# Spectrophotometric determination of promethazine HCl in pure and dosage forms

**Rawa M.M Taqi Raad J.M.Al-Timimi* Muna M.Hasan* Mohammed J.Hamzah**

Pharmaceutical chemistry department / Pharmacy College / Al-Nahrain University
* Chemistry and Clinical Biochemistry department / Medicine College / Al-Nahrain University
E-mail : mohammedlord2003@yahoo.com

**Abstract**

**Background: The research is involved development a new spectrophotometric method based on the oxidative coupling reactions for determination of important phenothiazine drug which is promethazine HCl in pure solutions and local pharmaceutical preparations.**

**Materials and methods: The Standard promethazine HCl was treated with organic reagent of P-Chloroaniline as a coupling reagent in the presence of oxidizing agent Ammonium Cerric (IV) Sulphate, the reaction leads to the formation a blue –greenish color product that has a maximum absorption at 603nm.**

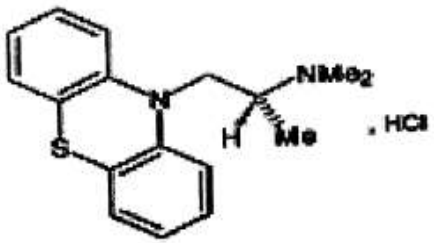
**Results: The variables of reaction conditions including optimum volumes of both reagent and oxidizing agent, acidity of the reaction medium, order of addition and stability time were studied. The obtained results of the purposed method shows that a Beer law is obeyed in the range of 7-40ppm with a correlation coefficient ($r^2$) of 0.9981. While the molar absorptivity (ξ) of $1.861x10^3$ $L.mol^{-1}.cm^{-1}$, sandal sensitivity(s) of 0.172µg.$cm^{-2}$, limit of detection (LOD) of 4.02ppm and limit of quantification (LOQ) of 13.39ppm were obtained. The developed method was compared with the standard method adopted by USP using F and t-tests and the results shows no significant deferent between both methods.**

**Conclusion: The analytical method was also applied successfully for pharmaceutical preparations containing promethazine HCl.**

**Key words: Spectrophotometric , promethazine HCl .**

## Introduction

Promethazinehydrochloride, l0-(2-(dimethyl-amino)propyl) phenothiazine monochloride,is adrug frequently used m pharmaceutical preparations and it has the following structure showing in Figure (1-1)(1-4).




It is commonly known as neuroleptic tranquilizer and commonly used as a sedative, antihistamine, antiemetic and anaesthetic agent (5-7). For the control of pharmaceutical preparations and analysis of promethazine HCl in body fluids, a spectrophotometric and chromatographic methods are most often used, although electro-analytical methods can also be employed. A numerous methods are already available in the literature. Among these methods used to estimate promethazine hydrochloride both in bulk and in pharmaceutical preparations and biological fluids are titrimetric (8-10), chromatographic (11-15) spectrophotometric (16-20) and electrochemical (21)procedures. Some of these methods lack sensitivity and specificity, require long heating times or involve non-aqueous media.

The present work is described a developed analytical spectrophotometric method for determination of promethazine HCl in pure and pharmaceutical preparations. The method is depend on reaction of Promethazine HCl with para-chloroaniline in the presence Cerric(IV) ion as oxidizing agent, the reaction product is greenish – blue color that absorbed at 603nm.

## Experimental

### Apparatus and Materials

A double beam UV-Vis (UV-1800) Shimadzu with 10mm glass cell spectrophotometric measurements. The pH meter/HM TDA electronic was used for pH measurements, and digital electronic balance – Sartorius was also used.

All chemicals and reagents used were of analytical reagent or pharmaceutical grade. Distilled water was used throughout.

### General Procedure for Standard Promethazine HCl

Increasing volumes of standard promethazine HCl were transferred to 25ml volumetric flasks to cover the standard curve range (5-40µg/ml). 1.3ml (0.01M) of para-Chloroanaline followed by addition 3ml(0.001M) of Cerric ammonium sulphate. The mixture was dilute to the mark with distilled water and left for about 15minutes, then the absorbance's of color product were measured at 603nm against reagent blank solution.

### General procedure for analysis pharmaceutical tablets

Ten tablets were weighed and powdered. An accurately weighed portion of the mixed powder, equivalent to about 100µg.ml$^{-1}$ of the drug, was dissolved with distilled water in a 100-ml standard flask for 20 min. The solution mixed well and then filtered through a dry filter-paper into a dry flask, and this solution was used to study the applications of the method.

## Results and discussions

### Absorption Spectra

A dilute concentration of standard promethazine HCl within the calibration curve was mixed with para-Chloroanline(0.01M) and Cerric(IV) ion (0.001M), an oxidative coupling reaction was occurred between promethazine HCl and para-Chloroaniline leading to formed a greenish –blue color product. A scanning the wavelength(nm) for the color product between 200-800nm was carried out, the spectra shows that the maximum absorption was obtained at 603nm as showing in Figure(1-2).

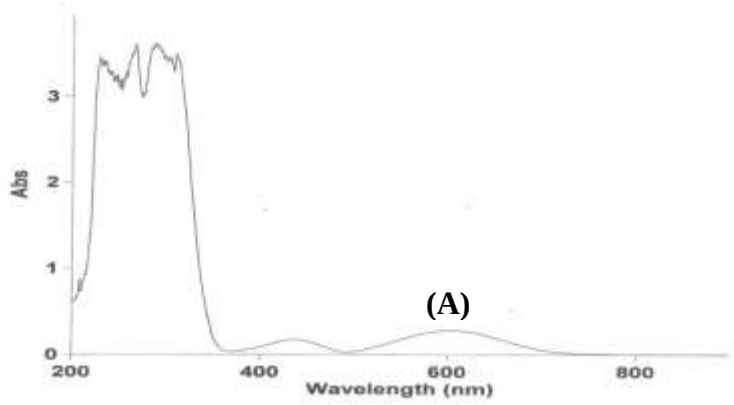



**Figure (1-2): Absorption Spectra of color product showing the maximum absorption at (A) 615nm**

### The Optimum experimental variables

The effect of the experimental variables on the optimum absorption of the color product were studied. The absorbance of a series solutions were measured by varying one with fixed the other parameters at 603nm against reagent blank solutions.

The effects of different volumes (0.1-2.5mL) of para-Chloroaniline(0.01M) and (0.5-4mL) of Cerric ammonium sulphate (0.001M) were examined on the maximum absorbance of the formed product. The obtained results as showing in Figure (1-3(a , b)) that shows 1.3ml and 3ml of reagent and oxidant respectively were enough to obtain the maximum absorbance.

The effect of temperature on the color intensity of the oxidative coupling reaction product was studied. In practice, high absorbance was obtained when the color was developed at room temperature (25 °C) that when in ice bath (5 °C) or in water bath (45 °C).

The pH of medium and order of additions were also optimized and the optimum conditions with the reaction must be carried out at normal pH (without addition any acid or base), while the order of addition was done when the drug mixed with para-chloroaniline followed by addition of ceric ammonium sulphate. The stability of the product was studied for 2h following the mixing of the reagents. The colored developed

rapidly after mixing and attained maximum absorbance about 20 min at room temperature. The color was stable for a period of one hour.

.

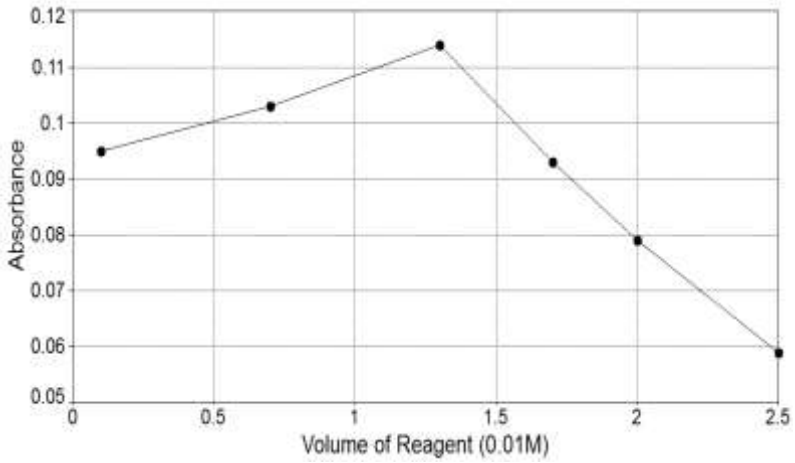



**Figure (1-3a): Effect of reagent volume on the color intensity**

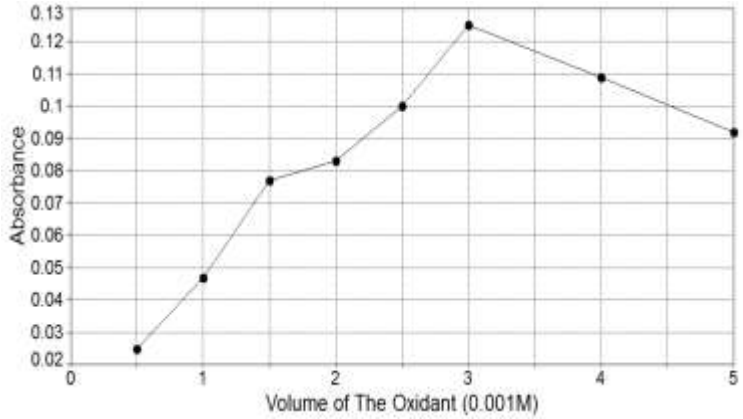



**Figure (1-3b): Effect of the oxidant volume on the color intensity**

**The stoichiometric Ratio**

The stoichiometry of the product was investigated using continuous variation method. In continuous variation method, in this method a volumes 0.5-4.5mL of 0.01 M portions of promethazine HCl (VD) were coupling using equimolar according to analytical procedure with the corresponding complementary volume 0.01M of para-chloroaniline solution (VR) to give a total volume of 5 mL for VD + VR and 3ml of oxidant then diluted the mixture to 25 mL with distilled water**.** The results obtained in Figure(1-4) that shows a 1:1 color product was formed between promethazine HCl and p-chloroaniline. Therefore, the reaction might occur as in following diagram (22).

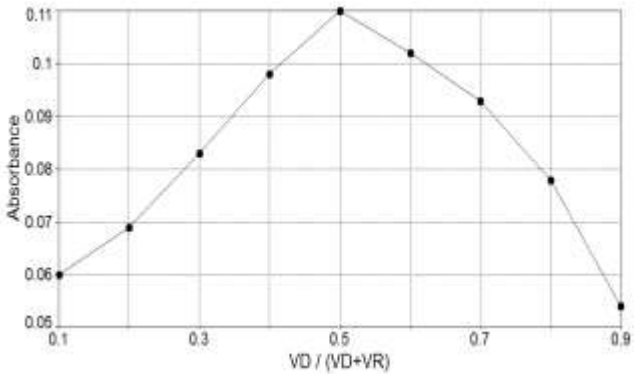
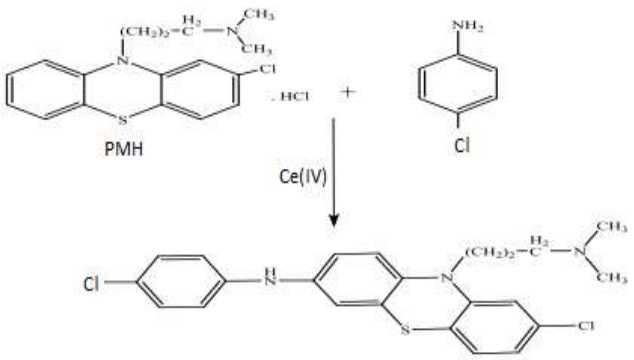



**Figure (1-4): Continuous variation (Jobs method) plot**




**Calibration Curve**

Employing the optimum conditions described in the above procedure, a linear calibration graph for promethazine HCl is obtained (Figure1-5), which shows that Beer's law is obeyed over the concentration range of 7-40µgml$^{-1}$ with correlation coefficient of 0.9988 and an intercept of 0.003. The conditional molar absorptivity of the orange product formed was found to be 1.86x10$^{3}$ L.mol$^{-1}$.cm$^{-1}$. The obtained analytical data of standard curve were listed in Table (1-1).

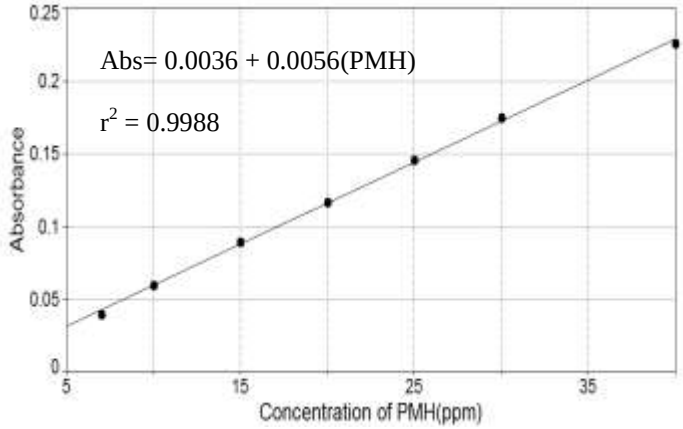



**Figure (1-5): The standard curve of PMH**

**Table (1-1): The obtained analytical data for determination of PMH**

| Parameter | Value |
|---|---|
| **Linear regression equation** | **Abs=0.0036 + 0.0056(PMH)** |
| **Linear dynamic range(µg.ml$^{-1}$)** | **7-40µg.ml$^{-1}$** |
| **Correlation Coefficient(r$^2$)** | **0.9988** |
| **Slope(b)** | **0.0056** |
| **Intercept(a)** | **0.0036** |
| **Molar Absorptivity(ξ)** | **1.861x10$^3$ L.mol$^{-1}$.cm$^{-1}$** |
| **Sanadall Sensitivity(S)** | **0.172µg.cm$^{-2}$** |
| **Limit of detection(LOD)** | **4.02µg.ml$^{-1}$** |
| **Limit of quantification (LOQ)** | **13.39µg.ml$^{-1}$** |

**Precision and Accuracy**

Promethazine HCl was determined at three different concentrations. The results shown in Table (1-2) satisfactory precision and accuracy that obtained with the proposed method (23).

**Table (1-2): Accuracy and Precision of the proposed method**

| PMH Concentration(µg.ml$^{-1}$) | | *Recovery% | *Error% | *RSD% |
|---|---|---|---|---|
| Taken | Found | | | |
| 20 | 20.8 | 104 | 4% | 2.4% |
| 25 | 24.7 | 98.8 | -1.2% | 1.5% |
| 30 | 30.08 | 100.26 | 0.26% | 0.58% |

*Average of three determinations

**The Applications of proposed method**

The applicability of the method for the assay of pharmaceutical formulation was examined.

The result of assay for available formulations of promethazine HCl drugs are summarized in Table (1-3).

**Table (1-3): The application of the proposed method**

| Promethazine HCl Form | PMH Concentration (µg.ml$^{-1}$) | | *Recovery% | *Error% | *RSD% |
|---|---|---|---|---|---|
| | Taken | Found | | | |
| Tablets HISTAZIN 25mg | 20 | 19.7 | 98.5 | -1.5% | 2.3% |
| United pharmaceuticals | 25 | 24.5 | 98 | -2% | 1.8% |

*Average of three determinations

The proposed method was compared with the official method using F-test and t-test, the obtained results shows there is no significant differences between the proposed method and the official method, therefore the proposed method can be used as an alternative method for determination of promethazine HCl in pure and dosage form.

**Conclusion**

A fast and accurate method for determining of Promethazine Hydrochloride was developed by using coloring reactions. The advantage of this method is that promethazine HCl can be determined directly in a single sample without the need to be separated. It was also found that the additives compounds had no effect on the results of determination obtained under the established conditions.

**References**

1. British pharmacopoeia .(2000), CD, ROM.
2. Theia'a NA, Nief RA , Mona II. Spectrophotometric Determination of Promethazine hydrochloride via Oxidative Coupling Reaction with Sulfanilic Acid. J.of P.& App.Sci. (2006); 3(1): 1-10.
3. Daniel D, Gutz IGR. Flow injection spectroelectroanalytical method for the determination of promethazine hydrochloride in pharmaceutical preparations. Anal. Chim. Acta. (2003); 494(1-2): 215-224.
4. Sultan SM, Hassan YAM, Abulkibash AM. Chemiluminescence assay of promethazine hydrochloride using acidic permanganate employing flow injection mode operated with syringe and peristaltic pumps.Talanta. (2003); 59( 6): 1073-1080.
5. Abdulrahman LK, AL-abachi AM, AL-qaissy MH. Spectrophotometric micro determination of promethazine hydrochloride in pharmaceutical dosage forms via oxidative coupling reaction with p-aminobenzoic acid and N-bromosuccinimide. Um-Salama Science J.. (2005); 2: 471-47.

6. AL-ayash AS, Jasim F, Zair T. Spectrophotometric micro determination of drug promethazine hydrochloride in some pharmaceutical by chelating with Rhodium. Um-Salama Science J.. (2008) 5: 638-645.
7. AL-khadimy ASH. Flame emission and molecular absorption spectrophotometric determination of promethazine hydrochloride via potassium dichromate as oxidant reagent. World J. of Pharmaceutical Sciences. (2016);4: 323-329.
8. Zhang Qi, Xiancheng Zhan, Chengrong Li, Tao Lin, Linli Li, Xiaodong Yin, Ning He, Yan Shi. Determination of promethazine hydrochloride and its preparations by highly accurate
nephelometric titration. Int J Pharm. (2005);1(2):10-7.
9. Ajay Kumar Pandey, Dharmendra Dwivedi. Micro Determination of Promethazine Hydrochloride Drugs in Pure form and in Their Pharmaceutical Preparation with Pyridinium Fluorochromate (Pfc) Reagent. International J. of Pharmaceutical, Chemical and Biological Sciences. (2017); 7(4): 335-340.
10. Basavaiah K, Somashekar BC, Anilkumar UR, Ramakrishna V. New Titrimetric and Spectrophotometric Methods for the Assay of Promethazine in Pharmaceuticals Using N-Chlorosuccinimide and Two Dyes' ACAIJ. (2007); 4(4-6): 96-103.
11. Borkar DD, Godse VP, Bafana YS, Bhosale AV. Simultaneous Estimation of Paracetamol and Promethazine Hydrochloride in Pharmaceutical Formulations by a RP-HPLC Method. International J. of ChemTech Research. (2009); 1(3) :667-670.
12. Jack E Wallace, Eugene L Shimek, Jr ,Steven C Harris, Salomon Stavchansky. Determinationof Promethazinein Serum by Liquid Chromatography. CLIN.CHEM. (1981); 27(2): 253-255.
13. Ping Liu, Sun Liang, Ben-Jie Wang, Rui-Chen Guo. Development and validation of a sensitive LC-MS method for the determination of Promethazine hydrochloride in human plasma and urine. European J. of Drug Metabolism and Pharmacokinetics.
(2009); 34 ( 3– 4): 177–184.
14. Jack E Wallace, Eugene L Shimek, Salomon Stavchansky, Steven C Harris. Determination of promethazine and other phenothiazine compounds by liquid chromatography with electrochemical detection. Anal. Chem. (1981); 53 (7): 960–962.
15. Sreenivasa R Vanapalli, Sivarama P Kambhampati, Lakshmi Putcha, David W A Bourne. A Liquid Chromatographic Method for the Simultaneous Determination of Promethazine and Three of Its Metabolites in Plasma Using Electrochemical and UV Detectors. J. of Chromatographic Science. (2001); 39:70-72.
16. Khaleda H Al-Saidi, Rana A Hammza. Spectrophotometric Determination of Promethazine Hydrochloride and Paracetamol in Pharmaceutical Tablets. J. of Al-Nahrain University. (2014); 17 (1): 14-23.
17. Daniel D, Gutz IGR. Flow injection spectroelectroanalytical method for the determination of promethazine hydrochloride in pharmaceutical preparations. Anal. Chim. Acta. (2003); 494(1-2): 215-224.
18. Abdol-Ali M, Emami K. Spectrophotometric Promethazine Hydrochloride Determination Using Bromcresol Green. J. of pharmaceutical sciences. (1983); 72(6): 704–705.
19. Dwi Nurahmanto. Development and validation of UV spectrophotometric method for quantitative estimation of Promethazine HCl in phosphate buffer saline pH 7.4. International Current Pharmaceutical J.. (2013); 2(8): 141-142.
20. Muhammad JS, Jamil Anwa. A new spectrophotometric method for the determination of promethazine–HCl from pure and pharmaceutical preparations. Talanta. (2005); 67(5): 869-872.
21. Nabil S Nassory, Shahbaz A Maki, Bashaer A AL-Phalahy. Preparation and Potentiometric Study of Promethazine Hydrochloride Selective Electrodes and
Their Use in Determining Some Drugs. Turk J Chem. (2008); 32 : 539 – 548.
22. Mohammed JH, Ahamed MS AL-Anbakey. New Chromogenic Reagent for the Spectrophotometric Determination of Chlorpromazine HCL in Aqueous Solutions and Pharmaceutical Formulations. International J. of Pharmacy and Pharmaceutical Sciences. (2013); 5(3): 606-611.
23. Mohammed JH, Thesis. A Comparative Analytical Studies on Methyl Dopa In Pharmaceutical Tablets.
( 2003).