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A different analytical method for determination of Paroxetine HCl by UV-VIS

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Abstract: For the determination of Paroxetine HCl (PRX) from tablet form a sensitive, easy and selective spectrophotometric method was developed. This method is based on the formation of a colored Cu-dithiocarbamate derivative complex on the basis of the secondary amine group in the structure of the drug substance. The colored complex gives maximum absorbance at 435 nm in methylisobuthylketone by UV-VIS spectrometer. In the method, the effect of solvent, NH_3 concentration, CS_2 concentration, Cu^{2+} concentration and reaction time were investigated. Then, the method was statistically validated. For the validation of the method, the working range that obeyed to the Lambert-Beer law was determined, firstly. The range was found to be 0.005-0.16 $mmolL^{-1}$. The equation of the calibration curve obtained with 0.9987 correlation coefficient in the specified working range is y = 6.9023x-0.0147. In the method, limit of detection and limit of quantitative were found to be 0.0013 $mmolL^{-1}$, and 0.0045 $mmolL^{-1}$, respectively. It has been seen that the proposed method is applicable to tablet formulation of PRX.

Keywords: Paroxetine HCl; Spectrophotometric determination; Copper; Dithiocarbamate.

1. Introduction

The chemical name of paroxetine hydrochloride is (-)-trans-4R -(4' - fluorophenyl)-3S-[(3', 4' methylenedioxyphenoxy)methyl] piperidine hydrochloride. It is a serotonin reuptake inhibitor widely used in the treatment of major depressive disorder, social anxiety disorder, obsessive-compulsive disorder, panic attack, general anxiety disorder, posttraumatic stress disorder (FDA; Arshiya et al., 2011). The chemical structure of PRX drug is shown in Fig. 1.

There are many studies in the literature on the analysis of paroxetine such as electroanalytic (Nouws et al. 2006; Brycht et al 2015;), seperation (Zheng et al., 2021; Caris et al., 2012; Oztunc et al., 2002) and spectral studies (Omar et al., 2017; Sharma, 2010; Walash et al., 2010).

Dithiocarbamates (DTC) are ligands with a wide range of applications due to their biological and chemical properties such as antifungal, antitumor, antibacterial, antituberculosis, antioxidant (Balakrishan et al, 2019; Li et al, 2007; Mamba et al, 2010; Adeyemi et al, 2018) . In the literature, stable DTC derivatives are generally obtained by the reaction of molecules containing secondary amine groups with carbon disulfide in basic medium. It is known that they form stable complexes especially with transition metals (Adeyemi et al, 2018; Berry et al, 2012; Macias et al 1995;

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Andrew and Ajibade, 2018). The colored complexes they form with different transition metals offer an important advantage in terms of spectrophotometric measurements (Topuz et al, 2018). Method of forming a DTC complex with transition metals is used for the spectrophotometric analysis of some drugs containing secondary amine groups (Alpdogan and Sungur, 1999; El-Ries et al 2000; Golcu et al., 2001; Kamal et al 2018).

The proposed spectrophotometric method for PRX is based on the determination of colored Cu-DTC derivative of drug in the UV-visible region. The method was performed two stages: In the first stage, the secondary amine group in the structure of PRX is transformed into dithiocarbamate derivative with CS_2 in a basic environment and it is complexed with Cu^{2+}. In the second stage, the yellow complex is taken from the water phase into an organic solvent (does not mix with water) and analyzed at 435 nm (Alpdogan and Sungur, 1999; Golcu et al., 2001; Golcu and Yavuz, 2008).

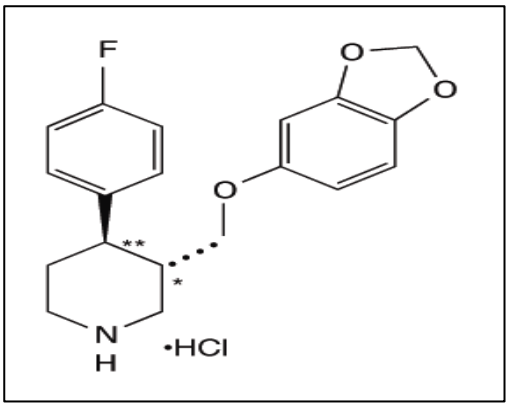

Figure 1. Chemical structure of Paroxetine HCl (FDA).

2. Materials and methods

Apparatus

All the absorption spectral measurements were made by using Perkinelmer Lambda 25 double beam UV–VIS spectrophotometers equipped with 1 cm matched quartz cells.

Materials and Reagents

All solvents (chloroform, MIBK, ethylacetate, dichloromethan) used in this work were of HPLC grade.

The PRX reference standard used in the study was supplied from Ali Raif Drug Company and Paxera branded tablet containing 20 mg PRX (Ali Raif Drug Company) was purchased from the local pharmacy.

Stock Solutions

A standard stock solution of the PRX containing 1.0 $mmol.L^{-1}$ was prepared by dissolving 0.0377 g in 100 mL distilled water. The solution was prepared every three days.

0.1% NH_3 solution: 421 µL of 25% NH_3 stock solution (d: 0.91 $g.mL^{-1}$) was transferred to 100 mL volumetric flask and completed to 100 mL with distilled water.

To prepare 2.0 $mmol.L^{-1}$ Cu^{2+} solution, 0.0341 g of $CuCl_2.2H_2O$ salt was dissolved in 100 ml of distilled water.

Construction of Calibration Curve

Aliquots in the range of 0.005-0.16 mmol L^{-1} PRX solutions were transferred into tubes. 0.4 mL of 0.1% NH_3 solution, 0.2 mL of 2.10^{-3} $mol.L^{-1}$ Cu^{2+} solution and 0.05 mL of 1% CS_2 (dissolved in MIBK) solution, were added into the tubes. Afterwards, the mixture was vortexed for about 1 min. 0.03 mL of 0.5% acetic acid solution was added into the tubes after CS_2 phase in the water phase turned to brown, immediately followed by 5 mL of MIBK and vortexed for about 2 more minutes. It was waited for 1 minute for phase separation. Then, 2 mL of MIBK phase was transferred into centrifuge tubes containing a small amount of anhydrous $MgSO_4$. The caps of the tubes were closed and mixed thoroughly. It was then centrifuged for 4 minutes at 14000 rpm and 4 ºC. Each solution was studied in 3 replicates. The absorbance of the solutions containing PRX in the range of 0.005-0.16 mmol L^{-1} was measured at 435 nm. As a consequence, absorbances measured against the concentration of PRX were plotted.

Assay Procedure for Tablets

The weights of 10 randomly taken tablets of the drug were weighed independently and then the average tablet weight was determined. Following that, the tablets were ground into powder by grinding in a dry and clean mortar. The powdered sample equivalent to the weight of one tablet of drug was transferred into a flask containing 30 mL of pure water. The mixture was mixed with a magnetic stirrer for 30 minutes and in an ultrasonic bath for 30 minutes to dissolve thoroughly. The solution was filtered off. The filtered solution was transferred to a volumetric flask and completed to 100 mL with distilled water. Aliquots in the working range taken from this solution were analyzed according to the proposed method.

3. Results and discussion

In the developed method for the determination of PRX, first the effect of the solvent on the absorbance was examined in accordance with the literature, and then the optimum amounts of NH_3, Cu^{2+}, CS_2 were determined, respectively. After determining the optimal conditions, the method was validated (Alpdogan and Sungur, 1999; El-Ries et al., 2000). These studies were carried out at a laboratory temperature of 21 ºC.

PRX has a secondary amine group in its chemical structure. In this study, colored PRX-DTC-Cu complex was sythesized by transforming the secondary amine group of the PRX into DTC derivative with CS_2 in the presence of NH_3. The resulting yellow complex was taken from the water phase into an organic solvent (does not mix with water) and was determined in UV-visible at 435 nm.

The Effect of Solvent Type

The solvent given the highest absorbance was determined as the optimum solvent. The optimum solvent was determined as the MIBK at which the maximum absorbance was taken. PRX-DTC-Cu complex gives maximum absorbance at 435 nm in MIBK solvent. El-Ries et al (2000) stated in their study that Cu^{2+}-dithiocarbamate complexes give characteristic maximum absorbance at 435 nm in MIBK. The results were given in Table 1.

Table 1. Effect of solvent type (N=3).

Solvent Type	A	±SD
Chloroform	0.030	0.0058
Ethyl Acetate	0.515	0.0587
MIBK	0.589	0.006
Dichloromethan	0.092	0.0010

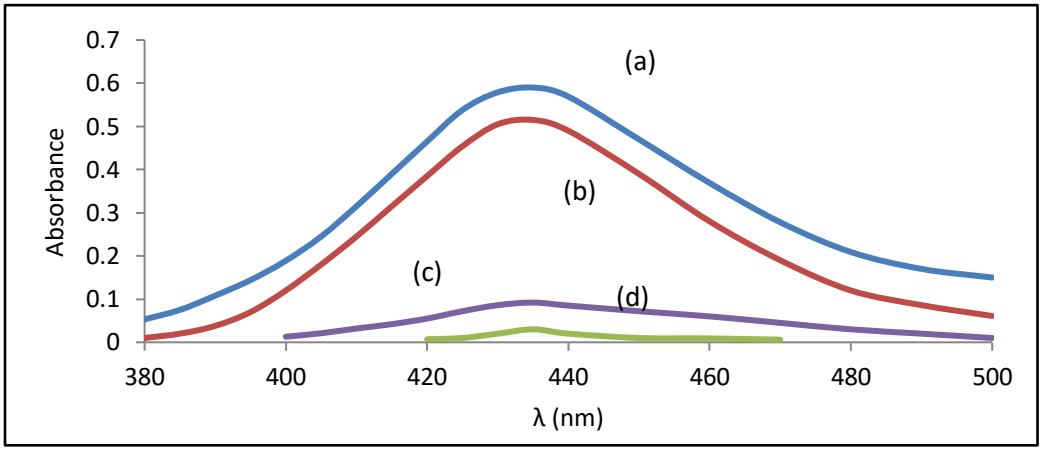

Figure 2. Absorbance of PRX-dithiocarbamate-Cu complex in different solvents; (a) MIBK, (b) Ethylacetate, (c) Dichloromethan, (d) Chloroform, (0.16 mmol L^{-1} of PRX, N=3).

Alpdogan and Sungur (1999) found that the optimum solvent was chloroform in their study of metoprolol-Cu-DTC derivative formation. MIBK is the second best solvent in its work. El-Ries et al. (2000) in their study with metoprolol tartrate and propranolol HCl, they used MIBK solvent as the optimum solvent for easy analysis of drug-Cu-DTC complexes by AAS. Golcu et al(2001) did not invastegated type of solvent for Ni(II), Cu(II), Co(II) dithiocarbamate complexes in their study with propranolol HCl, but developed the methods in ethanol.

The Effect of NH_3 Concentration

The influence of the concentration of NH_3 was invastegated by different volumes (0.1-0.8 mL) of 0.1% NH_3 solution. The absorbance increased rapidly up to 0.3 mL and remins almost constant after 0.4 mL. Therefore, 0.4 mL of 0.1 % NH_3 solution was chosen as optimum volume of NH_3 solution. The results were shown in Figure 3.

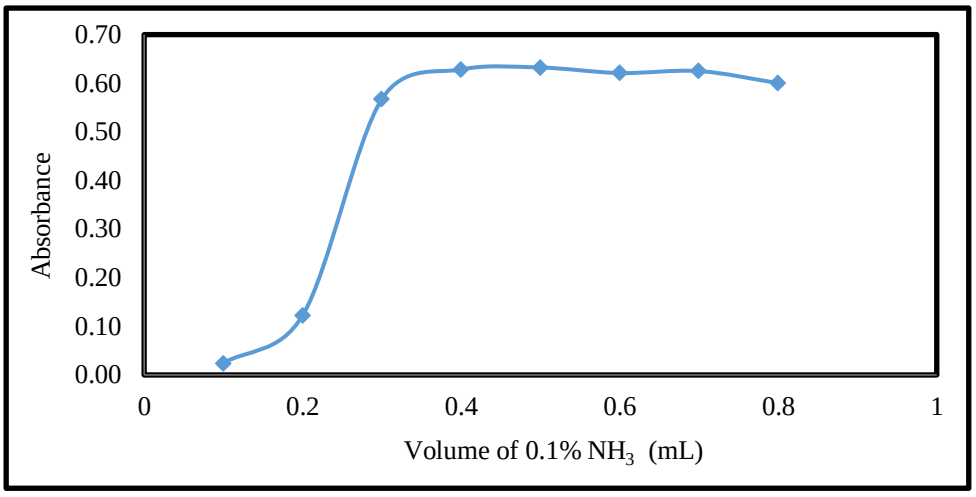

Figure 3. The effect of NH_3 concentration (0.16 mmol L^{-1} of PRX, N=3).

Alpdogan and Sungur (1999) found that the optimum NH_3 concentration was 0.6 mL of 25% NH_3 solution in their study of metoprolol-Cu-DTC derivative formation. El-Ries et al. (2000) found that drug-Cu-DTC complexes gave good results in 1 mL ammonia buffer solution of pH 10 in their study with metoprolol tartrate and propranolol HCl. Golcu et al (2001) found in their study with propranolol HCl that the optimum ammonia concentration for Ni(II), Cu(II), Co(II) DTC complexes was 0.5 mL of 25% NH_3 solution.

The Effect of Cu^{2+} Concentration

The influence of the concentration of Cu^{2+} was invastegated by different volumes (0.01-0.5 mL) of 2.10^{-3} $mol.L^{-1}$ Cu^{2+} solution. Increasing the volume of the reagent up to 0.2 mL, the absorbance increased rapidly and remins almost constant from 0.2 mL to 0.5 mL. Therefore, 0.2 mL of 2.10^{-3} mol L^{-1} Cu^{2+} solution was chosen as optimum volume of reagent (Figure 4).

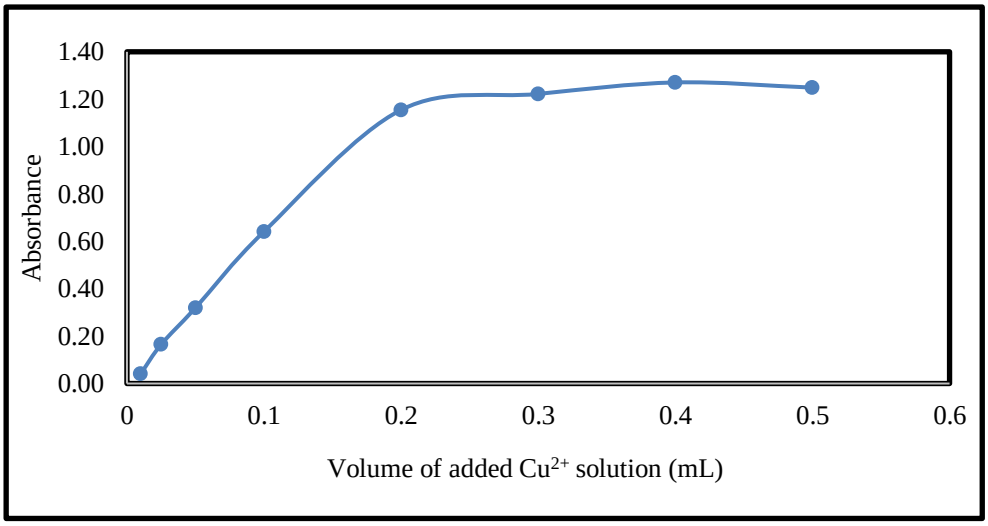

Figure 4. The effect of Cu^{2+} concentration (0.16 mmol L^{-1} of PRX, N=3).

Alpdogan and Sungur (1999) found that the maximum absorbance was reached at 1.6 .10^{-6} mol of Cu^{2+} ions in their study of metoprolol-Cu-DTC derivative formation. El-Ries et al. (2000) found that drug-Cu-DTC complexes gave maximum absorbance in 1 mL of 2.10^{-3} mol L^{-1} Cu^{2+} solution for determination of metoprolol tartrate and propranolol HCl in their study. Golcu et al (2001) found in their study for propranolol HCl that the optimum Ni(II), Cu(II), Co(II) concentrations for drug-metal-DTC complexes were 1 mL of 9.10^{-3} mol L^{-1} metal solutions (Ni(II), Cu(II), Co(II)).

The Effect of CS_2 Concentration

The influence of the concentration of CS_2 was invastegated by different volumes (0.01-0.5 mL) of 0.1% CS_2 solution (dissolved in MIBK). The absorbance increased up to 0.05 mL and slightly decrease after 0.05 mL. Therefore, 0.05 mL of 1.0% CS_2 solution was chosen as optimum volume of reagent. The results can be seen in Figure 5.

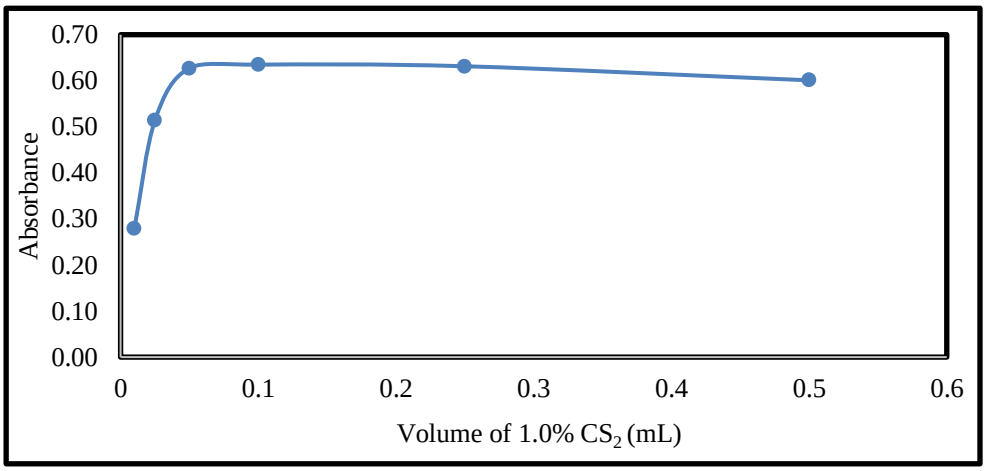

Figure 5. The effect of 1.0% CS_2 (dissolved in MIBK) (0.16 mmol L^{-1} of PRX, N=3).

Alpdogan and Sungur (1999) used 5 mL of chloroform containing 2% of CS_2 solution in their study of metoprolol-Cu-DTC derivative formation. El-Ries et al. (2000) used 1 mL of CS_2 as optimum volume in their study with metoprolol tartrate and propranolol HCl. Golcu et al (2001) found in their study with propranolol HCl that the maximum absorbance was obtained with ethanol containing 5% of CS_2 .

The Effect of Reaction Time

In the study of the effect of the time, it was observed that the absorbance decreased continuously. The effect of acetic acid was also investigated to increase the stability of the drug-DTC-Cu complex as in the study of El-Ries et al.(2000). According to this study, in order to increase the stability of Cu-PRX-DTC complex, aliquots in the range of 0.01-0.05 mL 0.5% acetic acid solution were added into 0.16 mmol L^{-1} PRX solutions. In this study, it was observed that 0.03 mL of 0.5% acetic acid solution stabilized it without changing absorbance of complex under optimum conditions.

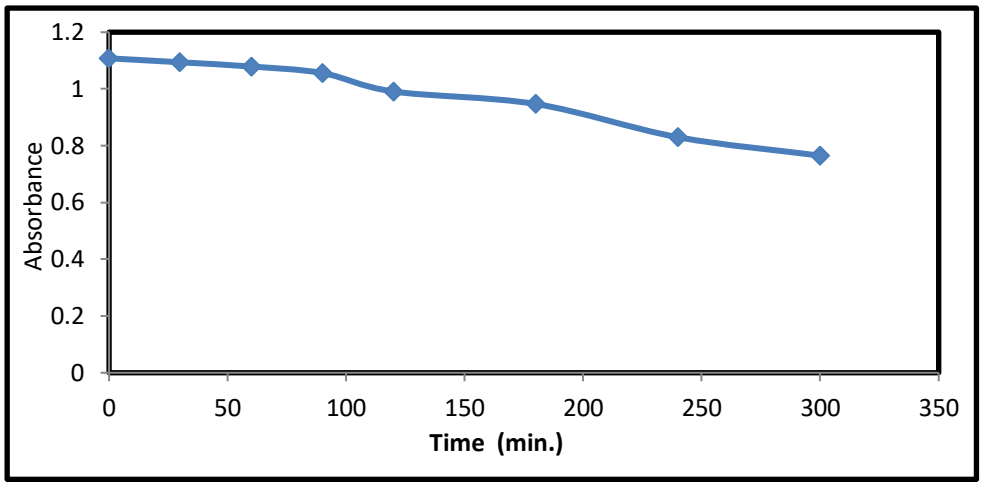

Figure 6. The effect of reaction time on absorbance of complex.

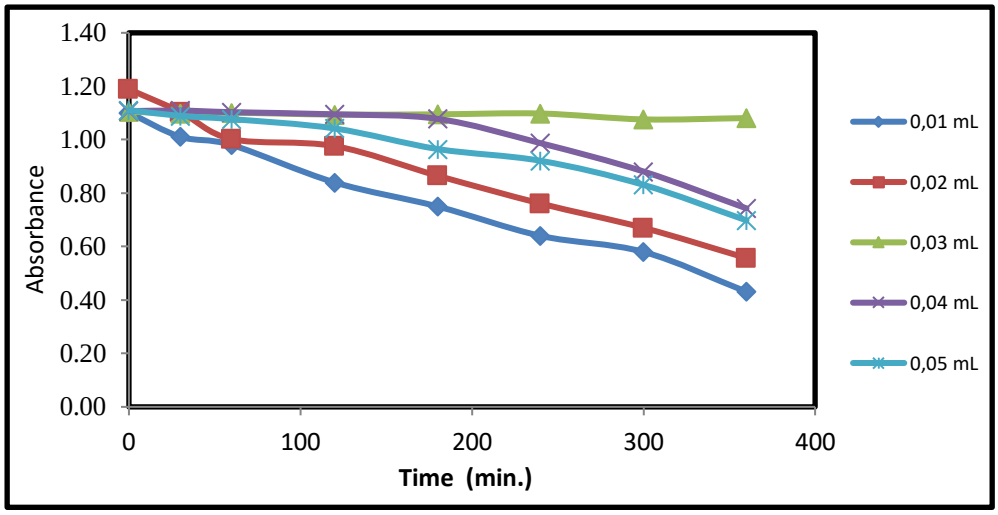

Figure 7. The effect of 0.5% acetic acid on the durability of the complex.

Validation of The Proposed Method

For the validation of the method, the working range that obeyed to the Lambert-Beer law was determined, firstly. This range was found to be 0.005-0.16 mmolL^{-1}. The equation of the calibration curve obtained with 0.9987 correlation coefficient in the specified working range is y = 6.9023x-0.0147 (Figure 8). The proximity of the correlation coefficient to 1 shows that the linearity, that is, the relationship between absorbance and concentration, is quite good (Gunduz 2010).

In this method, limit of detection and limit of quantitative were found to be (at 95% confidence level) 0.0013 mmol.L^{-1}, and 0.0045 mmol.L^{-1}, respectively. In addition, the all analytical parameters were given in Table 2.

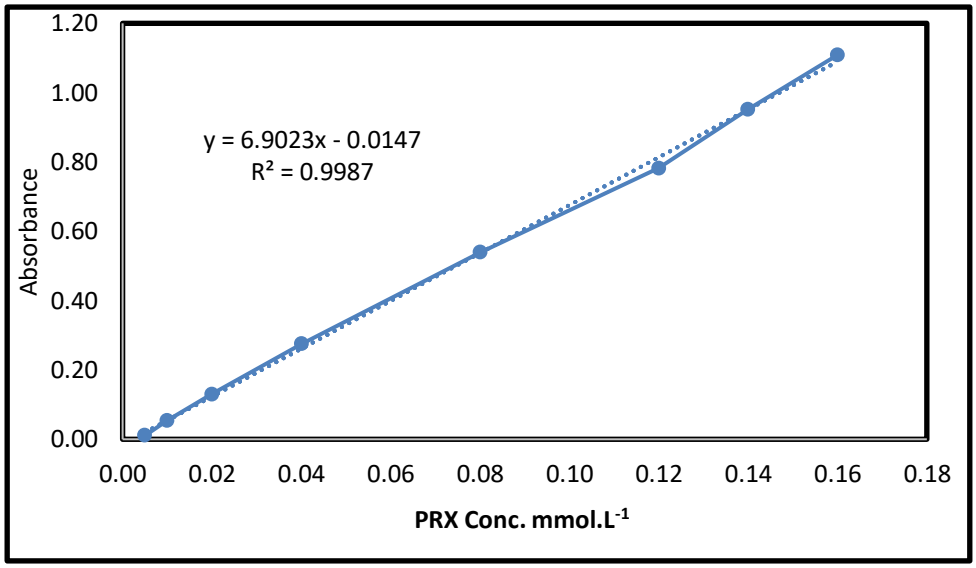

Figure 8. Calibration curve of PRX according to the proposed method.

Table 2. Calibration parameters in the method developed for PRX.

Parameters	**Values**
λ_{maks}	435
Linearity range (mmol.L^{-1})	0.005-0.16
Correlation coefficient (r^2)	0.9987
Regression equation	y=6.9023x+0.0147
Slope	6.9023
Interception	0.0147
LOD (mmol.L^{-1})	0.0013
LOQ (mmol.L^{-1})	0.0045

It can be said that the proposed method for PRX provides the advantage of working at much lower concentrations compared to other studies in the literature given in Table 3.

The accuracy of the proposed method was determined by recovery%, standard addition and t-test (ICH-Q2). The values between 99.7% and 100.4% were obtained in the recovery% study, related results were given showed in Table 4.

The obtained results in the standard addition method were showed in Table 5, the recovery% in the range of 98.9% -101.1% was obtained. In both of these methods, RSD% and RE% is generally lower than 1.3, 1.6%, respectively. The low% RSD and % RE shows that the accuracy of the method is good and the method has high sensivity.

In the tablet formulation containing 20 mg PRX (at 95% confidence level and 4 degrees of freedom) t_t value was taken as 2.777. It was found to experimental t and recovery % are 2.062, 99.2%, respectively. The fact that the experimental t value is smaller than the t_t value indicates that there is no systematic error in the method and it is applicable for determining PRX on tablets, related results were given showed in Table 6 (Gunduz, 2010).

Table 3. Comparison of previous spectrophotometric studies in terms of the working range.

Referance	Reagent	Reaction	Conc. (μgmL^{-1})	λ (nm)
Onal et al., 2005	bromthymol blue	ion pair	2-20	414
Onal et al., 2005	bromocresol green	ion pair	2-16	414
Onal et al., 2005	bromphenol blue	ion pair	2-16	412
Darwish et al., 2009	1,2-naphthoquinone-4-sulfonate	Nucleophilic substitution	1-8	488
Arshiya et al., 2011	2,3-dichloro-5,6-dicyano-1,4-benzoquinone	Charge transfer	5-70	545
Walash et al., 2010	2,4-dinitrofluorobenzene	Charge transfer	2-20	390
Nwodo and Ibezim, 2013	chloranilicasid	Charge transfer	5-40	540
Elqudaby et al., 2012	Mo(V) thiocyanate	Coordination	10-250	470
Elqudaby et al., 2012	Fe(III) thiocyanate	Coordination	10-250	500
Proposed method	dithiocarbamate-Cu^{2+}	Coordination	*1.8-58.5	435

* The working range of the proposed method has been converted to μg / mL from $mmol.L^{-1}$ for convenience.

Table 4. Recovery % of PRX in the proposed method.

Taken($mmol.L^{-1}$)	Recovery%	±SD	RSD%	RE%
0.025	99.7	0.0002	0.6699	0.1106
0.05	100.4	0.0003	0.6010	0.3627
0.075	100.3	0.0002	0.2943	0.2629
0.10	99.9	0.0001	0.1450	0.0768

Table 5. Application of the standard addition technique for the determination of the PRX'in pharmaceutical preparation using the proposed method.

Taken ($mmol.L^{-1}$)	Added ($mmol.L^{-1}$)	Recovery%	±SD	RSD%	RE%
0.05	0.02	98.9	$0.9.10^{-3}$	1.26	1.26
	0.03	99.5	$0.7.10^{-3}$	0.90	0.69
	0.04	99.2	$0.8.10^{-3}$	0.93	1.58
	0.05	99.1	$0.7.10^{-3}$	0.67	1.24
	0.06	101.1	$0.7.10^{-3}$	0.65	0.85

Table 6. t-test for pharmaceutical preparation of PRX.

Commercial Brand	Found Value ±SD	Recovery%	t test
Paxera (20 mg PRX)	19.84 ± 0.176	99.2	2.062

In the stability study, it was determined that the absorbances of 0.1 mmol.L^{-1} and 0.075 mmol.L^{-1} solutions, measured at certain intervals for 24 hours, did not change much until the 12th hours, but decreased at the 24th hours. As seen in Table 7, stability of the Cu-PRX-DTC complex is high until 12 hours.

Table 7. Stability of the method developed for the PRX.

	Inc.	2h	4h	6h	8h	12h	24h
0.1 mM	0.1001	0.0995	0.0993	0.0991	0.0989	0.0938	0.0496
±SD	0.0004	0.0002	0.0001	0.0001	0.0001	0.0001	0.0005
0.075 mM	0.0758	0.0748	0.0739	0.0736	0.0730	0.0644	0.0333
±SD	0.0002	0.0003	0.0002	0.0005	0.0001	0.0005	0.0008

In the precision study, the intermediate precision criterion (intra-day and inter-day) was examined (Table 8). In this study, in general, RSD% is lower than 1.6%. According to the obtained results, the precision of the proposed method is high (Gunduz, 2010).

Table 8. Intra-day and inter-day precision of proposed method (Taken Concentration: 0.075 mmol.L^{-1} and 0.1 mmol.L^{-1} PRX solutions).

İntra-day			İnter-day		
Found Conc. (mmol.L^{-1})	0.0736	0.1003	Found Conc. (mmol.L^{-1})	0.074	0.1
±SD	$1.2.10^{-3}$	$5.8.10^{-4}$	±SD	$0.7.10^{-3}$	$1.1.10^{-3}$
RSD%	1.57	0.57	RSD%	0.93	1.06

In the interference study for specifity (Table 9), the effects of Lactosemonohydrate (LMH), Starch, Hydroxypropylmethylcellulose (HPMC) and Magnesiumstearate (MgStr.) on absorbance were investigated. In this method, it was observed that the excipients at high concentrations reduce absorbance much.

Darwish et al (2009) found that excipients in the PRX tablets such as starch, magnesium stearate, glucose, lactose, and talc have no effects on PRX determination, in their method. Nwodo and Ibezim (2013), excipients in the PRX tablets such as Lactose, Microcrystalline cellulose, Magnesium sterate, Sodium laury sulphate, Starch, found that in the their method have no effects on the determination of PRX from tablets.

Table 9. Effect of interfer substances in proposed method (N=3).

C_I/C_{PRX}	LMH Recovery%	Starch Recovery%	HPMC Recovery%	MgStr. Recovery%
0	100	100	100	100
1	81.95	93.4	97.3	91.5
10	70.76	86.0	73.2	91.0
100	54.24	81.7	71.9	91.3

C_I: interfer substance C_{PRX}: Concentration of PRX

4. Conclusions

Alpdoğan and Sungur (1999) developed a spectrophotometric analysis method by converting the antihypertensive metoprolol drug to dithiocarbamate derivative in basic medium. In their study, they first decided on the optimum solvent and then determined the optimum amounts of NH_3, Cu^{2+}, CS_2. In the study, the same procedure was applied for PRX.

In addition, the effect of acetic acid was also investigated to increase the stability of the PRX-DTC-Cu complex. In their study, El-Ries et al. (2000) managed to increase the stability of drugs-DTC-Cu complex with 1.0 mL of 25% (v:v) acetic acid dissolved in MIBK for metoprolol tartrate and propranolol HCl. As seen in Figure 7, it was obtained that 0.03 mL of 5% acetic acid solution stabilized the PRX-dithiocarbamate-Cu complex without changing its absorbance.

It is found that Beer's law is obeyed in the range 0.005–1.6 $mmolL^{-1}$ with 0.9987 correlation coefficient. Precision and accuracy studies have gave very good results. In the specificity study, the absorbance was considerably reduced at very high concentrations of excipients. Statistical studies have shown that this method is reliable and has no systematic error.

The proposed method has great advantages in terms of being easy, fast, economical and low LOD compared to other studies in the literature. This study demonstrated that the method can be applied to tablets and pure formulations for the determination of PRX.

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