Spectrophotometric Assay of Prothipendyl through the Determination of Its Sulfoxide

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A new difference spectrophotometric method for the analysis of prothipendyl hydrochloride in commercial pharmaceutical preparations has been proposed. The method includes oxidation of an aliquot of the drug solution with potassium caroate to form the corresponding sulfoxide (ε_{278} = (13.69 ±0.01)×10^3 L mol/cm) and subsequent measurement of the optical density of the solution at 278 nm compared to that of the unoxidized drug solution of equal concentration. The graph of Beer's law for prothipendyl hydrochloride shows that the ΔA values measured at the corresponding wavelength are proportional to the concentration of the drug in the concentration range of 3.2-60 μg/mL. The characteristics of the curve calibration curve of the linear regression equation were as follows: ΔA = (0.0342±0.0006)*C* + (0.0501±0.025) (where *C* in μg/mL). The resulting difference in absorbance is independent of the presence of excipients and degradation products in the formulation. A new spectrophotometric technique has been developed and the possibility of quantitative determination of prothipendyl hydrochloride monohydrate in Dominal® tablets of 40 mg has been demonstrated. RSD =1.4% (δ= – 0.42%).

Introduction

Dominal, Timovan, and Tolnate are trademarks of prothipendyl (PTP, N,N-dimethyl-3-pyrido[3,2-b][1,4]benzothiazin-10-yl-propan-1-amine), which is classified as an azaphenothiazine or frenotropin compound. As a member of the azaphenothiazine category, PTP functions as an anxiolytic, antiemetic, and antihistamine. This compound is widely used in Europe to alleviate anxiety and agitation caused by psychotic syndromes (1–4). It differs from promazine only by substituting a single carbon

atom for a nitrogen atom in the tricyclic circular system. (**Figure 1**).

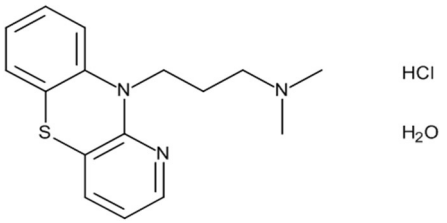

Figure 1. Structure of prothipendyl hydrochloride-1-water salt

In pharmaceuticals, the prothipendyl hydrochloride-1-water (INN) salt is used (**Figure 1**). It is a pastel yellow to greenish yellow odourless crystalline powder with the formula $C_{16}H_{19}N_3S \cdot HCl \cdot H_2O$ and a melting point of 108 to 112 °C (as anhydrous 177 to 178 °C) (5).

Due to their valuable therapeutic and pharmacological properties, phenothiazine and azaphenothiazine derivatives are the subject of many scientific studies. A review of the literature shows that methods for the determination of phenothiazine and azaphenothiazine derivatives mainly include chromatographic (6–9) and spectrophotometric (10–12).

The vital importance of this drug has prompted the development of many analytical methods for its determination. In addition to official methods based on non-aqueous titration (acidimetry) and direct UV spectrophotometry, various spectrophotometric methods based on oxidation reactions with the formation of intensely coloured radical cations have also been used (11,13). However, it is known that the colour stability of the radical cation (3a-3b) (**Figure 2**) depends mainly on the oxidizing agent used and the acidity of the medium. In the case of a strong oxidizing agent, the colour of the radical quickly disappears due to the second step of the reaction leading to the formation of a colourless sulfoxide (2) (**Figure 2**). This effect can lead to decreased assay sensitivity and reproducibility. Also, some of these methods have some disadvantages such as a high concentration of acid solution (analysis environment) and others do not have high enough sensitivity and require a very long heating time (11,13).

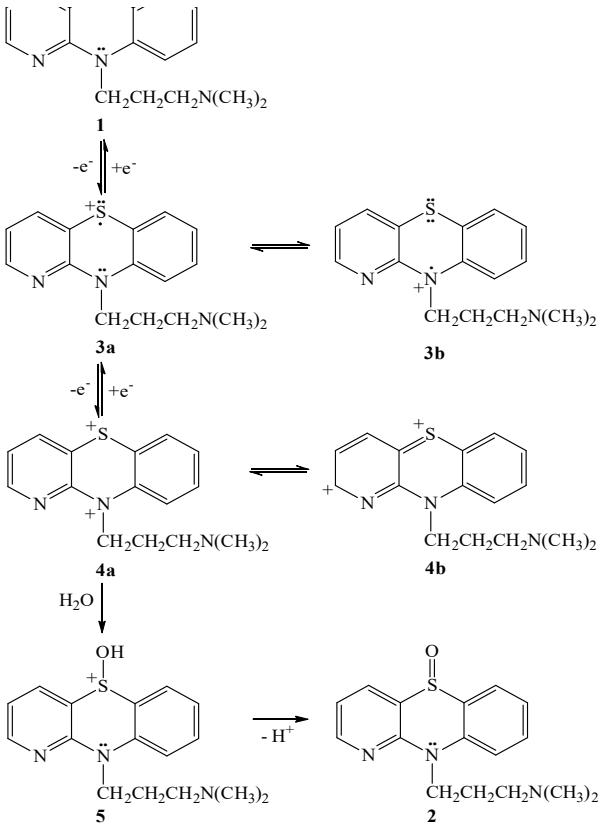

Figure 2. Scheme of prothipendyl oxidation

Phenothiazine drugs are currently manufactured in various dosage forms, either as a single drug or in combination with one or more

other drugs. Simple spectrophotometric methods, such as those used by the British Pharmacopoeia, typically involve extracting or diluting the drug, followed by measurement of ultraviolet absorbance. These procedures lack specificity and may be affected by other ultraviolet-absorbing drugs, dyes and flavours, or oxidation products of phenothiazine drugs, which are the corresponding phenothiazine sulfoxide and sulfone (8,14).

An indirect difference spectrophotometric method for the analysis of phenothiazine preparations in various commercial preparations is described. The assay can be performed as rapidly as the direct spectrophotometric method and is specific for an intact phenothiazine preparation. The method includes the oxidation of an aliquot of the drug solution with peroxyacetic acid (preliminarily obtained as a result of the reaction of hydrogen peroxide and acetic acid) with the formation of phenothiazine sulfoxide and the measurement of the optical density of the solution in the range of 340-360 nm using an unoxidized drug solution equal to the concentration in the reference cuvette. The resulting absorbance difference is proportional to the intact phenothiazine drug and is independent of the presence of excipients, degradation products, or other drugs in the formulation. Provided that these substances have not changed under the action of the oxidizing agent, their concentration in the test and reference solutions is the same, and their absorbance difference is zero (15).

However, peroxyacetic acid is an unstable compound, and its solution is an equilibrium mixture of hydrogen peroxide, acetic acid and, in fact, peroxyacetic acid in water. In addition, the peroxyacetic acid solution has a strong irritating malodour. Selective chromatographic methods (6,7) are sensitive enough to detect normally low therapeutic levels of prothipendyl in biological fluids. These methods are useful when the sample matrix is quite complex and the drug concentration is low. In pharmaceutical analysis, where analyte concentration levels are quite high, the main goal is to develop fast, simple, reproducible and inexpensive methods that can easily find application in routine analyses and quality control laboratories.

Spectrophotometry, due to its simplicity, is very useful for the quantitative analysis of drugs in pharmaceuticals. The number of spectrophotometric methods for determining the cited drug is very limited.

The application of difference spectrophotometry is very advantageous both in qualitative and quantitative analysis. However, the real great importance of difference spectrophotometry is in quantitative analysis as a consequence of its potential to increase the selectivity of the measurement (16).

The aim of this research is to develop a new and simple method for prothipendyl hydrochloride determination. It seems promising to carry out the analysis of prothipendyl hydrochloride in the form of the corresponding

stable S-oxide, which is easily obtained in a slightly acidic medium using aliphatic diperoxyacids or inorganic Caro peroxoacid (10,15,17,18).

Experimental part

Solutions of prothipendyl hydrochloride (LGC, Luckenwalde, Germany) and prothipendyl sulfoxide (Toronto Research Chemicals Inc.) were prepared by dissolving appropriate weighed amounts of the substances in water and a water-ethanol solution 1:1 (v/v) respectively. All other used chemicals were analytical grade. All excipients were of pharmacopoeial purity.

Dominal® 40 mg (TEVA GmbH) coated tablets, 600093498; E 307829.01-Z03; Identifier (PZL) - 14179534; (Ch. B.) 0602521. *Active ingredient*: prothipendyl hydrochloride $1H_2O$ (each film-coated tablet contains 40 mg of the active substance). *Excipients*: cellulose microcrystalline, lactose monohydrate 39.40 mg; corn starch; magnesium stearate; silica colloidal; talc; sucrose 55.43 mg; quinoline yellow aluminum salt/indigo carmine aluminum salt (7:3); titanium dioxide; macrogol 35000; calcium carbonate; carmellose sodium; povidone K25; polysorbate 20; mountain glycol wax. The average tablet weight is 0.29979 g.

Potassium caroate ($KHSO_5$), also known as potassium peroxymonosulfate, potassium monopersulfate, is a white powder and chlorine-free oxidizer. It is a strong oxidizing agent with an oxidizing potential similar to that of chlorine. The triple salt $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$ (known under the trade name Oxone, Acros Organics) is a higher stability form. The active ingredient in Oxone® is $KHSO_5$. Oxone has a longer shelf life than potassium peroxomonosulfate (19). A white, water-soluble solid, Oxon loses <1% of its oxidizing power within a month. The standard electrode potential for potassium peroxomonosulfate is +1.81 V with a half-reaction to form hydrosulfate (pH = 0) (20).

Preparation of $KHSO_5$ solution, 0.02 mol/L. About 0.7 g of Oxone was dissolved in 70 mL of double-distilled water in a 100 mL volumetric flask, made up to the mark with water and mixed thoroughly.

Preparation of $KHSO_5$ solution, 0.005 mol/L. A portion of about 0.175 g of Oxone was dissolved in 100 mL of double-distilled water.

The exact $KHSO_5$ content was determined by iodometric titration (18).

Preparation of 0.01 M sulfuric acid solution. The solution was prepared from the standard titre fixanal in a 1000 mL volumetric flask.

A double-beam Shimadzu UV-Visible spectrophotometer, with 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 were used to measure the absorbance of the resulting solutions.

The product formed by the reaction of prothipendyl hydrochloride with an oxidizing agent under analytical conditions was confirmed

to be prothipendyl sulfoxide (PTPO) by comparing its ultraviolet absorbance spectrum with that of an authentic sample of PTPO. Maximum and minimum absorbance bands of the product were at λ_{max} = 207, 239, 276, 340 nm and λ_{min} = 219, 258, 309 nm respectively (21).

Thin-layer chromatographic properties of tested compounds were investigated on TLC aluminium plates (10×15 cm) coated with 8-12 μm silica gel, 254 nm PTSH-AF-V-UF (Sorbfil). The extract of the oxidation product was evaporated at room temperature collected and identified with TLC using chloroform–methanol–ammonia (60:10:0.5) as a developing system followed by treatment of the adsorption zones with Wagner's reagent. The oxidation product was well resolved from the pure drug with significantly different R_f values (PTP, R_f= 0.74±0,02; PTPO, R_f = 0.58±0,01).

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

Preparation of a solution of working reference standard sample (WSS) of prothipendyl hydrochloride monohydrate, 0.40 mg/mL (335.9 μg/mL in terms of prothipendyl base). About 40 mg (accurately weighed) of a standard sample of prothipendyl hydrochloride monohydrate is placed in a 100 mL volumetric flask, dissolved in 70 mL of a 0.01 mol/L sulfate acid solution, and the volume of the solution is adjusted with the same solvent to obtain a solution containing about 0.03359% w/v (or 335.9 μg/mL) prothipendyl base.

Method for constructing a calibration graph. With the help of a microburette, sequentially measured 0.50; 1.00; 1.50; 2.00; 2.50; 3.00; 3.50 mL of a solution of WSS. prothipendyl hydrochloride monohydrate in volumetric flasks of 25 mL, add to each successively 0.50; 1.00; 1.50; 2.00; 2.50; 3.00; 3.50 mL of a 0.002 mol/L $KHSO_5$ solution, shake well and dilute the volume of the solution with 0.01 mol/L sulfuric acid, stopper the flask and mix thoroughly. The solutions are photometered at an analytical wavelength of 278 nm in a 1 cm quartz cuvette against a potassium caroate and 0.01 mol/L sulfuric acid solution as a compensation solution.

Method for the quantitative determination of prothipendyl hydrochloride content in coated tablets, 40 mg (TEVA GmbH)
Add 50-70 mL of 0.01 mol/L sulfuric acid solution to a weighed portion of powdered tablets equal to the average weight of the tablet, mix with ultrasound for 10 min, dilute with 0.01 mol/L sulfuric acid solution to 100 mL and filter through a paper filter with blue ribbon to obtain a clear solution containing about 0.03359% w/v (or 335.9 μg/mL) prothipendyl base (solution A).

Dilute 10.00 mL of solution A to 100 mL with 0.01 mol/L sulfuric acid solution (solution B). The solution is photometered at an analytical wavelength of 278 nm in a 1 cm quartz cuvette

against a 0.01 mol/L sulfuric acid solution as a compensation solution.

To another 10 mL of solution A add 10.00 mL of 0.002 mol/L $KHSO_5$ solution, mix and dilute with 0.01 mol/L sulfuric acid solution to 100 mL and leave for 5 min (solution C). The solution is photometered at an analytical wavelength of 278 nm in a 1 cm quartz cuvette against a $KHSO_5$ solution and sulfuric acid of the same concentration as in solution C as the compensation solution.

A procedure was repeated using a solution of RS prothipendyl hydrochloride monohydrate in 0.01 mol/L sulfuric acid (look preparation of a solution of working standard sample of prothipendyl hydrochloride monohydrate, 0.40 mg/mL (335.9 μg/mL in terms of prothipendyl base)) instead of solution A, starting with "Dilute 10.00 mL of solution A to 100 mL..." and calculate the $C_{16}H_{19}N_3S{\cdot}HCl{\cdot}H_2O$ content using the reported $C_{16}H_{19}N_3S{\cdot}HCl{\cdot}H_2O$ content in RS prothipendyl hydrochloride monohydrate.

The prothipendyl hydrochloride monohydrate $C_{16}H_{19}N_3S{\cdot}HCl{\cdot}H_2O$ content in the preparation as a percentage of the declared amount (X) is calculated by the formula:

$$X = (\Delta A_1 \times a_0 \times P \times G)/(\Delta A_0 \times a_1 \times L),$$

where ΔA_1 is the difference between optical densities of the test solution and prothipendyl hydrochloride monohydrate solution (solution C versus solution B);

ΔA_0 is the difference between the optical densities of the RS prothipendyl hydrochloride monohydrate test solution (solution C) and the RS prothipendyl hydrochloride monohydrate (solution B) (RS solution C versus RS solution B);

a_1 is weighed powder of crushed tablets, mg;

a_0 is the weight of a standard sample of RS prothipendyl hydrochloride monohydrate, mg;

P is the content of the main substance in the standard sample prothipendyl hydrochloride monohydrate, %;

G is the average weight of one tablet, mg;

L is the declared amount of prothipendyl hydrochloride monohydrate in one tablet, mg.

Results and discussion

It was found that the drug can be determined by an indirect difference spectrophotometric method based on the absorbance of the sulfoxide derivative of the drug in relation to the absorbance of the non-oxidized drug solution. The sulfoxide derivative is formed quickly and quantitatively at room temperature by adding a solution of $KHSO_5$ in the form of Oxone.

The UV absorbance spectra of the PTP, PTPO and $KHSO_5$ are shown in **Figure 3**. As seen, the PTPO showed an absorbance at 278 nm, while the absorbance of PTP at that wavelength was lower. The 278 nm wavelength was chosen to

follow and determine the reaction kinetics, taking into account the absorbance of PTP at that wavelength. $KHSO_5$ showed almost no absorbance in the UV region and thus didn't interfere with any UV measurements. An increase in the wavelength of maximum absorbance was realised with enhanced specificity.

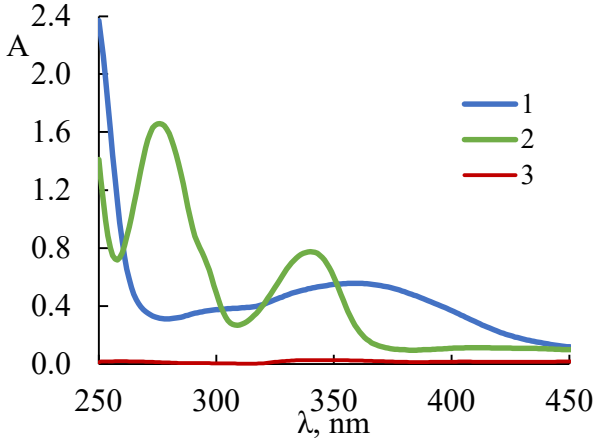

Figure 3. UV-spectrum of PTP (line 1), PTPO (line 2) and $KHSO_5$ (line 3). c(PTP·HCl) = 1.18×10^{-4} mol/L, $c(KHSO_5) = 5.04\times10^{-4}$ mol/L, $c(H_2SO_4)$ = 0.01 mol/L

The extinction coefficient found as the slope of the absorbance versus concentration plot or the molar absorbance ε (L mol/cm) at λ_{max} = 278 nm for PTPO in 0.01 mol/L H_2SO_4 solution (slope of absorbance on PTPO concentration is (13.692±0.010) $\times10^3$ (**Figures 4-5**).

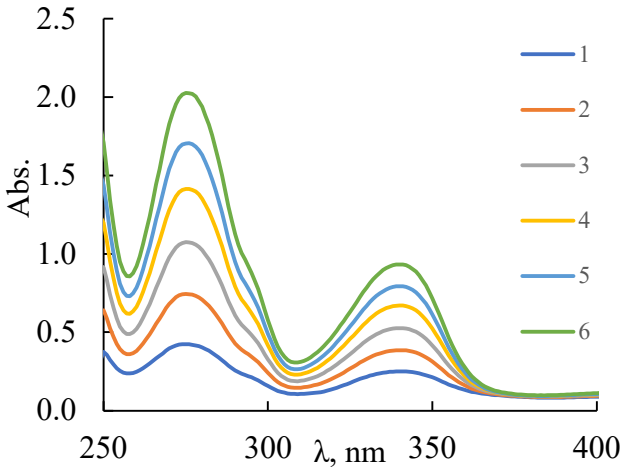

Figure 4. The concentration-dependent UV-spectra of the S-oxidation product of Prothipendyl. $c(KHSO_5)$ = $5{,}04\times10^{-4}$ mol/L, $c(H_2SO_4)$ = 0,01 mol/L; c(Prothipendyl·HCl), mmol/L: *1* – 0.024; *2* – 0.047; *3* – 0.071; *4* – 0.094; *5* – 0.118; *6* – 0.142.

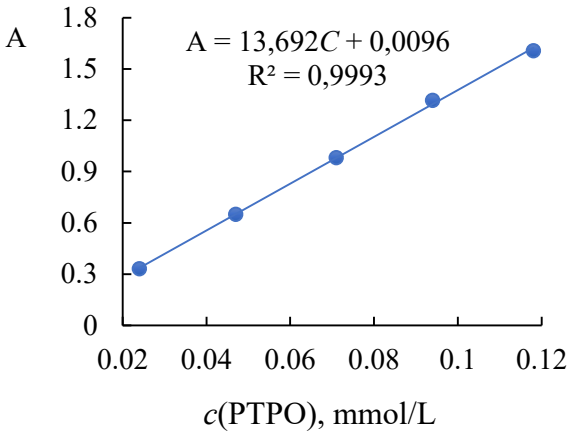

Figure 5. Extinction coefficient for PTPO at 278 nm. $c(H_2SO_4)$ = 0.01 mol/L

The graph of Beer's law for prothipendyl hydrochloride shows that the ΔA values measured at the corresponding wavelength of maximum absorbance difference are proportional to the concentration of the drug in oxidized and non-oxidized solutions in the concentration range of 0-0.006 % (m/v) (**Figure 6**).

The characteristics of the curve calibration curve of the linear regression equation were as follows: ΔA = (0.0342±0,0006) *C* + (0.0501±0,025) (where *C* in μg/mL) (**Table 1**).

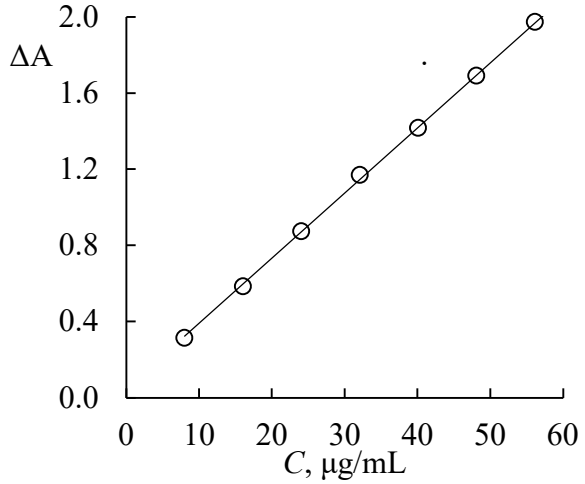

Figure 6. Difference in the absorbance of prothipendyl/potassium caroate mixture versus absorbance by prothipendyl solution (ΔA) at different concentrations of prothipendyl. $c(KHSO_5) = 5.04\times10^{-4}$ mol/L;
$c(H_2SO_4) = 0.01$ mol/L

Table 1. Characteristics of linear regression equation curve calibration graph

Characteristics	Parameters
Y=bx+a	y = 0.0342x + 0.0501
Correlation coefficient (r)	0.999
Linear regression equation	ΔA = 0.0342 *C* (μg/mL) +0.0501
Slope (b±Δb)	(0.0342±0,0006) (mL/μg)
Intercept (a±Δa)	0.0501±0.025
LOD	1.06 μg/mL
LOQ	3.21 μg/mL

Various quantities of interfering compounds that were possible during production were added to a fixed amount of prothipendyl hydrochloride (40 mg) studied, and the recommended procedure for the spectrophotometric determination was followed (**Table 2**).

Table 2. The quantitative assessment of tolerable amounts of 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 to 40 mg of prothipendyl hydrochloride, which does not cause absorbance changes by more than +0.005.

Specificity

Several substances that may be present in dosage forms of PTP, either in the form of degradation products or in the composition of drugs as auxiliary, were studied under analysis conditions for an optical density difference of about 340-342 nm. The following substances give a zero difference in absorbance and therefore do not

interfere with the analysis: PTPO and excipients in generally accepted prescribed amounts: microcrystalline cellulose, lactose monohydrate, corn starch, magnesium stearate, colloidal silica gel, talc, sucrose, quinoline yellow, quinoline aluminum salt yellow and aluminum salt of indigo carmine (7:3), titanium dioxide, macrogol 35000, calcium carbonate, carmellose sodium, povidone K25, polysorbate 20.

The difference in the absorbance of solutions is proportional to the concentration of the azaphenothiazine preparation in the preparation and is specific for the intact preparation in the presence of oxidative and photochemical decomposition products, dyes and other tablet excipients.

The UV spectrophotometric determination of sulfoxide proved to be a sufficiently reliable and sensitive method. The developed method of quantitative determination makes it possible to determine prothipendyl hydrochloride monohydrate in the concentration range of 3-60 μg/mL. The limit of detection, LOD (3S), is 1.1 μg/mL. A new spectrophotometric technique has been developed and the possibility of quantitative determination of prothipendyl hydrochloride monohydrate in Dominal® tablets of 40 mg has been demonstrated. RSD ≤ 1.4%; ($|\delta| <$ RSD). μ - quantification data, given in the Certificate of Quality (Tabl. 3). $\delta = (\bar{x}-\mu)\times 100\ \%/\mu$.

Table 3. The results of the analysis of tablets coated with Dominal® 40 mg (TEVA GmbH) according to the proposed method ($n = 5$; $P = 0.95$)

Detected substance / analyzed drug	Found ($\bar{x} \pm \Delta\bar{x}$), mg/tab	RSD, %	Certificate data (μ), mg/tab	$\frac{(\bar{x}-\mu)}{\mu}100$ (%)
Prothipendyl hydrochloride monohydrate / **Dominal® (TEVA GmbH)**, tabl. coated, 40 mg, 50 pcs. No.2; lot 0602521	39.88±0.71 (99.70±1.78 %)	1.44	40.05	δ = – 0.42

Conclusions

A technique has been developed and the possibility of quantitative determination of prothipendyl hydrochloride monohydrate in Dominal (TEVA GmbH) 40 mg tablets by indirect spectrophotometry using potassium caroate as an oxidizing agent has been developed (RSD =1.4%, δ= –0.42%).

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