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Spectrophotometric determination of Chlorpromazine Hydrochloride by oxidative coupling reaction with P-Bromo aniline using Ammonium Ceric Sulphate Dihydrate

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ABSTRACT

A new sensitive spectrophotometric method for the determination of chlorpromazine hydrochloride (CPZH) was developed. The method is based on an oxidative coupling reaction with p-bromoaniline using ammonium ceric sulphate dihydrate as oxidizing agent to produce a violet color, soluble in water, stable product and absorbs at 553 nm. Beer's law was in the linear range 2.5 - 30 µg/ml of CPZH, the molar absorptivity, Sandell's sensitivity index and detection limit were 6.5731 × 10^3 liter. $mol^{-1}.cm^{-1}$, 0.0541 $\mu g.cm^{-2}$ and 0.1361 µg/ml respectively. The RSD value was 1.20 - 1.36 % depending on the concentration. This method was applied successfully to the determination of chlorpromazine hydrochloride in two pharmaceutical formulations (tablets and injection).

Keywords: *spectrophotometric, CPZH, p-bromoaniline.*

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التقدير الطيفي للكلوربرومازين بوساطة تفاعل الازدواج التأكسدي مع بارا–بروموانيلين بوجود كبريتات السيريوم الامونياكية

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الملخص

يتضمن البحث تطوير طريقة طيفية حساسة لتقدير عقار هيدروكلوريد الكلوربرومازين، الطريقة تستند على تفاعل الازدواج التأكسدي مع الكاشف بارا– بروموانيلين باستخدام العامل المؤكسد كبريتات السيريوم الامونياكية لتكوين ناتج بنفسجي اللون ذائب في الماء ويعطي أعلى امتصاص عند الطول الموجي ٥٥٣ نانوميتر. كانت حدود قانون بير في مدى التراكيز ٢.٥– ٣٠ مايكروغرام/مل من هيدروكلوريد الكلوربرومازين. والامتصاصية المولارية 6.5731 × $١٠^{٣}$ لتر.مول$^{-١}$.سم$^{-١}$ ودلالة ساندل ٠.٠٥٤١ مايكروغرام .سم$^{-٢}$. وتراوحت قيمة الانحراف القياسي النسبي 1.20 – 1.36 % ، وحد كشف ٠.١٣٦١ مايكروغرام/مل. تمّ تطبيق هذه الطريقة بنجاح لتقدير هيدروكلوريد الكلوربرومازين في المستحضرات الصيدلانية حبوب وحقن.

الكلمات الدالة: الطريقة الطيفية، هيدروكلوريد الكلوربرومازين، بارا–بروموانيلين.

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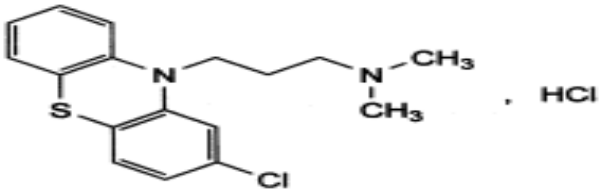
١. Introduction

The scientific name for the chlorpromazine hydrochloride (CPZH) is[1]: 3-(2-Chloro-10*H*-phenothiazin-10-yl)-*N*,*N*-dimethylpropan-1-amine hydrochloride.

The chemical structure is:



$C_{17}H_{19}ClN_2S,HCl$

M. wt = 355.3g/mol

Chlorpromazine hydrochloride (CPZH), white or almost white, crystalline powder, very soluble in water, freely soluble in ethanol. It decomposes on exposure to air and light[1]. Chlorpromazine is a psychiatric medication that belongs to the class of drugs called phenothiazine antipsychotics, it works by helping to restore the balance of certain natural substances in the brain[2]. It is used to treat various problems such as severe depression or behavioural disturbances and it is used to treat schizophrenia[3] and it also used to treat nausea, vomiting, severe pain, relieve prolonged hiccups, relieve restlessness/anxiety before surgery, and help treat tetanus[4]. side effects of chlorpromazine, HCl is low heat and drowsiness and nasal congestion and difficulty in urination and other side effects of low blood pressure and accelerated heart rate (in the case of intramuscular injection)[5].

Different analytical methods have been used for the determination of CPZH such as spectrophotometric methods[6-17], HPLC[18-24], gas chromatography[25-27],flow-injection techniques[28-34] and electrochemical method[35-36].

Aim of research

In this research a rapid, sensitive and simple spectrophotometric method for determining of chlorpromazine hydrochloride **(**CPZH) in pure form as well as in pharmaceutical formulations based on the oxidative coupling using p-bromoaniline in presence of ammonium ceric sulphate dihydrate.

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2. Experimental

Apparatus

The apparatuses used shown in the Table (١).

Table (1): Apparatuses used by origin.

No.	Apparatus used by origin
1	Shimadzu UV/VIS 160 spectrophotometer, Japan
2	pH meter UK Jenway 3310
٣	Sartorius BL210 S AG Germany
٤	Ultrasonic with water bath, power sonic 410 Lab tech Korea
5	Hot Plate with Magnetic Stirrer (BIOSAN MSH 300

Reagents and chemicals used

All chemicals and analytical reagents used in this research are high purity and shown in the Table (2).

Table (2): Reagents and materials chemistry used.

Chemicals	Chemical structure	Company
Chlorpromazine, HCl	$C_{17}H_{19}ClN_2SHCl$	SDI
Ammonium ceric sulphate dihydrate	$Ce(NH_4)_4(SO_4)_4.2H_2O$	Fluka
p-Bromoaniline	H_2SO_4	BDH
Sulphuric acid	C_6H_6BrN	BDH
Sodium hydroxide	NaOH	BDH

Preparation of solutions[37]

1-Standard CPZH solution,250 µg/ml

This solution is prepared by dissolving 0.025 g of CPZH in amount of distilled water and the volume is diluted to 100 ml with distilled water in a volumetric flask. This solution is kept in a brown bottle, where it is stable for one week, at least.

2- P- bromoaniline reagent solution (1×10^{-2}M)

This solution is prepared by dissolving 0.1720m g of p-bromoaniline in 5 ml of ethanol and the volume is completed to 100 ml in a volumetric flask with distilled water.

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٣- Ammonium ceric sulphate dihydrate solution (1×10^{-2}M)

A ٠.٦٣٢٥ g of ammonium ceric sulphate dehydrate (Ce^{+4}) is dissolved in amount of distilled water and the volume is completed to 100 ml in a volumetric flask with distilled water.

٤-Sodium hydroxide solution (approximate,0.1 M)

This solution is prepared by dissolving 4.000 g of pure sodium hydroxide in100 ml of distilled water.

5- Sulphuric acid solution(approximate,0.1M)

This solution is prepared by appropriate dilution of 0.5 ml of the concentrated sulphuric acid (18.289 M) solution to 100 ml with distilled water in a volumetric flask.

٦- Interference solutions 1000 µg/ml

A 0.1000 g of each foreign compounds is dissolved in distilled water then the volume is completed to 100 ml in a volumetric flask with distilled water.

7-Solution of CPZH tablets formulation (250 µg/ml)

Largactil Chlorpromazine –HCl (100mg), Oubari Pharma - Aleppo-Syrie, every tablet contains 100 mg of CPZH and the solution is prepared as follows:

Ten tablets are weighed (4.1649g) and powdered well, then a weight of 0.1041 g of this powder is dissolved in an amount of distilled water, and then the solution filtered by paper filtration (604, RUNFILTER, Q240 mm), the volume is completed with distilled water in a volumetric flask of 100 ml , which gives the concentration of 250 µg/ml.

8- Solution of CPZH injection formulation (25٠µg/ml)

Largactil Chlorpromazine –HCl (25mg/5ml), Oubari Pharma – Aleppo - Syrie, each injection contain of 25 mg of chlorpromazine and this solution is prepared by transferred of 50 ml of this formulation to volumetric flask and the volume was completed to 100 ml with distilled water to obtain a solution with a concentration of 250 µg/ml.

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Preliminary Investigations

A 1.0 ml of p-bromoaniline reagent is added to 2.0 ml of standard CPZH solution in the presence of 0.5 ml of ammonium ceric sulphate dehydrate(Ce^{+4}) solution and diluted with distilled water in a 25 ml volumetric flask, a violet color product. Absorption spectrum of the colored dye against its corresponding blank reagents shows maximum absorption at 55٣nm in contrast to blank reagent which shows no absorbance at this wavelength.

3. Results and Discussion

Optimization of the experimental conditions

To establish the optimum conditions, the effect of various variables on the intensity of the absorption was studied by adding ٢.0 ml of standard CPZH solution (250µg/ml),1.0 ml of p-bromoaniline and 0.5ml of Ce^{+4} and measuring the absorption at 553 nm versus the blank reagent.

Effect of acid

The effect of acid was studied by adding 0.5-3.5 ml of strong acids and weak acids (0.1 M). the results showed the H_2SO_4 solution gives a higher absorption for colored product at a wavelength of 553 nm compared with other acids used , so this acid was chosen in subsequent experiments. the results are shown in Table (3).

Table (3): Effect of acid

Acid (0.1M)	ml of Acid /Abs.							
	With out	0.5	1	1.5	2	2.5	3	3.5
H_2SO_4	0.275	0.397	0.425	0.43١	0.445	0.428	0. 3٨٤	0.36١
HNO_3	0.275	٠.22٣	٠.٢3٦	٠.٢5٤	٠.293	٠.٣1٥	٠.٢٨٤	٠.٢٤٢
HCl	0.275	0.166	٠.183	٠.219	٠.241	٠.٢46	٠.٢٣١	٠.١٢٤
CH_3COOH	0.275	0.083	0.096	0.105	0.117	0.112	0.073	0.051

The results shown in the Table (3) indicate that the volume of 2.0 ml (0.1M) of sulfuric acid (pH= 1.8) is the optimum amount because of highest absorbance, so it was used in subsequent experiments.

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Effect of the amount of oxidizing agent

This study was conducted to select the best amount of oxidizing agent (Ce^{+4}) (1×10^{-2} M) by adding different volumes (0.3-2.5 ml) of oxidizing agent to volumetric flasks containing 2.0 ml of CPZH (250 µg/ml) and 1.0 ml of the reagent solution (1×10^{-2}M), then addition of 2.0 ml of 0.1 M sulfuric acid and the volume was completed to 25ml with distilled water, the results are shown in Table (4).

Table (4): Effect of the amount of oxidizing agent.

ml of Ce^{+4} (1×10^{-2}M)	0.3	0.5	0.7	1.0	1.2	1.5	1.7	2.0	2.5
Absorbance	0.337	0.445	0.458	0.473	0.441	0.326	0.273	0.246	0.216

The results shown in the Table (4) indicate that the volume of 1.0 ml of (Ce^{+4}) (1×10^{-2}M) is the optimum amount because of highest absorbance, so it was used in subsequent experiments.

Effect of the amount of coupling reagent

The effect of the amount of coupling reagent was studied by adding different volumes (0.3-2.5ml) of p- bromoaniline reagent (1×10^{-2} M) to the volumetric flasks containing 2.0 ml of CPZH (250µg/ml) and 1.0 ml of the (Ce^{+4}) (1×10^{-2}M), then the addition of 2.0 ml of 0.1 M sulfuric acid and the volume is completed to 25ml with distilled water, the results are shown in Table (5).

Table (5): Effect of the amount of coupling reagent.

ml of p-bromoaniline (1×10^{-2}M)	0.3	0.5	0.7	1.0	**1.2**	1.5	1.7	2.0	2.5
Absorbance	0.359	0.416	0.451	0.474	**0.485**	0.481	0.473	0.452	0.436

It is clear that the volume of 1.2 ml of coupling reagent (1×10^{-2}M) is the optimum amount because it gave the highest absorption. So it is adopted in subsequent experiments

Effect of oxidation time

To a series of volumetric flasks, each containing 2.0 ml of CPZH (250 µg/ml), 1.0 ml of (Ce^{+4}) (1×10^{-2}M) and the solutions were left for different periods of time, then 1.2 ml of p-bromoaniline reagent (1×10^{-2}M) and 2.0 ml of 0.1 M sulfuric acid solution were added. The volume was completed to 25ml with distilled water, and the absorption of solutions was measured at a wavelength of 553 nm versus blank, the results are shown in Table (6).

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Table (6): Effect of oxidation time.

Time(min)	5	10	15	20	25	30	35	40	45	50
Absorbance	0.429	0.467	0.486	0.485	0.485	0.483	0.482	0.481	0.479	0.479

Table (6) shows that 15 min is sufficient for the oxidation to be completed , so it is adopted in the subsequent experiments**.**

Effect of temperature

The effect of temperature(5-60°C) on the absorption of the formed colored product were studied by using 2.0 ml of CPZH solution (250µg/ml) and 1.0 ml of (Ce^{+4}) (1×10^{-2}M), then 1.2 ml of p-bromoaniline reagent (1×10^{-2}M) and 2.0 ml of 0.1 M sulfuric acid solution were added, then the volume is completed to 25 ml with distilled water in a volumetric flasks, and the absorption was measured at a wavelength of 553 nm versus blank reagent, the results are shown in Table (7). The optimum temperature is 25°C , so it is adopted in the subsequent experiments

Table (7): Effect of temperature.

Temp (°C)	5	10	15	20	25	30	35	40	45	50	60
Absorbance	0.294	0.329	0.٣86	0.40٩	0.485	0.483	0.467	0.385	0.311	0.269	0.175

Effect of time on stability of the colored product

The stability time of the formed colored product was studied by taking ٢.0 ml of CPZH (250 µg/ ml) with addition 1.0 ml of (Ce^{+4}) (1×10^{-2}M) and the solution is left for 15 min for oxidation, then 1.2 of p-bromoaniline (1×10^{-2} M) and 2.0 ml of 0.1 M sulfuric acid solution were added,the volume is completed to 25 ml in a volumetric flasks with distilled water. It is observed that the absorption becomes constant directly after dilution and remain unaltered for ٦0 min. The results are shown on Table (8).

Table (8): Effect of time on stability of the colored product.

Time (min.)	Direct mixing time	5	10	15	20	25	30	35	40	45	50
Absorbance	0.485	0.484	0.485	0.385	0.485	0.486	0.485	0.484	0.484	0.483	0.482

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Effect of the solvents

The effect of the solvents on the formed colored product was studied, the dilution was carried out by different organic solvents instead of water. The results shown in Table (9) indicate that the water is a good medium for reaction and gives good absorption value at the wavelength of 553nm and due to its availability, it was used as the best solvent in the subsequent experiments.

Table (9): Effect of the solvents.

Solvent	Water	Acetone	DMSO	Methanol	Ethanol
Absorbance	0.485	0.426	0.257	0.195	0.216
λ_{max}, nm	553	551	552	555	551

Final absorption spectrum

The spectrum of the formed colored product by coupling of CPZH with p-bromoaniline (1×10^{-2}M) in the presence of Ce^{+4} (1×10^{-2}M) in acidic medium (pH 1.8) and temperature 25°C against its corresponding reagent blank show a maximum absorption at 553 nm in contrast to the blank reagent of zero absorbance at λ_{max}. The spectra are shown on Fig. (1).

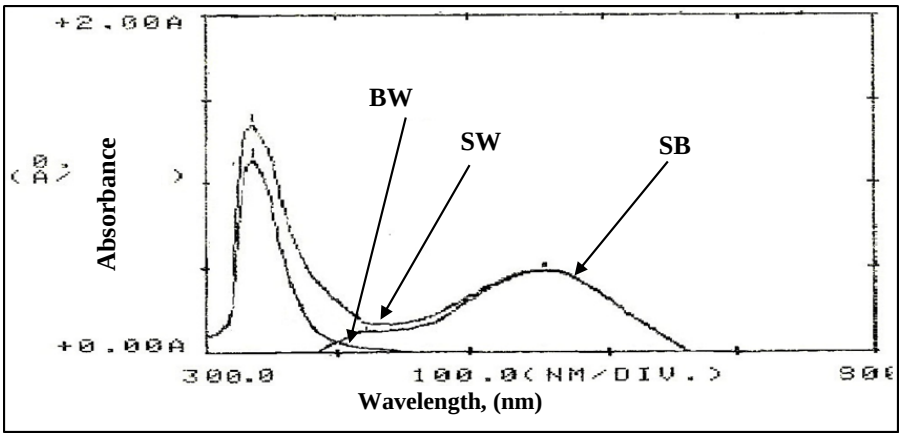

Fig.(1): Final absorption spectrum of the determination CPZH.

SB : Absorption spectrum of CPZH solution versus blank reagent.

SW: Absorption spectrum of CPZH solution versus distilled water.

BW: Absorption of blank reagent versus distilled water.

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Procedure for construction of calibration curve

To a series of volumetric flasks (25ml), 0.25-3.0ml of (250 µg/ml) of CPZH were transferred, 1.0 ml of Ce^{+4} (1×10^{-2}M) was added and the solutions are left for 15 min for oxidation, then 1.2 ml of p-bromoaniline reagent (1×10^{-2}M) and 2.0 ml of 0.1M sulfuric acid solution (pH 1.8) were added at 25°C and the volumes are completed to the mark with distilled water. The absorbance is measured directly after dilution at 553 nm against the blank reagent. Fig. (2) illustrates that the calibration curve is linear over the concentration range of 2.5 - 30 µg/ml while higher concentrations show a negative deviation from Beer's law. The molar absorptivity value is 6.5731×10^3 liter. $mol^{-1}.cm^{-1}$and the Sandell's sensitivity index 0.0541 $\mu g/cm^2$.

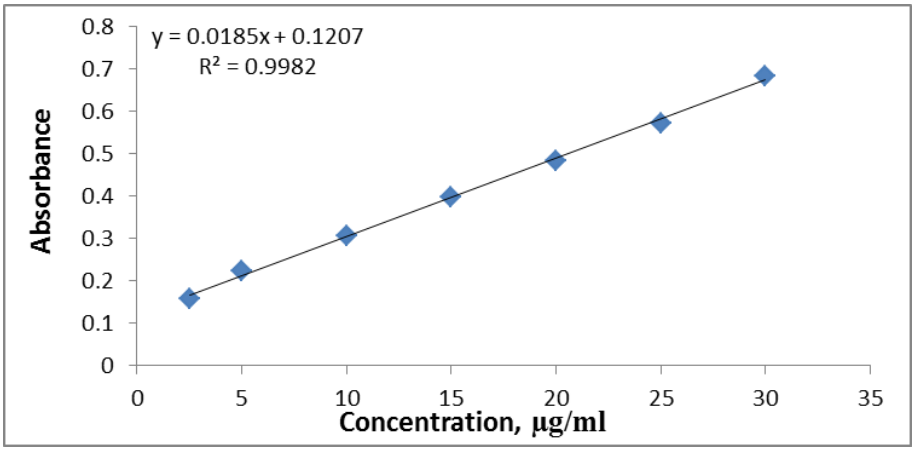

Fig.(2): Calibration curve for determination CPZH by oxidative coupling with p-bromoaniline reagent.

Accuracy and precision

Accuracy and precision were studied by measuring absorption (n=5) at 553 nm for two different concentrations of the drug within the limits of Beer's law, the average recovery (99.75 %) and the relative standard deviation (<1.39%) indicate that the method is of high accuracy and precision . The results are shown in Table (10).

Table (10): Results of accuracy and precision.

Conc. of CPZH(ppm)	RSD%	Recovery* %	Average recovery%	RE%
5	1.36	99.91	100.11	-0.0٩
10	1.20	100.30		0.30

*** Average of five determinations**

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Detection limit

Detection limit was calculated by measuring the absorption for the lower concentration 2.5 µg/ml at optimal conditions (ten times) at 553 nm. The results are shown in Table (11).

Table (11): Detection limit.

Concentration µg/ ml	$\overline{X}$	S.D	D.L µg/ ml
٢.5	0.158	0.0022	0.1361

*** Average of ten determinations**

The nature of the formed product

To know the nature of the formed violet color product (stoichiometry of drug with the reagent), Job's method and molar ratio method were applied. In both methods, the concentration of each of the standard CPZH solution and p-bromoaniline reagent solution is equal to ٧.٠٣٦٣ $\times 10^{-4}$ M. In Job's method, in a series of volumetric flasks (25 ml), different volumes of the drug solution ranging from1-9 ml and different volumes (9-1 ml) of reagent solution were mixed. A 1.0 ml of (Ce^{+4})(1×10^{-2} M) and 2.0 ml 0.1 M of sulfuric acid solution were added and volumes were completed to the mark with distilled water. The absorbance was measured at 553 nm against the blank reagent. The results Fig. (3) show that the ratio is 1:1.

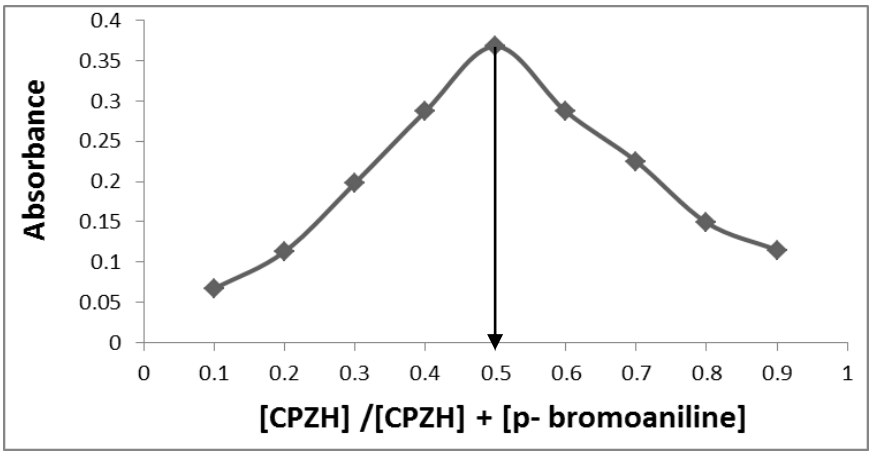

Fig. (3): Job's method of formed product by oxidative coupling of CPZH with p-bromoaniline reagent.

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In molar ratio method, ١ ml of the standard drug solution in a series of volumetric flasks (25 ml) were transferred and different volumes 0.2-3.5 ml of N,N-DMPPDADH reagent solution, 1.0 ml of (Ce^{+4}) (1×10^{-2}M) and 2.0 ml 0.1 M of sulfuric acid solution were added. The volumes were completed to the mark with distilled water and the absorbance was measured at 553 nm against the blank reagent. Molar ratio was found to be 1:1. The results are shown in Fig.(4) which is in agreement with the Job's method results.

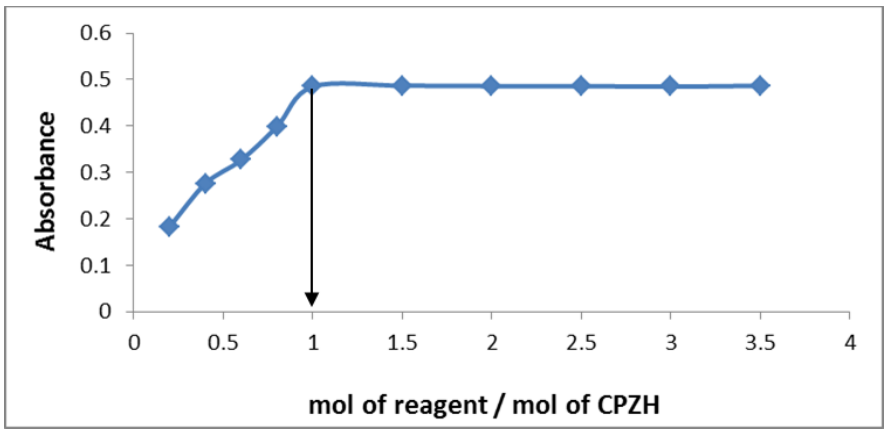

Fig. (4): Molar ratio method for the product formed by oxidative coupling of CPZH with p-bromoaniline reagent.

Effect of interferences

In order to test the efficiency and selectivity of the proposed method, the effect of some foreign substances (lactose, fructose , maltose, starch and glucose) that usually present in dosage forms are studied by taking volumetric flasks (25 ml) containing 2.0 ml of CPZH (250 µg /ml), then different volumes (2.5, 5.0 ,7.5 ml) of foreign substances (1000 µg/ml) have been added resulting in a final concentration of (100, 200 ,300 µg/ml). The optimum conditions have been applied and the volumes have been completed to the mark with distilled water.The absorbance was measured at 553 nm versus blank reagent and recovery is calculated. The results showed that there is no interferences Table (12).

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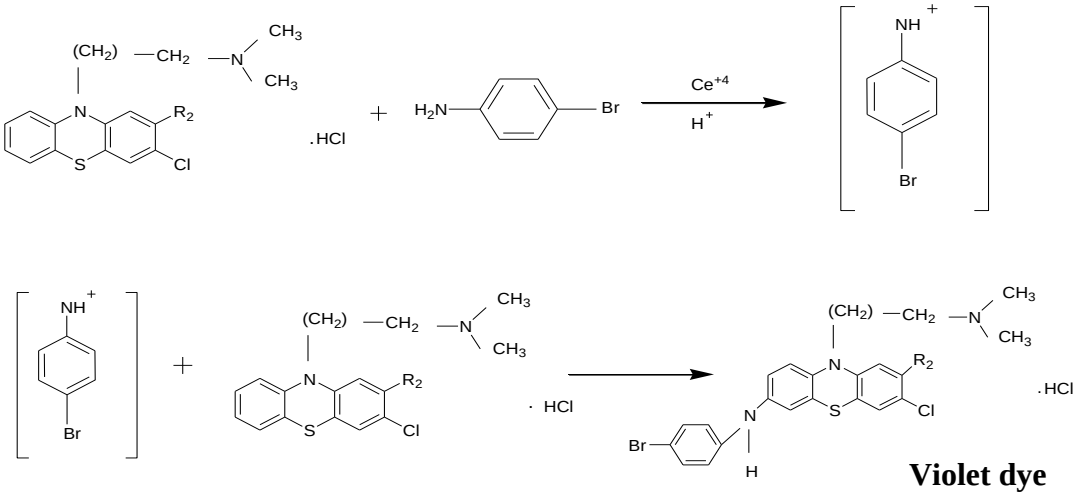
Table (12): Effect of interferences.

Foriegn compound	Recovery (%) of 20 µg/ml of CPZH per µg /ml foreign compound added		
	100	200	300
lactose	100.08	100.27	99.76
Fructose	98.48	99.35	97.55
Maltose	97.39	98.66	98.90
Starch	99.89	97.51	99.43
Glucose	100.47	99.52	100.12

The proposed equation for reaction can be written as follows:



Applications

This method was applied for the determination of CPZH in its pharmaceutical formulations (tablets and injection).

Direct method

In this method, different volumes (0.25, 0.5ml) of a pharmaceutical formulation solutions (250 µg/ml) were transferred to 25 ml volumetric flasks and the resulting concentrations (2.5, 5 µg/ml) and were treated as in construction of calibration curve. The absorbance was measured at 553 nm for five times. Recovery and RSD were calculated and the results are shown in Table (13).

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Table (13): Determination of CPZH in pharmaceutical formulation

pharmaceutical formulation	CPZH present µg/ml	CPZH measured µg/ml	RSD,%	Recovery*,%
Injection largapromatctil chlorpromazine -HCl 25 mg/5ml	2.5	2.49	1.44	99.60
	5.0	5.02	1.24	100.40
Tablets largapromatctil chlorpromazine -HCl 100 mg	2.5	2.52	1.56	100.8
	5.0	4.96	1.53	99.20

*** Average of five determinations**

Table (13) shows the efficiency and success of the developed method for the determination of CPZH in its pharmaceutical formulation.

standard additions method

To prove that the developed method is free from interferences , method of standard additions is applied for determining of CPZH in its pharmaceuticals. Different volumes (0.25,0.5 ml) of a pharmaceutical formulation solutions (250 µg/ml) were transferred to six volumetric flasks (25 ml) for each volume, then increasing volumes (0.25-2.0 ml) of 250 µg/ml of CPZH standard solution were added with leaving the sixth flask without addition. The solution was treated as in construction of calibration curve. The absorbance were measured at 553 nm Fig.(5,6) the measured concentration was calculated from the equation of the straight line and the results of Recovery and RE shown in the Table (14).

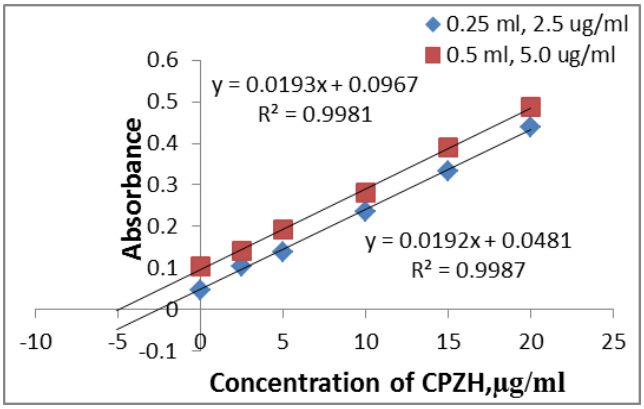

Fig.(5) Standard additions curve for the determination of CPZH in injection

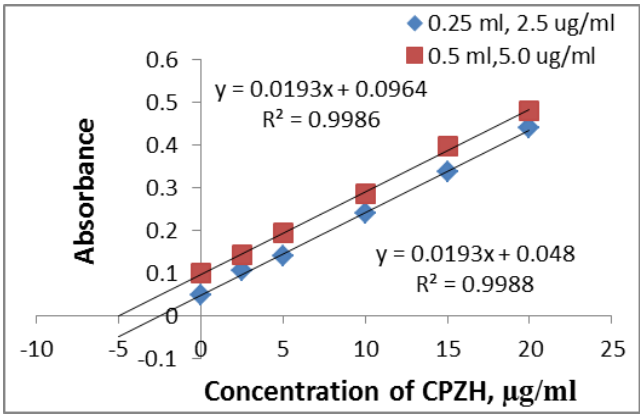

Fig.(6) Standard additions curve for the determination of CPZH in tablets.

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Table (14): Results of standard additions method.

pharmaceutical formulation	CPZH present µg/ml	CPZH measured µg/ml	Recovery*,%
Injection largapromatctil chlorpromazine -HCl 25mg /5ml	2.5	2.51	100.40
	5.0	5.01	100.20
Tablets largapromatctil chlorpromazine -HCl 100mg	2.5	2.49	99.60
	5.0	4.99	99.80

The results shown in table 12 indicate that method of standard additions is in agreement with the direct method within the acceptable range of error, indicating that the method is satisfactory and free from interferences.

4.Conclusions

The results obtained confirm that the proposed method is simple, rapid and of good sensitivity for the determination of chlorpromazine hydrochloride CPZH. The method is based on oxidative coupling between CPZH and p-bromoaniline reagent in presence of ammonium ceric sulphate dehydrate (Ce^{+4}) in acidic medium to form a violet colored dye which is water soluble, stable and shows a maximum absorption at 553 nm. This method does not require temperature control, nor use of organic solvents, or solvent extraction and it can be applied successfully for determination of CPZH in pharmaceuticals formulation.

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