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Determination of Micro Amounts of Promethazine Hydrochloride in Pure and Pharmaceutical Samples Using UV-visible Spectrophotometry

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Abstract: This study presents the development of a novel, facile, and overly sensitive spectrophotometric approach for quantifying promethazine hydrochloride (PRO) within its pharmaceutical formulations. The method capitalizes on an oxidative coupling reaction, achieved through the oxidation of the compound in an acidic milieu utilizing ammonium cerium (IV) sulfate dehydrate (Ce^{+4}) solution. This process leads to the creation of a green-colored solution, which, upon conjugation with 5-aminosalicylic acid, exhibits maximum absorption at a wavelength of 598 nm. The methodology investigated several parameters, encompassing oxidation duration, temperature, quantities of oxidizing agent and coupling reagent, and determining the stoichiometric ratio between promethazine hydrochloride and 5-aminosalicylic acid. The established ratio was confirmed to be 1:1. Numerous organic solvents were evaluated, with water emerging as the optimal choice due to its pronounced absorption characteristics at the 598 nm wavelength. The applicability of Beer's law was verified over a concentration range of 2 - 28 µg/mL of promethazine hydrochloride, with a calculated molar absorption coefficient of 1.9606 x 10^4 L/mol·cm. The Sandell sensitivity index was determined as 0.0164 µg/cm^2, while the relative standard deviation (RSD) ranged from 0.8553- 1.2671%. Notably, recovery percentages were also within the 99.88 – 100.34% range. The efficacy of this technique was effectively demonstrated through its successful application in the analysis of pharmaceutical formulations containing promethazine hydrochloride, employing the standard method as a benchmark.

Keywords: Spectrophotometric; Promethazine hydrochloride; 5-Aminosalicylic acid.

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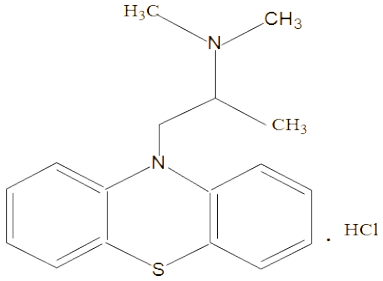
1. INTRODUCTION

As a neuroprotective antidepressant, promethazine hydrochloride belongs to the first generation of antihistamines in the phenothiazines pharmacological class (1). It is frequently utilized because of its sedative, antihistamine, antipsychotic, anticholinergic, and analgesic effects. On the other hand, Promethazine hydrochloride can affect humans by altering their reproductive, endocrine, and cardiac systems. Therefore, it is crucial to check for it in commercial and pharmaceutical formulations (2).

This medication treats respiratory allergies (such as allergic rhinitis), skin allergies, motion nausea, and as an analgesic before and after surgery. However, it is only a weak antipsychotic (i.e., schizophrenia). Because it has anti-emetic qualities, it is also used as an analgesic to treat post-operative vomiting. It

also treats eczema and itching in adults and children (3, 4). Promethazine hydrochloride has negative effects on the cardiovascular system, the central nervous system, the gastrointestinal tract, and the central nervous system, which include dry mouth, sleepiness, blurred vision, and dizziness (5). Take the medication 30 minutes before your trip to prevent dizziness. To avoid additional symptoms, take the tablets or drink them with food. You can also use the medication as a suppository (6).

Promethazine hydrochloride is easily dissolved in water, and Scheme 1 depicts its structural formula (7).



Scheme 1: The chemical structure of promethazine hydrochloride.

Promethazine hydrochloride has been measured using various analytical techniques due to the medication's therapeutic value, such as the ion-selective electrode, which relies on the drug and tetraphenyl boron (III) forming an ion pair (8).

The synthesis of ionic selective electrodes for promethazine hydrochloride with molybdophosphoric acid also involved the utilization of various plasticizers: dibutyl phthalate (DBPH), dibutyl phosphate (DBP), dioctyl phthalate (DOP), and tributyl phosphate (TBP) (9). Furthermore, the synthesis of a highly sensitive and selective electrode for promethazine incorporated the use of ammonium phosphomolybdate (10). Promethazine hydrochloride has been quantified utilizing a few flow injection techniques, such as continuous flow injection through the oxidation of the drug with sodium persulfate in an aqueous solution and the detection of colored cationic radicals produced using a home-made 3SX3-3D sun photometer (11). Promethazine hydrochloride was also measured using a 3SX3-3D solar cell microphotometer, and persulfate was trapped in water crystals using the flow/stop injection method (12). Additionally, promethazine was detected utilizing the flow injection approach with chemiluminescence, which was based on the Luminol-H_2O_2-Fe (III) system's merging region principle (13).

A mixture of water, methanol, and acetic acid (79:20:1 v/v/v) was employed as the eluting phase on a Kromasil Silica column with a detector of prominent diode array at 249 nm and a flow rate of 1 mL/min to estimate Promethazine hydrochloride using the RP-HPLC method (14). Promethazine hydrochloride was separated and quantified using a different HPLC technique on a column of Vancomycin Chirobiotic V (250 mm, 4.6 mm) utilizing methanol, acetic acid, and triethylamine as the mobile phase at a flow rate of 1 mL/min with a UV-detector at 254 nm (15).

Finally, several spectrophotometric techniques have been described for measuring Promethazine hydrochloride. Some of these techniques involve oxidizing Promethazine hydrochloride with iron (III), and the resulting iron (II) reacts with 1,10-phenanthroline at pH 3.01 to form a stable complex, giving a maximum absorption at 504 nm (16) or sodium hypochlorite in a medium of sulfuric acid to develop a pinkish-red product with maximum absorption (17). Additionally, when chromium trioxide was used as an oxidizing agent in an acidic solution to oxidize promethazine hydrochloride, the resultant product had the maximum absorption at 515 nm (18).

Promethazine hydrochloride was determined in pharmaceuticals by using p-amino benzoic acid as a coupling reagent in the presence of N-bromosuccinimide, and the reaction resulted in the production of a bluish-green product with maximum absorption at 603 nm (19). Promethazine hydrochloride was also determined in pharmaceuticals by using p-chloroaniline as a coupling reagent in the presence of ammonium cerium (IV) sulfate dehydrates as an oxidizing agent (20).

Another spectrophotometric method for measuring promethazine hydrochloride was used, and it was based on the formation of a colored ion-pair complex between promethazine hydrochloride and methyl blue dye in an acidic medium, which gave a maximum absorption of 480 nm (21); the resulting spectrophotometric method was also used for the measurement of Promethazine hydrochloride and paracetamol by using the zero-pass method, and (22). Additionally, metoclopramide hydrochloride

(23), hypochlorite in environmental samples (24), chloramphenicol (25), and procaine (26) have all been determined using methazine as a coupling reagent in addition to several pharmaceutical drugs in their pure form (27).

The study aims to present a straightforward spectrophotometric method for determining promethazine hydrochloride in its pharmaceutical and pure forms due to its significance in the medical field and its use in treating numerous diseases. This method involves oxidizing the drug with ammonium cerium (IV) sulfate dehydrate as an oxidant, then pairing it with 5-aminosalicylic acid as a coupling reagent. The process was successfully applied to identify Promethazine hydrochloride in pharmaceutical formulations.

2. EXPERIMENTAL

2.1 Apparatus used

The experiments were conducted using the following equipment: Shimadzu UV- Visible Spectrophotometer 1800, double beam, with quartz cells (1cm), water bath (Clifton), pH meters 3310 (Janeway), delicate balance type (Sartorius BL 210).

2.2. Chemical reagents and materials used

The Pharmaceutical and Medical Supplies Company-SDI, Samarra, Iraq, provided the promethazine hydrochloride (pure standard powder), and Fluka and Sigma-Aldrich provided all other analytical chemical reagents (5-aminosalicylic acid, ammonium cerium (IV) sulfate dehydrate, sulfuric, nitric, hydrochloric, acetic, and phosphoric acids, phenergan injection, histazine syrup, and organic solvents) that were of the highest possible quality. Each solution was made from scratch with distilled water.

2.2.1 The parent solution, 250µg/mL

Promethazine hydrochloride was dissolved in 1.0 g of distilled water, and a 100 mL volumetric flask was used to add more distilled water to create a parent solution of the medication (1000 µg/mL). Transferring 25 mL of the parent solution into a volumetric flask (100 mL), adding distilled water to the mark, and shielding it from light by placing it in a darkened bottle were the steps needed to create the working solution (250 µg/mL), which is the concentration utilized in the suggested approach.

2.2.2. 5-aminosalicylic acid solution (1×10^{-2}M)

To get the appropriate concentration, 0.1531 g of 5-aminosalicylic acid powder was dissolved in 10 mL of ethanol, and the volume was then increased to 100 mL in a volumetric flask with distilled water.

2.2.3 Ammonium cerium (IV) sulfate dehydrate solution(2×10^{-2}M)

Ammonium cerium (IV) sulfate dehydrate powder ($Ce(NH_4)_4(SO_4)_4.2H_2O$)weighing 1.2651 g is dissolved in a suitable volume of distilled water, and the volume is then filled with 100 mL distilled water.

2.2.4 Sulfuric acid solution (1.5 M (

In a 100 mL volumetric flask, a precise 8.20 mL of concentrated sulfuric acid (18.29 M) was added to a certain amount of distilled water. The volume was then brought to the target using the same solvent.

2.2.5 Pharmaceutical solutions

2.2.5.1 Phenergan injection solution 250 µg/mL

Phenergan is available as a 2 mL injection with a promethazine HCl dosage of 2.5 percent.

This solution was created by adding one injection of 2 mL to a volumetric flask (100 mL) and filling the remaining space with distilled water to the top to create a preparation solution with a concentration of 500 µg/mL. then 50 mL of the above solution was diluted with distilled water to 100 mL to make one with a concentration of 250 µg/mL.

2.2.5.2 Histazine syrup solution 250 µg/mL

Each 5 mL of the histazine preparation, which is made by the United Company for Pharmaceutical Industries and Medical Supplies in Amman, Jordan, contains 5 mg Promethazine hydrochloride, and the solution was made by adding 50 mL of this composition to a volumetric flask (100 mL) and filling the volume to the mark with distilled water to get a solution with a 500 µg/mL concentration, then 50 mL of the above solution was diluted to 100 mL with distilled water to obtain a concentration of 250 µg/mL.

Photograph 1: Left, Phenergan injection solution 250 µg/mL; right, Histazine syrup solution 250 µg/mL.

3. PRELIMINARY STUDY

Promethazine hydrochloride is first oxidized in an acidic medium with the help of an oxidizing agent (ammonium cerium (IV) sulfate dehydrate). Then, the product is combined with the 5-aminosalicylic acid reagent, producing a green solution with maximum absorption at 598 nm compared to the blank solution.

3.1 Calibration curve with its statistical data

Using the ideal conditions described in the general approach above, the following were used to construct a titration curve for Promethazine hydrochloride: - For a set of volumetric flasks (25 mL), different volumes (0.2-2.8 mL) of promethazine hydrochloride (250 µg/mL) were taken as represented (2.0 - 28.0 µg/mL). To complete the oxidation reaction and stabilize the generated product, 2.0 mL of reagent (1 x 10^{-2} M), 1.2 mL of an oxidizing agent (2 x 10^{-2} M), and 1.8 mL of sulfuric acid solution (1.5 M) were added and left for 15 minutes.

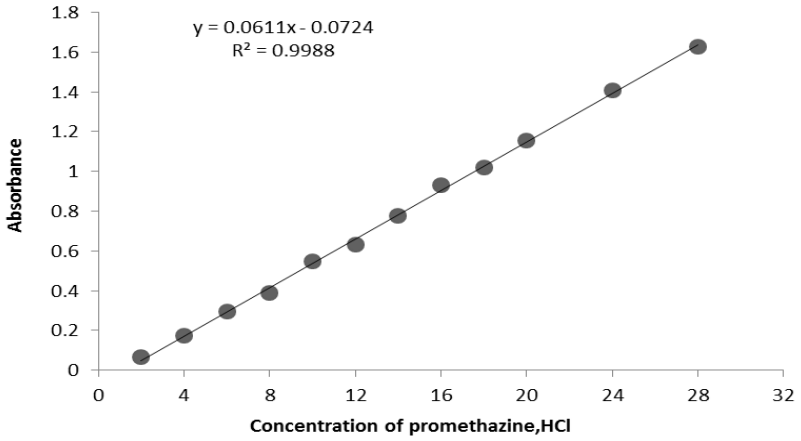


Figure 1: Promethazine calibration curve.

The components in each standard flask were diluted to the mark with distilled water, and the absorbance of each solution was measured against a reagent blank produced in the same manner but without promethazine hydrochloride. By plotting absorption versus concentration, it was discovered that Beer's law obeys a concentration range of 2-28 µg/mL with a correlation coefficient of 0.998 and that the molar absorbance value of the green color product was 1.9606 x 10^4 L/mol.cm and the Sandell's sensitivity index was 0.0164 g/cm^2, Figure 1.

3.1.1 The proposed method's precision and accuracy

The proposed method's efficiency was statistically assessed (accuracy and precision measurement) by measuring the absorbance of two distinct concentrations of promethazine HCl placed within the Beer-Lambert limits at 598 nm. The results shown in Table 1 demonstrate that the procedure is effective and satisfactory.

Table 1: The accuracy and precision results

RE%	Average recovery%	Recovery*%	RSD%	Conc. of PRO µg/mL
-0.12	100.11	99.88	1.2671	4
0.34		100.34	0.8553	6

* Average of five determinations

3.1.2 Study of LOD& LOQ

The drug's limit of detection (LOD) was calculated by determining the lowest detectable concentration of the analyte (LOD = 3.3 B / S). The drug's quantification limit (LOQ) was calculated by determining the lowest detectable concentration (LOQ = 10B / S), where S represents the slope of the standard curve, and B represents the standard deviation of the blank reagent (28).

Table 2 summarizes the LOD and LOQ results for the current approach, which include critical features in the analysis such as Beer's law concentration range, molar absorption coefficient, Sandell's sensitivity, LOQ, LOD, slope, R, RSD, and RE.

Table 2: A summary of analytical quantitative properties and statistical data of the coupling reaction of promethazine hydrochloride with 5-amino salicylic acid reagent.

Statistical values	Analytical quantitative parameters
1.9606×10^4	Molar Extinction Coefficient (liter/mol.cm)
2 - 28	Beer's law range (µg/mL)
0.0164	Sandell's sensitivity (µg/cm^2)
0.0611	Slope
0.0724	Intercept
0.876489	LOD (µg/mL)
2.92163	LOQ (µg/mL)
-0.12 – 0.34	Range of relative error*(%)
0.8553- 1.2671	RSD* (%)
100.11	Average recovery*(%)
70	stability of formed product (min.)

* Average of five determinations

3.2. 10 study the stoichiometry of the analytical reaction

Two approaches were used to determine the chemical stoichiometric ratio of the coupling product under optimal working conditions (continuous variation and molar ratio). Equal concentrations of drug and reagent (7.79×10^{-4}M) were created using these two procedures. In the first method (continuous variation), increasing amounts of drug solution (1.0 -9.0 mL) and decreasing amounts of reagent solution (9.0 - 1.0 mL) were placed in a series of volumetric flasks (25 mL), then the optimum amounts of the remaining additives were added and diluted with distilled water to the mark. At 598 nm, the solutions' absorbance was measured compared to their blank solutions. The results confirmed that the chemical stoichiometric ratio of the coupling product was created in a 1:1 ratio when promethazine HCl was combined with a 5-aminosalicylic acid reagent, as shown in Figure 2 (29).

The second method (molar ratio) was used to ensure that the chemical ratio of the reaction between the promethazine HCl and the 5-aminosalicylic acid reagent is 1:1. The technique was implemented by adding increasing volumes of the reagent (0.25- 4.50 mL) to a few volumetric flasks (25 mL) holding a fixed volume (2 mL) of the drug, then the remaining additives are supplemented according to optimal conditions. The solutions were diluted to the proper volume with distilled water, and the absorbance at 598 nm was measured in comparison to the respective blank solutions. The second method (molar ratio) was used to ensure that the chemical ratio of the reaction between the promethazine HCl and the 5-aminosalicylic acid reagent is 1:1. The method was implemented by adding increasing volumes of the reagent (0.25- 4.50 mL) to a few volumetric flasks (25 mL) holding a fixed volume (2 mL) of the drug, then the remaining additives are supplemented according to optimal conditions. The solutions were diluted to the proper volume with distilled water, and the absorbance at 598 nm was measured compared to the respective blank solutions. It was discovered that the method complies with the continuous variation method, and Figure 3 demonstrates that the ratio is 1:1 in the two methods (29).

The proposed form of the oxidative coupling reaction created by promethazine hydrochloride (PRO) with the 5-aminosalicylic acid reagent in the presence of ammonium cerium (IV) sulfate dehydrate as the oxidizing agent is illustrated below based on the results reported in Figures (2,3).

4. RESULTS AND DISCUSSION

4.1 The final UV- Visible spectra

After achieving optimal conditions, UV-Vis spectrophotometry of the compound formed by the reaction of 5-aminosalicylic acid reagent with promethazine hydrochloride in the presence of ammonium cerium (IV) sulfate dehydrate as an oxidizing agent in a dilute acidic medium of sulfuric acid was performed to obtain a maximum absorption at 598 nm against the blank reagent, which does not absorb in this region. The final absorption spectra of the generated, green-colored complex against the blank reagent are depicted in Figure 4.

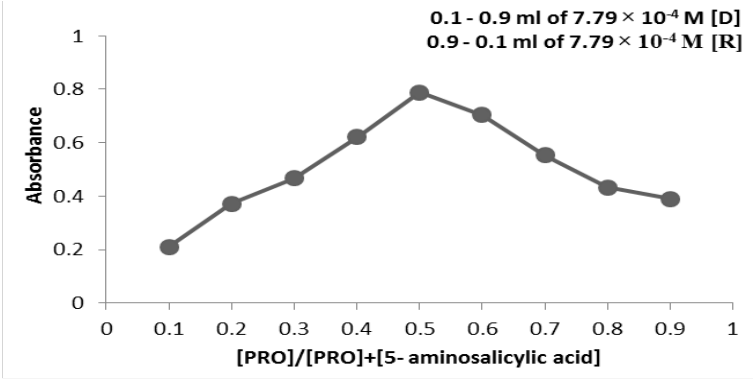


Figure 2: Continuous variation diagram of coupling product: promethazine hydrochloride - 5-aminosalicylic acid.

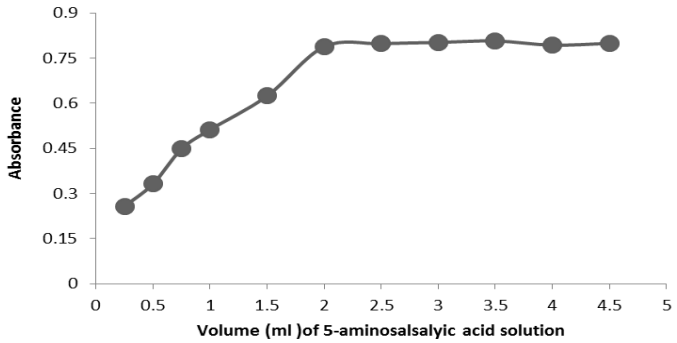


Figure 3: Molar ratio diagram of coupling product: promethazine hydrochloride - 5-aminosalicylic acid

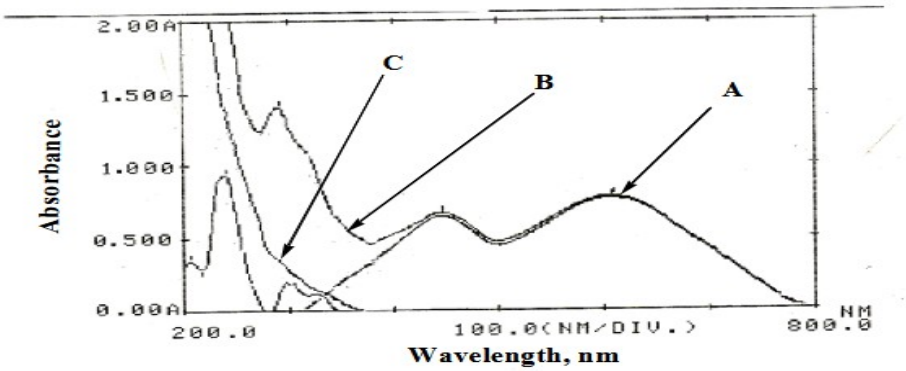


Figure 4. The ultimate absorption spectrum A = resulting complex versus the blank solution B= resulting complex versus the distilled water C= the blank solution versus distilled water

4.2 Optimal Experimental Variants

The green color changes depending on the parameters of the coupling reaction. As a result, it is critical to optimize the reaction conditions by investigating the various elements that influence the absorption of the green-colored product by adjusting one factor while keeping the other constant at 598 nm versus the blank reagent solution.

4.2.1 Choice of the most appropriate acid

In this study, different concentrations (0.25 - 1.5 M) of strong and weak acids (1.0 mL) were used, including sulfuric, nitric, hydrochloric, acetic, and phosphoric acids to determine the effect of acid type and concentration on the absorption of the green product, with sulfuric acid (1.5 M) chosen as the best acid because it gave the maximum absorption of the product at 598 nm, as shown in Table 3.

Table 3: Acid type effect.

Type of acid (1.0 mL)	Absorbance			
1.5 M	1.0 M	0.5 M	0.25 M	
0.645	**0.603**	**0.458**	**0.352**	**H_2SO_4**
0.287	0.265	0.248	0.225	HNO_3
0.585	0.521	0.436	0.358	HCl
0.147	0.126	0.119	0.103	CH_3COOH
0.079	0.063	0.057	0.029	H_3PO_4

4.2.2 Study the influence of the acid function

After selecting the optimal acid and maintaining its concentration, the pH influence was investigated using several amounts of sulfuric acid ranging from (0.3 - 3.0 mL) (1.5 M). According to Table 4, 1.8 mL of this acid was enough to complete the reaction, and it was thus recommended for future research.

Table 4: Influence of the acid function

pH	Absorbance	Volume of H_2SO_4 (1.5M)
3.3	0.415	0.3
3.1	0.537	0.5
2.9	0.608	0.8
2.7	0.645	1.0
2.4	0.721	1.3
2.1	0.738	1.5
1.7	**0.755**	**1.8**
1.4	0.725	2.0
1.2	0.611	2.5
1.1	0.569	3.0

4.2.3 Effect of the amount of Ammonium cerium (IV) sulfate dehydration

During the testing to determine the most appropriate oxidizing agent, ammonium cerium (IV) sulfate dehydrate was discovered as an acceptable oxidizing agent. It was used in the coupling reaction of promethazine hydrochloride with 5-aminosalicylic acid, and the influence of different quantities (0.2 - 2.6 mL) of 0.02 M ammonium cerium (IV) sulfate dehydrate solution was tested. Figure 5 showed that 1.2 mL of ammonium cerium (IV) sulfate dehydrate solution was the ideal amount for obtaining the maximum absorption at 598 nm; hence, it was recommended for use in the following research.

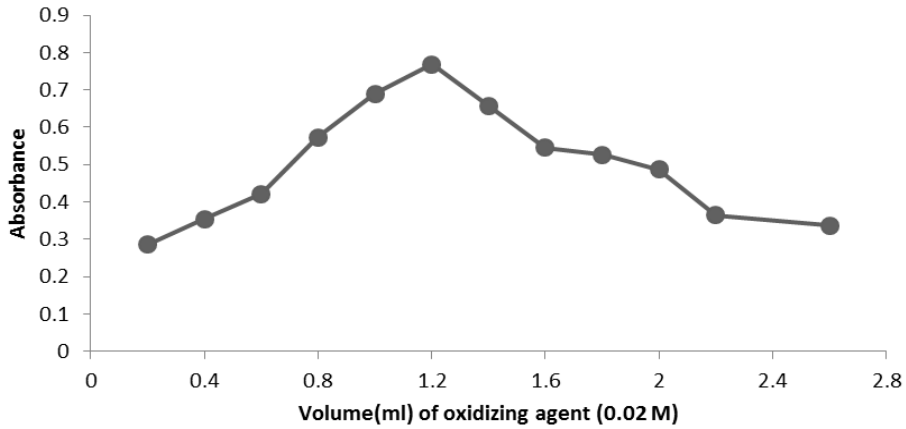


Figure 5: Effect of oxidizing agent volume

4.2.4 Effect of the amount of 5-aminosalicylic acid reagent

Following multiple testing of several conjugation reagents, including 4-chloroaniline, pyrocatechol, 5-aminosalicylic acid, and meta-

aminophenol, the best reagent was determined to be 5-aminosalicylic acid. The best volume of the 5-aminosalicylic acid reagent was then determined by experimenting with various amounts (0.250-4.000 mL) of (0.01 M) 5-aminosalicylic acid reagent. Due to the maximum absorption at 598 nm, a volume of 2.00 mL of reagent was adequate for developing the green hue of the produced product. As a result, it was used in the following investigations, as shown in Figure 6.

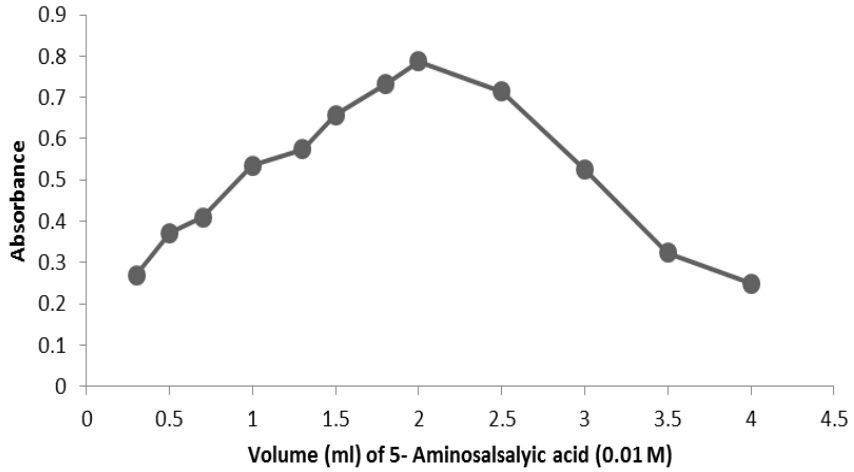


Figure 6: Effect of 5-aminosalicylic acid volume.

4.2.5 Effect of oxidation time and stability on the coupling reaction

The influence of oxidation duration on the period of color development and the stability of the created product was investigated, and the analytical data presented in Figure 7 revealed that the formed product requires 15 minutes to achieve maximum absorption and remains stable for around 60 minutes.

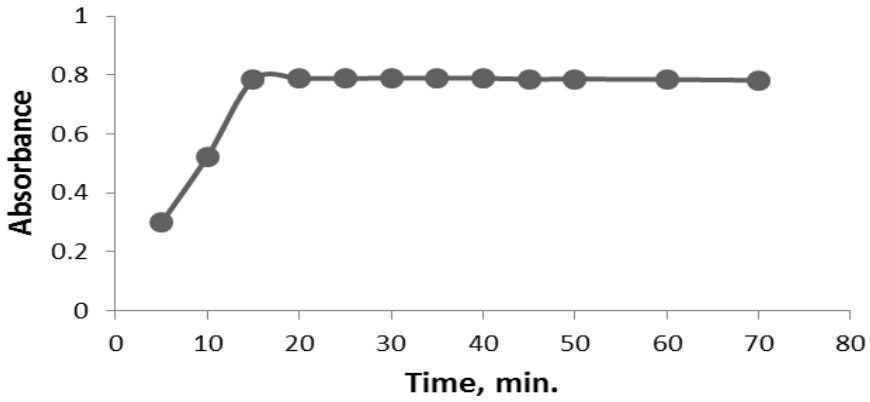


Figure 7: Effect of oxidation time.

4.2.6 Effect of temperature on the oxidative coupling reaction

The effect of temperature on coupling product absorption was investigated. In actuality, the color is created at room temperature (25°C); hence, it is recommended that the reaction be performed at room temperature because the absorbance value decreases at higher temperatures, indicating product dissociation, Figure 8.

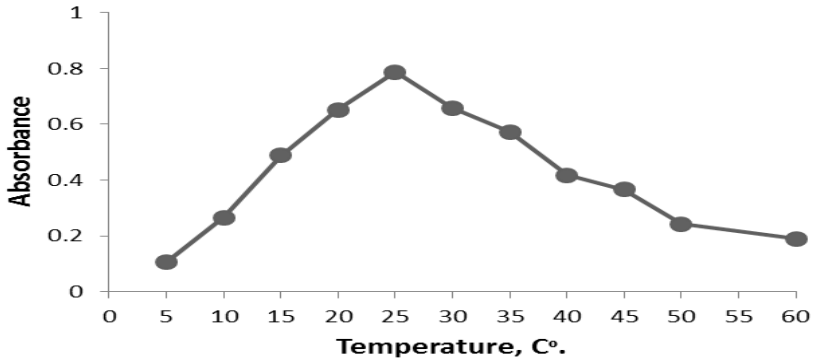


Figure 8: Effect of temperature.

4.2.7 Effect of the order of adding materials

Table 5: *Effect of the order of additions*

Absorbance	Order of addition	Order number
0.316	PRO + R + Ox + A	i
0.571	PRO + Ox + A + R	ii
0.788	**PRO + Ox + R + A**	**iii**
0.165	PRO + R + A+ Ox	iv
0.209	PRO +A + Ox + R	v
0.075	PRO + A+ R+ Ox	vi

A series of experiments were undertaken with a series of different additives according to the optimal circumstances and quantities discussed above to clarify the effect of the components sequencing addition on the absorption of the green product. The solutions' absorption was then measured compared to the blank solution.

Table 5 demonstrates that configuration (iii) is the correct layout for the coupling reaction, as used in future research.

Where:(PRO) promethazine hydrochloride solution, (R) 5-aminosalicylic acid solution, (Ox) ammonium cerium (IV) sulfate dehydrate solution, and (A) hydrochloric acid solution.

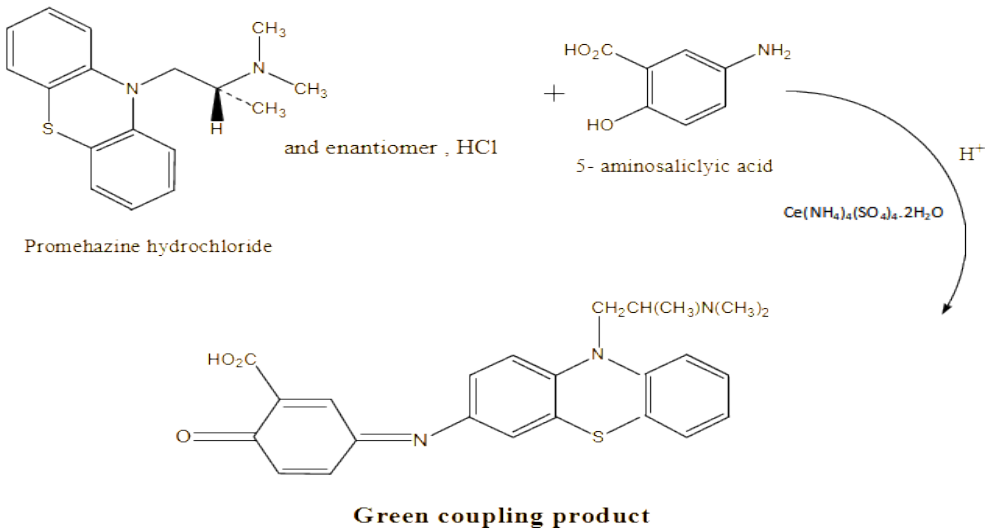
4.2.8 Effect of solvent types

Since dilution was done using these solvents rather than water, the influence of different organic solvents on coupling product absorption was investigated. The results in Table 6 clearly reveal that water is the best solvent because it showed the maximum absorption of the resultant solution at the wavelength of 598 nm when compared to the solvents employed; hence, it was chosen as a solvent in the following tests.

Table 6: The effect of different solvents.

Organic solvent	Acetone	CH_3OH	C_2H_5OH	$CHCl_3$	DMSO	Water
Abs	0.379	0.324	0.571	0.455	0.453	**0.788**
λ_{max}, nm	558	567	598	598	556	**598**

Based on the results presented in Figures (2,3) and in the sequence of additions, the proposed form of the oxidative coupling reaction formed by promethazine hydrochloride with 5-aminosalicylic acid reagent in the presence of ammonium cerium (IV) sulfate dehydrate as the oxidizing agent is shown below:



Scheme 2: Proposed chemical reaction between 5-aminosalicylic acid reagent and promethazine hydrochloride.

4.2.9 Proposed method applications to pharmaceutical preparations

Through the application of the standard addition method, the applicability of the proposed method has been successfully studied to examine several commercially available pharmaceutical preparations containing promethazine hydrochloride, as well as to know their efficacy, accuracy, and freedom from additives interference, Figures (9,10), Table 7.

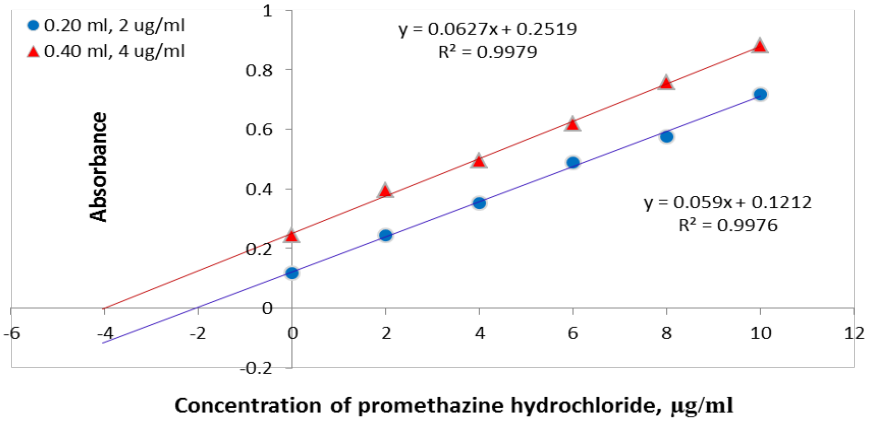


Figure 9: Standard addition procedure for promethazine hydrochloride in Phenergan injection

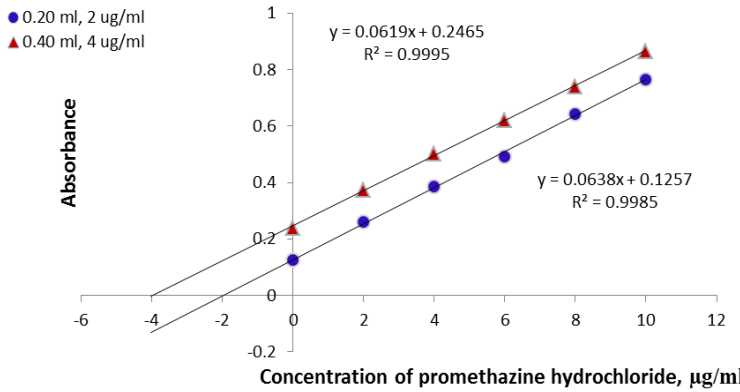


Figure 10: Standard addition procedure for promethazine hydrochloride in histazine syrup.

Table 7: Analytical results for determining promethazine hydrochloride in pharmaceutical formulations

Average content of the drug	Recovery*,%	PRO measured µg/mL	PRO present µg/mL	Pharmaceuticals used
101.58	102.7	2.054	2.000	**Phenergan injection**
	100.45	4.018	4.00	
99.025	98.50	1.970	2.00	**Histazine syrup**
	99.55	3.982	4.00	

* Average of five determinations.

The analytical results of the current method were compared with the official method using the F-test and the T-test, and the analytical results obtained showed no statistically significant differences, indicating that the current method can be used as an alternative method for determining promethazine hydrochloride in pure form and doses.

The current method was statistically evaluated by comparing it to the official method. It was discovered that the computed t value (0.258) is less than the tabulated t value (2.571) at a 95 percent confidence level for five degrees of freedom for PRO. The calculated F value (1.211) is less than the tabulated value (5.05) at a 95 percent confidence level for five degrees of freedom for promethazine hydrochloride. Statistical evaluation, T-test, and F-test results show that the present approach is reliable, and there is no discernible difference between the two ways because the present method is virtually additive-free.

5. CONCLUSIONS

The low value of comparative standard deviation and high value of recovery indicate that the colorimetric method used to assess the amount of promethazine hydrochloride is accurate and precise. The analytical results demonstrated that the innovative approach is simple, accurate, and appropriate for measuring the quantity of promethazine hydrochloride in pharmaceutical formulations, and it has also been used successfully to evaluate promethazine hydrochloride in pure and medicinal dosages (Phenergan injection and histazine syrup). Practically, it has been discovered that the main advantage of this method is that it is inexpensive and can save a significant amount of time and money when compared to HPLC and other modern technologies. Furthermore, this approach makes use of simple and commonly available chemicals to determine the promethazine hydrochloride formulation in pure and medical items without the need for special working conditions such as the use of expensive organic solvents, elevated temperatures, or extraction. The current procedure proved that additives (glucose, lactose, talc, sucrose, and starch) have no effect on the findings of the determination achieved under optimal conditions.

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