolyte, 9.5 mg L^{-1} of PTP standard solution, and an excess of oxone stock solution (0.18 mL) to generate the sulfoxide derivative. The sulfoxide reduction voltammograms in the differential pulse mode by varying such parameters as pulse amplitude, pulse time, and scan rate (while the other two parameters were kept constant) were recorded. Figure 5 shows the results.

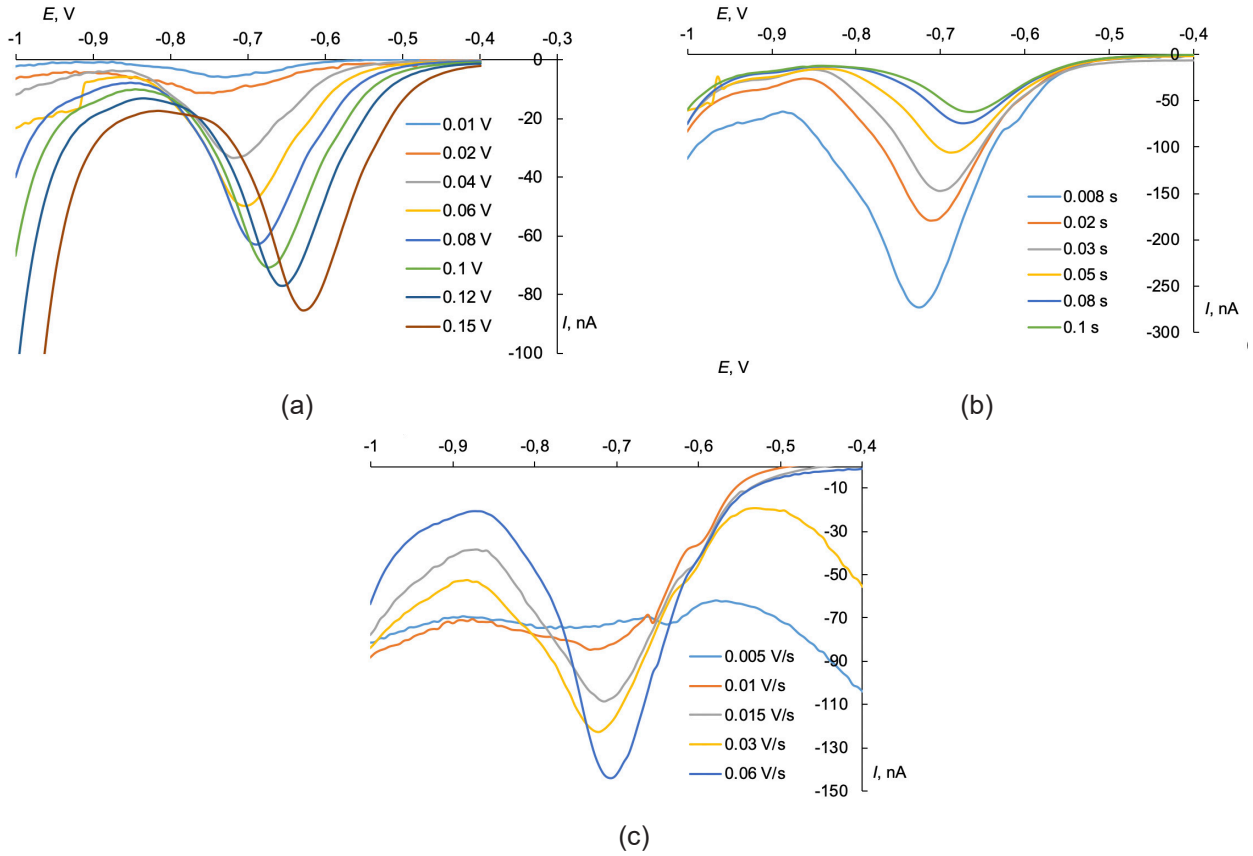


Figure 5. Differential pulse voltammograms of PTP oxidation product reduction at different pulse amplitudes (a), pulse time (b) and scan rate (c).

Optimal differential pulse voltammetry parameters were selected by maximizing the signal-to-background current ratio, as summarized in Table I. Under these optimized conditions, a pulse amplitude of 0.15 V, a pulse duration of 0.008 seconds, and a scan rate of 0.06 V s^{-1} were identified as providing the most favorable analytical performance.

Table I. Optimized instrumental parameters for the differential pulse voltammetric determination of PTP sulfoxide

Parameter	Optimized value
Initial purge time (s)	120
Equilibration time (s)	10.000
Start potential (V)	–0.400
End potential (V)	–1.000
Voltage step (V)	0.006
Voltage step time (s)	0.100
Sweep rate (V s^{-1})	0.060
Pulse amplitude (V)	0.150
Pulse time (s)	0.008

Determination of the optimum oxone content

To determine the optimal amount of oxidizing agent required for complete conversion of PTP to its sulfoxide derivative, a series of experiments were conducted by adding different volumes of oxone stock solution to the electrochemical cell. Each cell contained 10 mL of 0.02 mol L^{-1} hydrochloric acid, a fixed aliquot of PTP standard solution (9.5 mg L^{-1}), and incremental volumes of oxone stock solution ranging from 40 to 515 µL. Differential pulse voltammograms were recorded under previously optimized instrumental conditions. The resulting voltammetric responses, reflecting the oxidation efficiency, are shown in Figure 6.

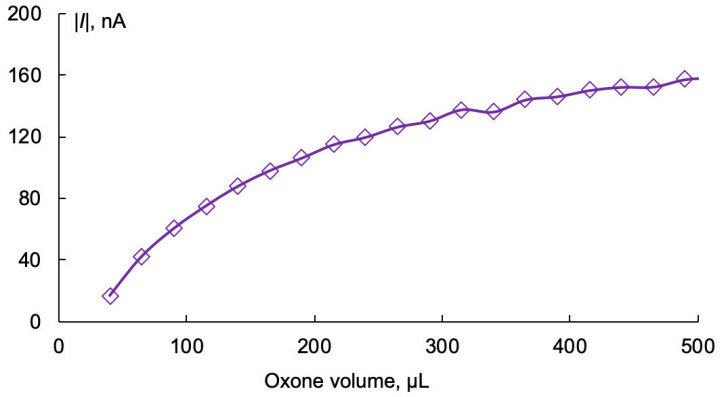


Figure 6. Effect of oxone solution volume on the reduction peak current of PTP sulfoxide recorded by differential pulse voltammetry.

The reduction peak current corresponding to the sulfoxide form of PTP increased proportionally with increasing amounts of oxone solution, indicating the need to use an excess oxidant to ensure complete conversion during quantitative analysis. Calibration curve data revealed a linear correlation between peak current (I_p) and PTP concentration over the range of 0.3–3.3 µg L^{-1}, described by the equation: $I_p = (26.3 \pm 1.9)\ c + (8.2 \pm 3.7)$, with a correlation coefficient of $R = 0.9975$. From the linear segment of the calibration curve, the limit of detection (LOD) and the limit of quantification (LOQ) were calculated by applying the formulas $LOD = 3(S_a)/b$ and $LOQ = 10(S_a)/b$, where S_a is the standard deviation of the intercept and b is the slope of the calibration curve. LOD and LOQ were determined as 0.17 µg mL^{-1} and 0.57 µg mL^{-1}, respectively (Figure 7). A summary of these results is provided in Table II.

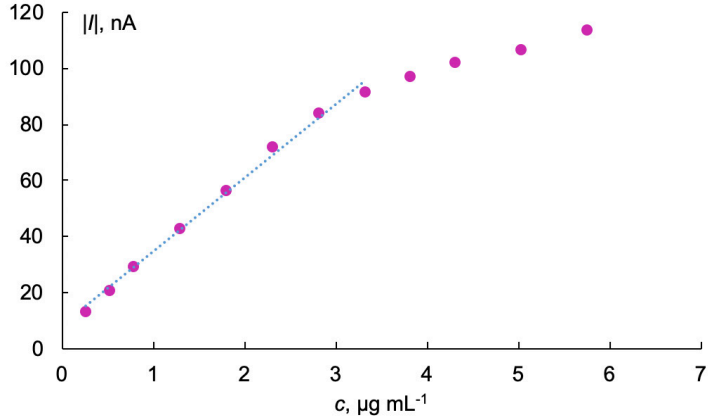


Figure 7. Relationship between the reduction peak current of PTP sulfoxide and its concentration.

Table II. Key analytical parameters derived from the calibration curve

Characteristics	Parameters
y = bx + a	y = 26.3x + 8.2
Correlation coefficient (r)	0.9974
Linear regression equation	I_p = 26.3*c* (μg mL^{-1}) + 8.2
Slope (b±Δb)	26.3266±1.9050
Intercept (a±Δa)	8.18±3.70
S.D. of slope (S_b)	0.7785
S.D. of intercept (S_a)	1.5110
LOD ($3S_a$/b), μg mL^{-1}	0.17
LOQ ($10S_a$/b), μg mL^{-1}	0.57

For determination of repeatability, PTP standard of 1.294, 1.805 and 2.815 μg mL^{-1} concentration were used. Recovery was determined from analysis of PTP standard solutions and was calculated as ratio of measured and real concentration multiplied by 100 to achieve value in % and applying the criterion $|(\bar{x} - \mu)\times 100\%/\mu| < t\alpha\times RSD/\sqrt{n}$ with n = 7 and a confidence level of 95% (P = 0.95). Results are presented in Table III.

Table III. Results of the analysis of standard solutions of prothipendyl hydrochloride obtained using the developed method (n = 7, 95% confidence level)

Amount taken (μ), mg L^{-1}	Amount found, ± Δ	Recovery ± RSD%	δ*
1.294	1.28±0.017	99.15±1.47	– 0.85%
1.805	1.80±0.022	100.04±1.31	+0.04%
2.815	2.81±0.035	99.82±1.33	– 0.32%

*δ = (–μ)×100%/μ.

Interference study

To evaluate the selectivity of the developed analytical method, the potential interference effects of substances commonly found in PTP hydrochloride formulations were systematically examined. These included both excipients and possible oxidation byproducts present in the dosage form. Under controlled analytical conditions, the reduction current of PTP sulfoxide was measured in the presence of each additive to assess any impact on the electrochemical signal. The results demonstrated that none of the tested excipients, including lactose monohydrate, microcrystalline cellulose, magnesium stearate, corn starch, talc, colloidal silica gel, sucrose, quinoline yellow, indigo carmine, aluminum salts of quinoline yellow (3:7 ratio), macrogol 35,000, sodium carmellose, $CaCO_3$, TiO_2, povidone K25, and polysorbate 20, induced significant changes in the reduction current (Table IV). Additionally, the interference from the impurity PTP sulfoxide was controlled through blank measurements, confirming the method's robustness and specificity for quantifying PTP hydrochloride in pharmaceutical preparations.

To validate the analytical method further, various interfering compounds that may arise during production were introduced to a fixed amount of PTP hydrochloride (40 mg). The standard procedure for the DPV determination of PTP was then applied. The value is 40 mg of PTP hydrochloride to 1 mg of the drug excipient, which does not cause a reduction in current changes by more than 0.15 nA.

Table IV. The quantitative assessment of tolerable amounts of the possible interference

Possible interfering Inactive Excipients of the drug	Amount without interfering[a] (mg)
Excipients	
Cellulose microcrystalline	60
Lactose monohydrate	114
Corn starch	12
Calcium stearate	3
Magnesium stearate	3
Talk	9
Shell Excipients	
Sucrose	55
Calcium carbonate	10.8
Povidone K25	0.6
Colloidal silicon dioxide	1.8
Yellow Quinoline	0.006
Indigo Carmine	0.006
Macrogol 35000	0.85
Titanium dioxide	0.8
Carmellose sodium	0.8
Polysorbate 20	0.6
Mountain glycol wax	0.024

[a]The value is mg of the drug excipient with respect to 40 mg prothipendyl hydrochloride, which does not cause peak current of PTP sulfoxide changes by more than 0.15 nA.

An excellent reproducibility accompanies the high sensitivity of this method. Reproducibility was evaluated by 7 repeated electrochemical signal measurements of the test solutions. The precision of the technique, as measured by the relative standard deviation (RSD), was 1.70% (δ = +0.73%). The analytical results obtained for the coated tablets using the proposed method are summarized in Table V.

The method's trueness was assessed by comparing the mean measured value ($\bar{x}$) against the accepted reference value (μ), applying the criterion $|(\bar{x} - \mu) \times 100\%/\mu| < t_{\alpha} \times RSD/\sqrt{n}$ with $n = 7$ and a confidence level of 95% ($P = 0.95$).

Table V. Summary of analytical results for coated tablets Dominal® 40 mg (TEVA GmbH) obtained using the developed method (n = 7, 95% confidence level)

Taken	Found, mg/tablet	Statistical characteristics
1.5025 g of Dominal tablet powder, 40 mg, dilution 500	41.1 40.9 39.9 40.5 39.3 39.5 40.0	±Δ =40.17±0.63 percentage recovery (%R) = 100.425 RSD=1.70% δ* =0.73%

*The calculation is based on the mean content obtained through the reference method.[9]
$\delta = (-\mu)\times 100\%/\mu$. $|\delta| < t\alpha\times RSD/\sqrt{n}$

CONCLUSIONS

The therapeutic importance of prothipendyl hydrochloride underscores the need for accurate, reliable, and environmentally sustainable analytical methods for its quantitative determination in pharmaceutical dosage forms. In this study, an alternative electroanalytical approach was successfully developed for the determination of prothipendyl hydrochloride based on the indirect polarographic analysis of its sulfoxide derivative, formed by oxidation with oxone. The use of oxone as a mild, environmentally benign oxidizing agent aligns well with the principles of green analytical chemistry, given its high oxidative efficiency, water solubility, and decomposition into non-toxic byproducts.

Differential pulse polarography proved to be a sensitive and selective technique, providing well-defined and reproducible signals for the oxidized prothipendyl derivative while requiring minimal sample volumes, low reagent consumption, and no costly and potentially hazardous organic solvents commonly associated with HPLC techniques. The conditions for differential pulse voltammetric determination of PTP sulfoxide were established experimentally. The optimized procedure exhibited good linearity over the concentration range of 0.3–3.3 μg mL^{-1}, with limits of detection and quantification of 0.17 μg mL^{-1} and 0.57 μg mL^{-1}, respectively. Method precision and accuracy were validated through seven replicate analyses of Dominal® 40 mg tablets, yielding a relative standard deviation (%RSD) of 1.70% and an analytical recovery (%Re) of 100.425%. The method's trueness was assessed by comparing the mean measured value ($\bar{x}$) against the accepted reference value (μ), applying the criterion $|(\bar{x} - \mu)\times 100\%/\mu| < t_{\alpha}\times RSD/\sqrt{n}$ with n = 7 and a confidence level of 95% (P = 0.95). The proposed method offers a solution for routine pharmaceutical quality control, batch release testing, and stability studies in industrial quality assurance laboratories, as well as in academic and regulatory analytical settings.

Accurate determination of PTP is essential not only for quality control during drug manufacture but also for therapeutic drug monitoring, pharmacokinetic studies, and bioavailability assessments. Future studies may extend the proposed method to other prothipendyl derivatives and related phenothiazine compounds in pharmaceutical and biological matrices. Further improvements in electrode design and integration with portable electrochemical devices could also enable its use for on-site analysis and rapid screening applications.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Use of Artificial Intelligence (AI) Tools

The authors declare that they used Grammarly for language editing. The authors take full responsibility for the accuracy, integrity, and originality of the article's content and confirm that no AI tool was used to generate novel scientific ideas, analyze data independently, or replace the critical role of the authors.

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