A SENSITIVE SPECTROPHOTOMETRIC METHOD FOR TRACE AMOUNTS DETERMINATION OF PROMETHAZINE IN DRUG FORMULATIONS VIA ION PAIR COMPLEX FORMATION

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ABSTRACT This paper discusses a quick and easy spectrophotometric approach for the estimation of promethazine HCl drug in a pure and pharmaceutical formulation. This system relies on the instruction of colour ion-pair between complexes. Promethazine HCl is reacted in acidic medium with methyl blue dye resulting in the formulation of a coloured product with a maximum absorption of 480 nm. In order to increase the sensitivity of the system, parameters of the reaction conditions were studied and optimised. Beer's law was applied on all the concentrations of 2.0 – 100.0 μg/ml, with 1.420 μg/ml and 6.088×10^4 l/mol.cm as detection limit and molar absorptivity respectively. After plotting the calibration graph, the method's precision was checked and it was found the values were within the accurate range. The impact of widespread interferences on the current approach was examined. The method was utilised to estimate promethazine HCl in various pharmaceutical products available with fine recoveries in the market.

Keywords: Promethazine HCI, sensitivity of system, spectrophotometric approach, ion pair complex, pharmaceutical products.

1. INTRODUCTION

Phenothiazines are extensive medicines utilized for illness in medical care. Promethazine HCl (PZ) is chemically10- [2-(Dimethyl amino) propyl] phenothiazine mono hydrochloride (Her Majesty, 2009) as shown in Figure 1.

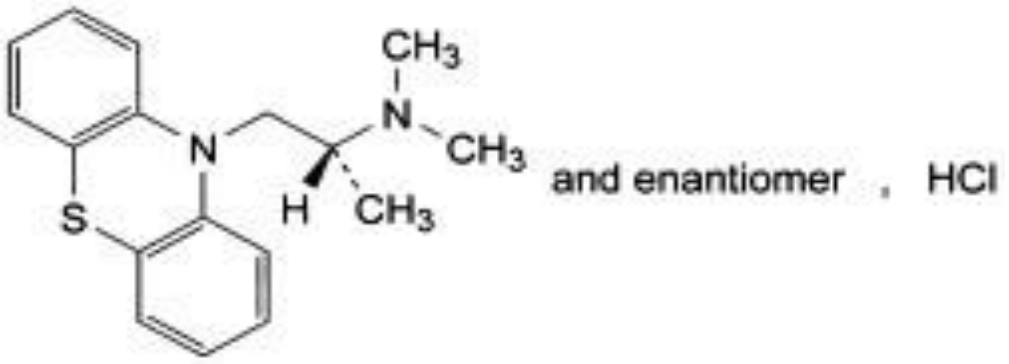

Figure 1. Chemical structure of Promethazine HCl drug PZ

It is identified an antipruritic agent, antiallergic agent, antagonist of histamine H1, derivative of phenothiazine. It operates mainly as a powerful H1 receptor antagonist (antihistamine) as well as an antagonist (anticholinergic) of a progressive m Ach receptor (Howard et al., 1990). Like other H1 antagonists, promethazine is competing in the digestive tract, abdomen, major blood vessels, and bronchial muscle with abundant histamine for attachment at H1 receptor sites. Nausea relaxation seems to be associated with main anticholinergic efforts and may involve interaction in the activate region of the epithelial chemoreceptor. Blocks influence, but not the buying of histamine, and also have a powerful adrenergic impact. It also decreases the stimulus region of the chemoreceptor in the medulla and enhances the influences of serotonin by implicitly reducing CNS1-2 reticular enhancement (Tepper & Sheftell, 2002; Shadi Asadollahi et al., 2000). Chromatographic HPLC techniques (Taylor & Houston 1982; Salah & Yoong, 1993; Saleh et al., 2009; Muijselaar et al., 1996), capillary zone electrophoresis (Kubacak et al., 2005; Baxter et al., 1984), potentiometric and voltammetric techniques (Ahmed et al., 2011; Khaleda & Zainab, 2011; Nabil et al., 2008; Yongnian, & Kokot, 2001), chemiluminescence as well as UV spectroscopy (Theia et al., 2006; Najim et al., 2006; Basavaiah, 2004; Daniel & Gutz, 2003; Sultan et al., 2003; Regulska et al., 2002; Pena et al., 1993; Calatayud et al., 1992; Sultan & Suliman, 1992; Catatayud & Sancho, 1992; Ibrahim et al., 1983) have been previously researched for PZ quantitative evaluation of pharmaceutical composition and biological fluids independently or in collaboration with other drugs.

The work is focused on ion pair colour content creation between the tested methyl blue and the drug. This approach was used with relatively lower detection limit, high sensitivity and broader dynamic range. An important characteristic of this approach is that no extraction is essential and it is practicable at room temperature.

2. EXPERIMENTAL

2.1 Ingredients and reagents

All chemicals and substances used in the experiment were of analytical grade, and they did not require further purification or disinfection. The methyl blue solution (with a concentration of 0.001 M) was achieved by combining 0.079 gm concentration of methyl blue with 1M hydrochloric acid. The reagent grade BDH.A 250 μg/ml was added to 25 mg of Promethazine HCI mixed with 100ml deionised double-distilled water. The reagent and the drug were purchased from SDI (State Drug Industries and Medical Appliances Company, Iraq). Three formulations were prepared and their compositions are described in Table 1.

Table 1. Pharmaceutical preparations

Drugs	Declared composition	Company
Promethazine	Promethazine HCl 10 mg per tab	SDI
Coldin	Promethazine HCl 5 mg per tab	SDI
Promethazine	Promethazine HCl, Syrup 5mg/5Ml	Sina Darou, Iran

2.2 Apparatus

- Spectral and absorbance calculations were carried out on 160 optical
- Double beam UV-Visible spectrophotometer
- Ph meter, Jenway 3020
- Thermal-coling of the water bath (Haake, Fe3)
- Susceptible balance (BL 210S from Sartorius)

2.3 Procedure for calibration curve

Applicable aliquots of Promethazi ne HCl solutions were converted to 10 ml volumetric flask in volumes of 0.1 ml – 4.0 ml and they were added to 0.5 ml of 1 M solution of hydrochloric acid. After this, 1.25 ml of $1x10^{3}$ M methyl blue solution was introduced and up to10 ml of deionised water was applied. The coloured component was spectrophotometric-ally measured with a blank reagent at 480 nm after 25 minutes (the blank reagent was formulated in the same way, but without the PZ drug (Nina & Zahra, 2012).

2.4 Tablet samples solution

Ten tablets of PZ medication were accurately evaluated and their components mixed and carefully powdered after their average weight was calculated. The 25 mg equivalent product was checked and stirred with water after mixing a few drops of HCl 2 M. The volumetric flask was filled with deionized water up to 100 ml. Upon filtration, the solution was prepared. The suggested procedure for evaluating PZ was adopted and implemented. Based on the calibration curve, the method was successfully used for reliable determination of PZ components in these samples (AL-Ward, 2005).

2.5 Syrup sample solution

This solution was produced by taking 25 ml of the syrup solution consisting of 25 mg of PZ medication and diluted in a 100ml deionized water. Depending on the design calibration curve, the tested method was effectively utilised for the precise calculation of PZ components in this sample (Hemn & Nabil, 2017).

3. RESULTS AND DISCUSSION

3.1 Absorption spectra

One ml of 250 μg/ml standard solution for promethazine hydrochloride was poured into 10 ml volumetric flask, after adding 0.5 ml of 1 M solution of hydrochloric acid. Following this, 1.25 ml of $1x10^{-3}$ methyl blue solution and 10 ml of deionised water were introduced. The absorption rate and spectrum of this solution were then evaluated at 200 to 800 nm utilising a reagent blank solution as reference. Figure 2 shows the maximum absorption for the colour component was 480 nm. The Absorption Spectra followed the prescribed protocol. However, the reagent blank did not lead to any notable absorbance as shown in Figure 2 (Al-Rufaie et al., 2013).

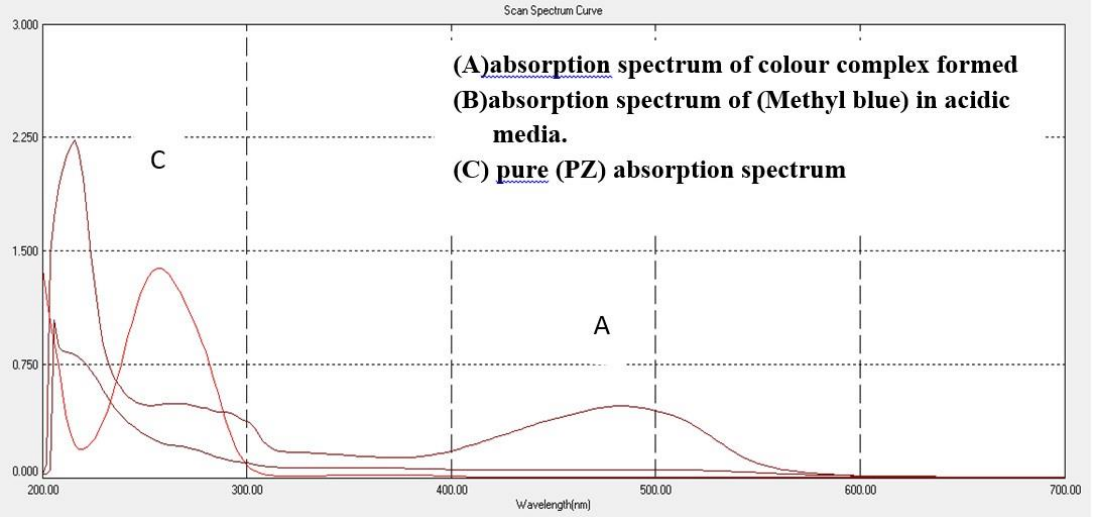

Figure 2. (A) absorption spectrum of colour complex formed by(PZ)(25mg/ml),(Methyl blue) in acidic media, (B)absorption spectrum of (Methyl blue) in acidic media. (C) pure (PZ) absorption spectrum

3.2 Optimization of reaction conditions

The concentration was analysed, and the results revealed the acidic medium enhanced the strength of colour. Consequently, several acids, namely HCl, CH_3COOH, H_2SO_4 as well as HNO_3 were evaluated at 1 M concentration (see Table 2) (Al-Rufaie, 2016).

Table 2. Effect of types of acid on the absorbance of colour

Acid Type	Absorbance
HCl	0.605
HNO_3	0.555
H_2SO_4	0.572
CH_3COOH	0.512

HCl had the greatest absorption power as shown in the above table. Figure 4 shows 1 ml of this acid produces the greatest strength.

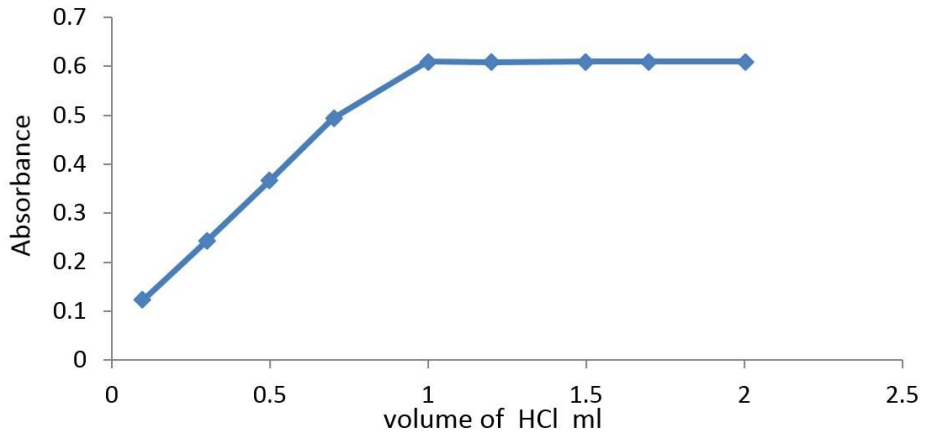

Figure 3. Volume of HCl (ml) on the absorbance of colour

3.3 Separate solvents

Such as dichloromethane, acetone, methanol, ethanol, chloroform, dimethyl sulphoxide, acetonitrile and water, were used to test solubility and complex synthesis in acidic solution between PZ and methyl blue to ensure maximum susceptibility as well as product stabilization (Al-Rufaie et al., 2013) (see Table 3).

Table 3. Effect of solvents on the absorbance of colour

Solvent	Absorbance	ε ,L.mol^{-1}.cm^{-1}
acetone	0.321	1.068×10^{2}
dichloromethane	0.201	0.018×10^{2}
methanol	0.242	0.555×10^{3}
chloroform	0.401	5.065×10^{2}
acetonitrile	0.279	1.055×10^{2}
ethanol	0.586	0.422×10^{4}
Dimethyl sulfoxide	0.421	1.222×10^{2}
Dimethyl formamide	0.301	2.014×10^{2}
Teri butyl alcohol	0.221	0.033×10^{2}
Benzene	0.124	0.231×10^{3}
Di ethyl ether	0.233	0.451×10^{1}
Formic acid	0.444	2.134×10^{2}
2- propanol	Two layers	Two layers
Water	0.656	6.088×10^{4}

3.4 Dye concentration effect

By adding different volumes of 0.001 M methyl blue dye to the drug, the ideal concentration was assessed. With the addition of 1.2 ml of methylblue dye, the colour became more prominent and stable. The colour absorbance at this volume (Figure 5) was at its maximum. All measurements were performed in triplicate and the median of the three values were plotted in each graph (Hemn & Nabil, 2017).

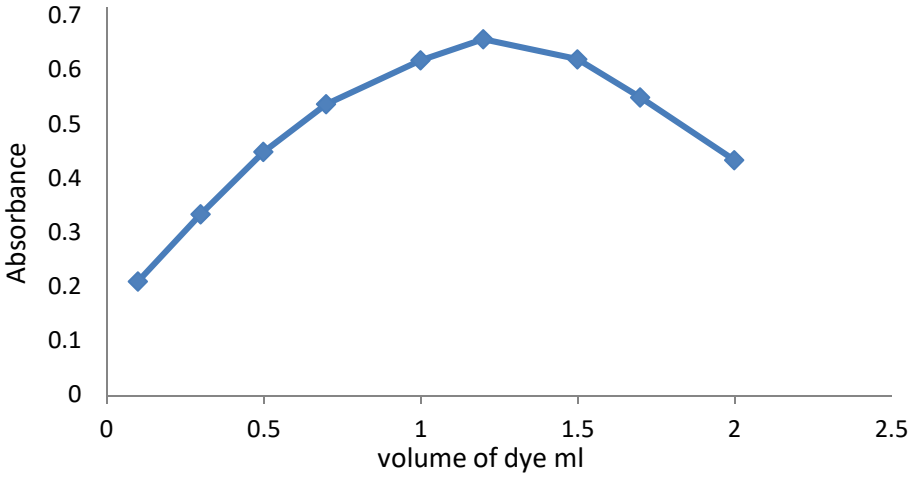

Figure 4. Volume of dye (ml) effect on the absorbance of product colour

3.5 Time effect

The drug and dye mixtures were mixed in acidic media; the ideal reaction time was assessed by documenting the rate and extent of absorption at separate time intervals of the created complexes. The modification is shown in Figure 5. It was noticed that at room temperature, the complexes were created spontaneously. After 60 minutes and with 5 minutes as interval time, the absorbance was observed to be constant. Therefore, greater absorption was seen after 25 minutes and this was replicated in the next experiments. All findings were conducted after the current time periods of complex creation in order to eliminate the time effect. Product solutions were kept in air tight flasks to prevent evaporation and to maintain their freshness for at least three days (Al-Rufaie et al., 2013).

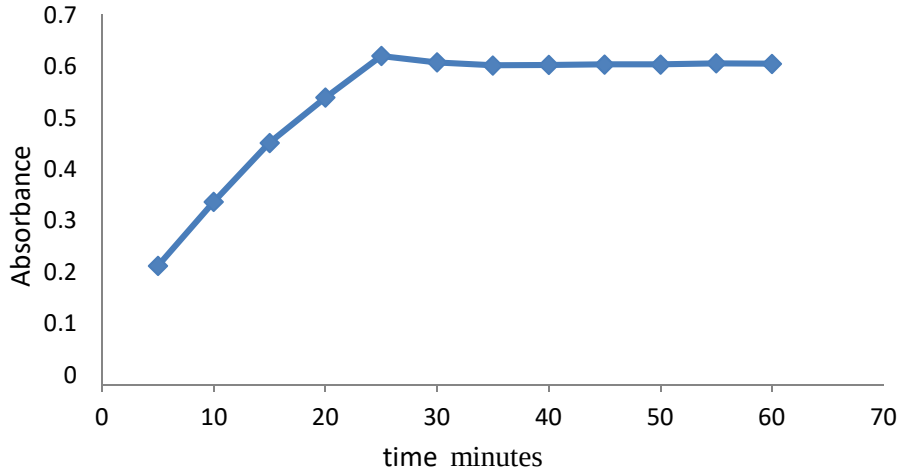

Figure 5. Time effect on the absorbance of colour product

3.6 Temperature effect

Temperature effect was tested on the product's absorbance level and the results indicated that there was no substantial difference in the compound's absorbance parameters under examination, and they were highly absorbent at room temperature. Therefore, all tests were performed at room temperature as shown in Figure 6. (Theia et al., 2006).

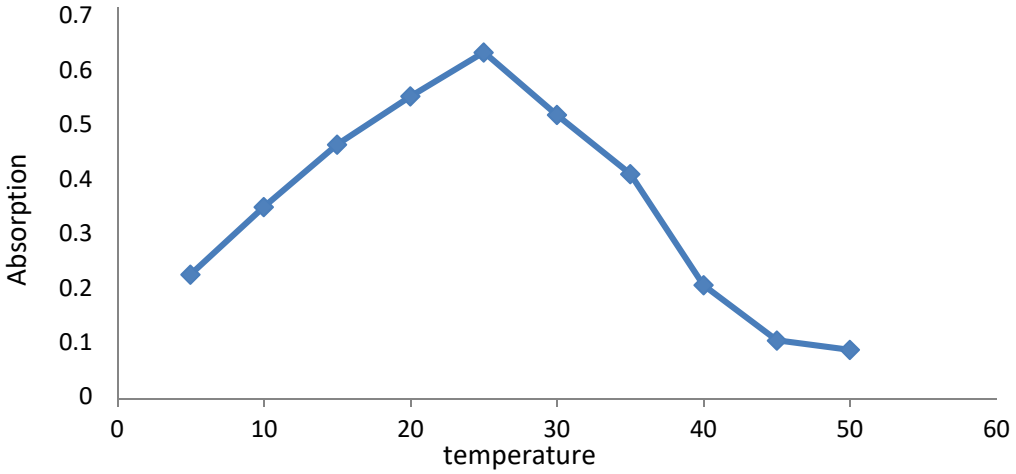

Figure 6. Temperature effect on the absorption of product colour

3.7 Calibration curve and its statistical data

A calibration curve was built under selected ideal circumstances (Figure 7). The graph shows the colour system in a 10 ml final volume (i.e. 2 – 100.0 µg / ml of PZ) which adhered to Beer's law throughout the experiment. Table 4 summarizes the statistical data of the proposed calibration curve. The molar absorption levels were simultaneously identified to be L mol^{-1} cm^{1}. The limits of detection and the quantification were measured and they were found to be 1.420 and 1.752 µg ml^{-1} respectively with the sensitivity µg cm^{2} of Sandell. Different analytical specifications were acquired under ideal conditions (Table 4). The correlation coefficient for all three systems showed a good linearity. The value of molar absorptivity and the Sandell's value point to accuracy and high sensitivity of these methods (Hemn & Nabil, 2017).

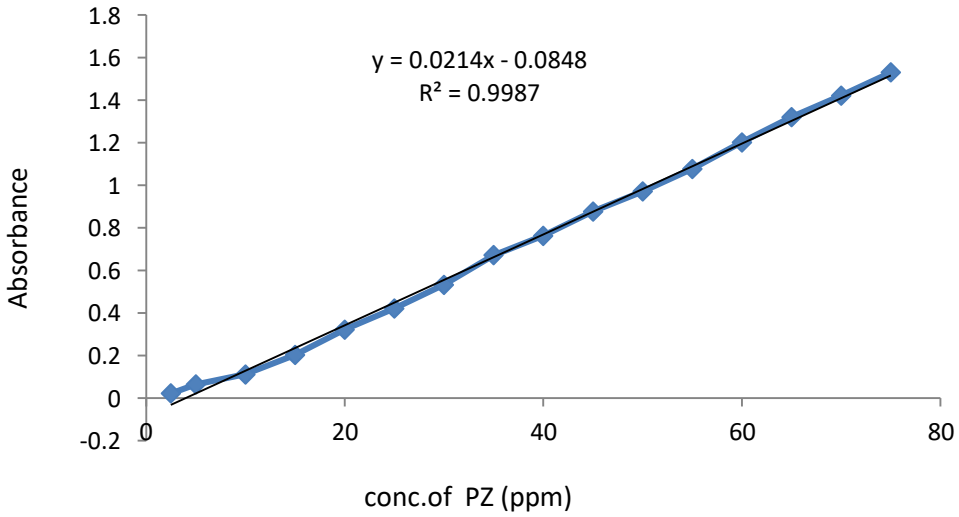

Figure 7. Calibration curve of PZ assay

Table 4. Analytical characteristics of experimental abatement from the constant approach of the calibration curve

Parameter	Values of approach
Correlation coefficient	0.9987
limits of Beer's law	(2 – 100) (μg/ml or ppm)
Molar absorptivity	6.088×10^4 (L . mol^{-1}. cm^{-1})
Sandell's sensitivity	0.004 μg . cm^{-2}
Limit of quantification	1.752 (μg/ml)
Limit of detection	1.420 (μg/ml)
Regression equation	Y= 0.0214X - 0.0848
Intercept	0.0848
Slope	0.0214
Average recovery	% 99.850
RSD*	% 0.925

3.8 Accuracy and precision

Based on the relative error percentage (Error percent) and relative standard deviation percentage (RSD percent), the precision and robustness of the recommended PZ evaluation process was measured in five duplicate standard PZ solutions at three concentration levels separately. The findings are listed in Table 5 (Al-Rufaie, 2016).

Table 5. The current approach is precise as well as accurate

No	Conc. Of PZ (μg/ml)		R.S.D%	Recovery%
	Present	Found		
1	5	4.911	1.082	98.220
2	25	25.123	0.815	100.490
3	50	50.421	0.880	100.842

3.9 Stoichiometric relationship and stability studies

Stability constants of these complexes in formation and flexibility were formulated using Job's continuous variation method. Equi molar medicine and reagent solutions were combined in different quan tities and each combination was absorbed.

The findings showed that the com plexes were generated in the 1:1 ratio (D: R).The composition mechanism (PZ) I to formulate certain complexes was also observed.Promethazine's proposed ion pair complex structure is shown in Figure 6. The stability constant K levels was calculated to be 6.19 ± 0.04 indicating high complex flexibility. Figure 7 describes this (AL-Ward, 2005; Nina & Zahra, 2012).

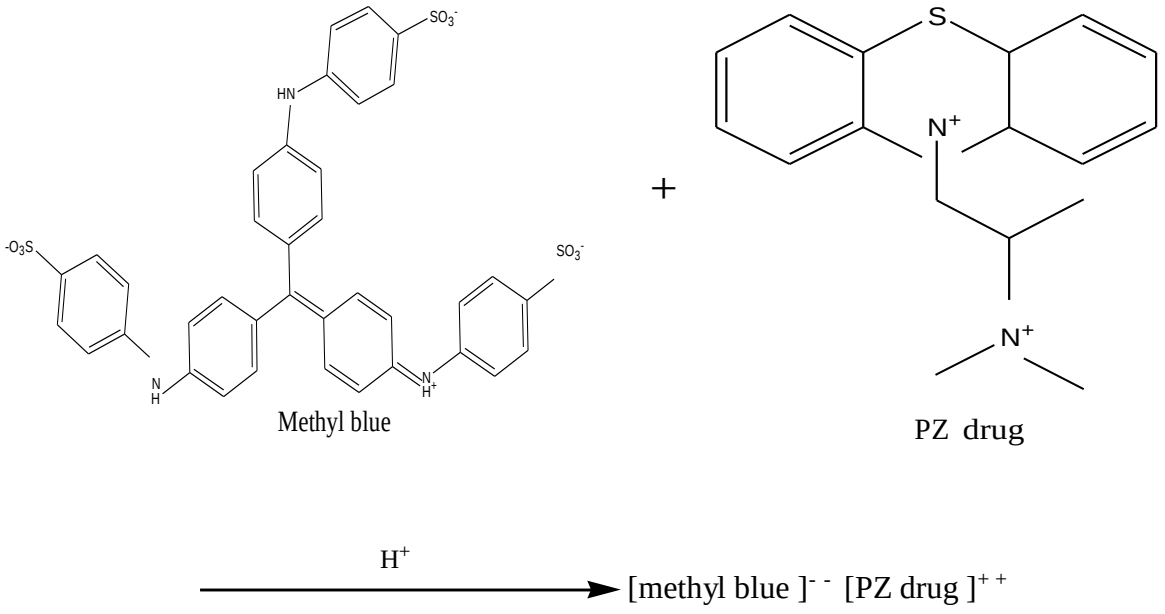

Figure 8. Possible reaction with dye for ion pair (PZ) compound.

3.10 Testing of interferences

The specificity of the current approach was tested by looking at the effects of various additives as well as excipients that typically occur in dosage of PZ, such as talc, starch, lactose, fructose, mannitol, glucose, Mg-stearate, aspartate, vitamin C, PVP, Acacia, glycerine and sucrose on 25 μg/ml of PZ. The interference generates a relative percentage of sample absorption error above ±2.0 point. The findings suggest that the analysed excipients did not interfere with the process, even if they are more than 100-folds of the mentioned product, except if the dosage is in Mg-stearate which begins to influence the system when its concentration reaches 10-fold due to the formation of colloidal solution (Hanaa et al., 2018).

Table 6. Estimations of (PZ) (25 ppm) in excipients.

Excipients	% Error	% Recovery
Aspartate	+1.600	101.600
Mannitol	- 0.830	99.170
Glucose	+ 1.310	101.310
Starch	- 1.550	98.450
Lactose	+ 1.500	101.500
Sucrose	- 1.500	98.500
Vitamin C	-.1.300	98.700
Glycerine	+ 1.610	101.610
Acacia	+1.210	101.210
Talc	- 1.330	98.670
PVP	- 1.350	98.650
magnesium stearate	colloidal	Colloidal

3.11 Application of the technique

The suggested approach was succe ssfully used in various pharmaceutical formulations (tablet, syrup) in Iraq. Regular PZ dosage was used in the prescribed formulations. The concentration of PZ was then measured and the difference pointed to the increase in the drug amount.

The results of the study were statistically compared with a common approach using a variation precision ratio (F-test) and precision test (T-test) with a confidence level of (95%) as shown in Table (3). The results showed the F-test and T-test were lower than the fundamental value (F= 9.28, t= 2.45). The values of (F = 0.899) and (t = 0.433) were examined. No clear distinction was made between the investigated approach and the regular approach based on three examinations. In addition, the procedure was compared with certain recorded techniques as shown in Table 8 which describes manuscripts, company brand names, the identification of PZ found in pharmaceutical substances using the process recommended, and the recovery of the suggested approach (Jawad & Kathem, 2013; Al-Rufaie,2016; Al-Rufaie et al., 2017).

Table 7. Evaluation of (PZ) in pharmaceutical products

Pharmaceutical preparations of (PZ)	**Deliberated process**		**Official process**		**Official Values (t),(F)**
	Recovery %	**RSD%**	**Recovery %**	**RSD%**	
Pure Promethazine	99.850	0.925	99.430	1.21	
Promethazine, 10 mg ,S.D.I, Iraq	99.450	1.022	98.660	1.05	0.899 **(**F)Value = 9.28
Coldin, 5 mg, S.D.I, Iraq	100.120	0.912	99.150	0.933	0.433 (t)Value= 2.45
Promethazine , Syrup 5mg/5Ml , Sina Darou, Iran	99.120	0.686	100.280	0.877	

4. CONCLUSIONS

The current method was used to estimate PZ composition in pharmaceutical products. The findings indicated this approach had multiple benefits in terms of ease of use, speed, flexibility, greater sensitivity, as well as being easy to replicate. Heating or extraction is also not required.

5. ACKNOWLEDGEMENTS

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6. REFERENCES

Al-Rufaie, M. M., Al-Sharefy, A.N. & Kathem, K.H. (2013): Spectrophotometric Determination of Doxycycline Hyclate in Pharmaceutical Preparations Using Oxidative coupling reaction. J. of Applicable Chemistry 2(4), 931-936.

Al-Rufaie, M.M., Al-Sharefy, A.N. & Kathem, K.H. (2013): New spectrophotometric method for the determination chlorpromazine hydrochloride in pharmaceutical preparations by using oxidative coupling reaction. Inter. J. of Uni. Pharmacy and Bio Sciences 2(4), 19-26.

Al-Rufaie, M. M. (2016): New spectrophotometric method for the determination of Sulfamethoxazole drug. W. J. of pharmacy and pharmaceutical sciences. 5(3), 172-180.

Al-Rufaie, M.M. (2016): Modern kinetic spectrophotometric procedure for estimation of furosemide drug as bulk form and in pharmaceuticals preparations. Curr. Issues Pharm. Med. Sci. 29(4), 184-190.

Al-Rufaie, M.M., Al-labban, H. M.Y. & Salih, N.S. (2017): Reduction and assessment of chloramphenicol antibiotic as pure from and in various kinds of pharmaceuticals by utilizing spectrophotometric approach. Iran. J. of Org. Chem. 9(2), 2087-2092.

AL-Ward, H. S. (2005): Spectrophotometric micro determination of promethazine hydrochloride in pharmaceutical preparations via oxidative coupling reaction with sulphanilamide and in the presence of ferric chloride. Journal of Um-Salama for Science 2, 110-119.

Ahmed K. H., Bahruddin, A. Sulaiman S. & Rohana A. (2011): Ionophore-Based Potentiometric Sensors for the Flow-Injection Ionophore-Based Potentiometric Sensors for the Flow-Injection "Determination of promethazine Hydrochloride in Pharmaceutical Formulations and Human Urine.J. Sensors. 11(1), 1028-1132.

Basavaiah K. (2004): Determination of some psychotropic phenothiazine drugs by charge-transfer complication reaction with chloranil acid.IIFarmaco 59, 315-322.

Baxter, R.I., Svehla, G. Kerr, B. & Woolfson A.D. (1984): Determination of promethazine by anodic differential pulse voltammetry. Anal. Chim. Acta 64, 171-176.

Calatayud, J. M. & Sancho T.G. (1992): Spectrophotometric determination of promethazine by flow-injection analysis and oxidation by Ce IV. J. Pharm. Biomed. Anal. 10, 7-13.

Calatayud, J. M, Sarrion, S.N., Sampedro A.S., & Benito C.G. (1992): Determination of promethazine hydrochloride with bromophenol blue by a turbid metric method and flow injection analysis. Microchem. J.45, 129-137.

Daniel, D. & Gutz I.G.R. (2003): Flow injection spectroelectro analytical method for the determination of promethazine hydrochloride in pharmaceutical preparations. Anal. Chim. Acta.494 (1-2), 215-222.

Hanaa, K.A.T., Al-Rufaie, M.M. & Zahraa, Y.M. (2018): Spectrophotometric determination of metoclopramide medicine in bulk form and in pharmaceuticals using orcinol as reagent. Ovidius University Annals of Chemistry 29 (2), 85-89.

Hemn, A.Q. & Nabil, A. F. (2017): Spectrophotometric Determination of Promethazine Hydrochloride in Pure and Pharmaceutical Dosage Forms. ZANCO J. of Pure and Applied Sci.29 (s4), 107,118.

Howard, C.A., Loyd, V. A. & Nicholas, G. P. (1990): Pharmaceutical dosage forms and Drug Delivery Systems, Lippincott Williams & Wilkins Publishers, p.51.

Ibrahim, E.A., Issa, A.S., Abdel salam, M.A. & Mahrous, M.S. (1983): The use of chloranil for spectrophotometric determination of some tranquillizers and antidepressants. Talanta 30, 531-540.

Jawad, A.A. & K. H. Kathem (2013): Spectrophotometric determination of metoclopramide hydrochloride in bulk and pharmaceutical preparations by diazotization-coupling reaction. Inter. J. of Pharmacy and Pharmaceutical Sciences, 5, 294-299.

Khaleda, H. A. & Zainab, W. A. (2011): Construction of promethazine Hydrochloride Selective Electrode in a PVC matrix Membrane. J. of AL-Nahrain University- Sci. 14(4), 11-17.

Kubacak, P., Mikus, P., Valaskova I. & Havranek, E. (2005): Determination of promethazine hydrochloride in pharmaceuticals by capillary isotachophoresis. Methods Findings Exp. Clin. Pharmacol. 27, 529-531.

Muijselaar, P.G.H.M., Claessens H.A. & Cramers, C.A. (1996): Determination of structurally related Phenothiazines by capillary zone electrophoresis and micellar electro kinetic chromatography. J. Chromatogr. A 735, 395-401.

Nabil, S. N., Shahbaz, A. M.S. & Bashaer, A. A. (2008): Preparation and Potentiometric Study of promethazine Hydrochloride Selective Electrodes and Their Use in Determining Some Drugs. Turk J Chem.32, 539-544.

Najim, A. S., Nief, R.A. & Mona, I.I. (2006): spectrophotometric determination of promethazine hydrochloride VIA oxidative coupling reaction with sulfanilic acid. App.Sci.3, 1-8.

Nina, A. & Zahra, R. (2012): Extractive Spectrophotometric determination of Ketoconazole, Clotrimazole AND Fluconazole by ion –pair complex formation with bromothymol blue and picric acid. J. Chil. Chem. Soc.57 (2), 1104-1111.

Pena, L. D. L., Gomez-Hens, A. & Perez-Bendito, D. (1993): Kinetic fluorimetric determination of promethazine by a stopped- flow mixing technique, J. Pharm. Biomed. Anal.11, 893-900.

Regulska, E., Tarasiewicz, M. & Puzanowska T.H. (2002): Extractive-spectrophotometric determination of some Phenothiazines with dipicrylamine and picric acid. J. pharm.Biomed.Anal.27, 335-342.

Salah, M. I. & Yoong, C.S. (1993): Chromatographic Method for Separation and Determination of Promethazine HCl in Pharmaceutical doses.J.Phys.Sci.4, 55-60.

Saleh, O., El-Azzouny, A., Aboul-Enein, H. & Badawy, A. M. (20090: A Validated HPLC Method for Separation and Determination of Promethazine Enantiomers in Pharmaceutical Formulations. Drug Dev. Ind. Pharm.35, 19-23.

Shadi Asadollahi, M.D., Kamran Heidari, M.D., Reza Vafaee, M.D., Mohammad Mahdi, M.D., Afshin Amini, M.D. & Ali Shahrami, M.D. (2000): Promethazine Plus Sumatriptan in the Treatment of Migraine: A Randomized Clinical Trial. Wiley Periodicals, Inc. p.12259.

Sultan, S. M. & Suliman, F. (1992): Application of super modified simplex optimization to the flow-injection spectrophotometric determination of promethazine hydrochloride in drug formulations. Anal.Sci.8, 841-849.

Sultan, S.M. Hassan, Y.A.M. & Abulkibash, A.M. (2003): Chemiluminescence assay of promethazine hydrochloride using acidic permanganate employing flow injection mode operated with syringe and peristaltic pumps. Talanta 59(6) (2003) 1073-1079.

Taylor, G. & Houston, J.B. (1982): Simultaneous determination of promethazine and two of its circulating metabolites by high performance liquid chromatography. J. Chromatogr. B 23, 194-201.

Tepper, S.J., Rapoport, A.M. & Sheftell, F.D. (2002): mechanism of action of the 5-HT1D/1B receptor agonist. Arch Neurol. 59 (7), 1084-1089.

The British Pharmacopoeia (2009), Her Majesty's Stationary Office. London, pp.5010, 5013, 9844, 9848**.**

Theia'a, N. A. Nie, R.A. & Mona, I.I. (2006): Spectrophotometric Determination of Promethazine hydrochloride via Oxidative Coupling Reaction with Sulfanilic Acid. J. of P. & App.Sci. 22, 321-329.

Yongnian, LW.N. & Kokot, S. (2001): Voltammetric determination of chlorpromazine hydrochloride and promethazine hydrochloride with the use of multivariate calibration. Anal. Chim. Acta 439, 159-165.