

Spectrophotometric Determination Of Chlorpromazine Hydrochloride By Oxidative Coupling Reaction With Picric Acid Using Sodium Periodate

طريقة طيفية لتقدير عقار كلوربرومازين هيدروكلورايد باستعمال الكاشف اللوني حامض البكريك وبوجود بيريويدات الصوديوم كعامل موكسد

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ABSTRACT

A simple and accurate spectrophotometric method for determination of chlorpromazine (CPZ) in pure form and in dosage forms. The current method was developed based on chlorpromazine oxidative coupling reaction using picric acid in presence of sodium periodate to form red product was measured at 526 nm. Beer's law was in the linear range 4 - 60 µg/ml of CPZ, the molar absorptivity, Sandell's sensitivity index and detection limit were (0.5×10^4) liter. $\text{mol}^{-1} \cdot \text{cm}^{-1}$, $0.0592 \mu\text{g} \cdot \text{cm}^{-2}$ and $(0.355) \mu\text{g/ml}$ respectively. The RSD value was (0.154) % depending on the concentration. The results showed that this method can be successfully applied for the determination of CPZ in pure and in pharmaceutical formulations.

Keywords: Chlorpromazine, Spectrophotometric.

الخلاصة:

التقدير الطيفي للكلوربرومازين بواسطة الازدواج التاكسدي مع حامض البكريك يتضمن البحث بابتكار طريق بسيطة وحساسة وغير مكلفة لتقدير عقار الكلوربرومازين باستعمال تفاعل الازدواج التاكسدي باستخدام حامض البكريك وبوجود بيريويدات الصوديوم كعامل موكسد لتكوين ناتج ملون ذائب في الماء يمتص عند 526 نانوميتر وكان مدى الخطية بين (4 - 60) مايكروغرام /مل وكان مقدار الامتصاصية المولارية ودلالة ساندل وحد الكشف بمقدار (0.5×10^4) لتر.مول⁻¹.سم⁻¹، (0.0592) مايكروغرام سم⁻²، (0.355) مايكروغرام /مل) على التوالي كما تم قياس الاستيعادية (102.3%) وكانت مقدار الانحراف القياسي (0.154) وقد طبقت الطريقة بنجاح على المادة الفعالة وعلى المادة بهيئة حبوب .

INTRODUCTION

Chlorpromazine HCl is 3-(2-chloro-10-*H*-phenothiazin-10-yl)-*N,N*-dimethyl-propan-1-amine, Figure (1). It shows molecular formula as $\text{C}_{17}\text{H}_{19}\text{ClN}_2\text{S} \cdot \text{HCl}$ with molecular weight $355.33 \text{ g mol}^{-1}$ [1]. Its hydrochloride salt is white or cream coloured powder. It is very soluble in water and freely soluble in alcohol. Chlorpromazine HCl (CPZ.HCl) is a phenothiazine drug with an aliphatic side chain, used in the management of psychotic conditions [2]. It controls excitement, agitation and other psychomotor disturbances in schizophrenic patients and reduces the manic phase of manic-depressive conditions. It is used to control hyperkinetic states and aggression and is sometimes given in other psychiatric conditions for the control of anxiety and tension, CPZ.HCl is also used in palliative care to act as an antiemetic [3,4]. A literature survey reveals a spectrophotometric determination of chlorpromazine – HCl using potassium permanganate. Absorbance was measured at 525 nm. At ranges 5-45 $\mu\text{g} \cdot \text{mL}^{-1}$ the calibration curves were linear [5]. A previous study has determined chlorpromazine – HCl the maximum absorbance at 590nm the detection limit $1.7 \mu\text{g} \cdot \text{mL}^{-1}$ [6]. Another study determine chlorpromazine in pharmaceutical preparations, the maximum absorbance at 459 nm [7]. Some workers determine chlorpromazine based on charge transfer complexation reaction of the drug ones as n-donor at 450nm and another as π -accepter at 550nm. Beer's law obeyed in a concentration rang of (8-50) $\mu\text{g} \cdot \text{mL}^{-1}$ and (10-70) $\mu\text{g} \cdot \text{mL}^{-1}$ respectively [8]. Chlorpromazine has also been assayed by direct [9]. and indirect spectrophotometric method the

detection limit (0.157) $\mu\text{g}\cdot\text{ml}^{-1}$ [10]. Chlorpromazine determination by titmetric and spectrophotometric in various study [11]. Analytical method depend on oxidation reduction method to determine chlorpromazine at 521 nm. Beer's law was obeyed over the concentration range of 2.5 to 300 $\mu\text{g}/25\text{ ml}$ [12,13]. Different analytical methods and techniques have been developed for Chlorpromazine determination, including HPLC [14-16], GC [17], electrochemical method [18-24], and miscellaneous methods [25-30].

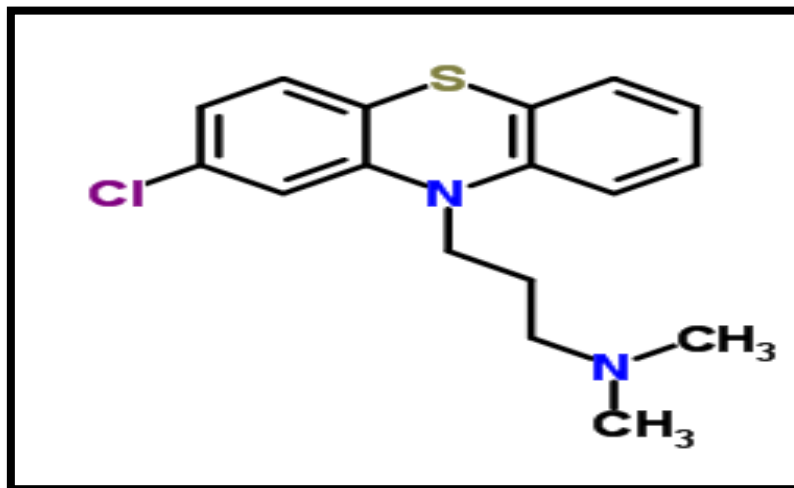


Figure (1):The structure of Chlorpromazine(CPZ)

EXPERIMENTAL

• Apparatus:

1. A shimadzu Uv-vis 1800 spectrometer (Japan) equipped with a quartz cell of 1.0 cm width was used for the determination and all absorbance measurements.
2. Labtech water bath (manufacture of lab institute).
3. Denver sensitive balance instrument ISO 9001.

• Reagents and Materials:

All chemicals and reagents used were of analytical reagent grade.

- Pure drug were provided by SDI.
- Standard solution of Chlorpromazine $100\ \mu\text{g}\ \text{ml}^{-1}$ was prepared by dissolving 0.0100 g in distilled water. This solution is kept in a brown bottle, where it is stable for one week, at least.
- Working standard solutions were prepared by appropriate dilution immediately before use.
- Dosage forms containing the studied drug being purchased from local market sources provided by SDI.
- Picric acid 0.001 M solution was prepared by dissolving 0.0229 g of $\text{C}_6\text{H}_2(\text{NO}_3)_3\text{OH}$ in 100 ml of distilled water.
- Sodium periodate 1.0×10^{-2} M solution was prepared by dissolving 0.214 g of NaIO_4 in 100 ml of distilled water.
- Hydrochloric acid 1M solution was prepared by dissolving (8.7) ml of concentrated HCl in 100 ml of volumetric flask and made to the mark by distilled water.

Preliminary investigation

General procedure:

Aliquots of the working standard solution of Chlorpromazine ($100\ \mu\text{g}/\text{ml}$) were transferred in a series of 25 ml volumetric flask after added 1 ml of picric acid. Then 0.50 ml of sodium periodate, and 1.5 ml of hydrochloric acid were successively added to each flask and the volume was made up to the mark with distilled water. The solutions were allowed to stand for 5 minutes to complete the reaction. The absorbance was measured at 526 nm against reagent blank prepared in similar manner.

Pharmaceutical Applications

Procedure for tablets:

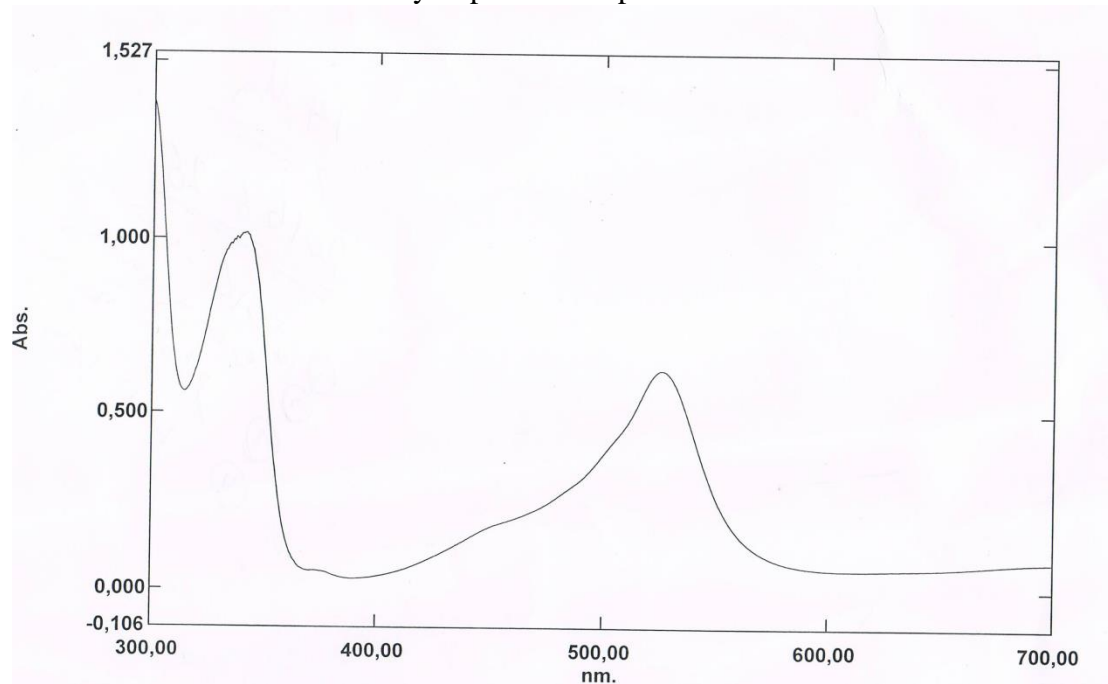
Ten tablets were weighed and well pulverized to get fine and homogenous powder. Exactly weighed quantity of the powdered tablets equivalent to 1000.0 mg of (CPZ) was transferred into a 250ml conical flask and extracted with 100 mL of distilled water. The extract was filtered using filter paper and transfer. The filtrate was transfer to 100 mL volumetric flask and make up to the mark with distilled.

Different volumes from this solution covering the working concentration range were transferred into a series of 25 mL volumetric flasks. The procedure mentioned under "Construction of calibration graph" was exactly done. The nominal content of the tablets was determined either from the previously plotted calibration graph or using the corresponding regression equation.

Results and discussion

The UV-visible Spectrum

The (UV- vis.) spectrum for the resulting compound that formed by react the picric acid with chlorpromazine in presence of oxidizing agent in the acidic solution was conducted to obtain the greater wavelength against blank at 526 nm. The development of the color depends on the reaction conditions. Therefore it is very important to optimize the reaction conditions.



Figure(2):Absorption spectrum of red product formed at $100 \mu\text{g.ml}^{-1}$ of CPZ and 0.001M picric acid and 0.1M oxidant and 1.5MHCl

Optimization of Experimental Conditions

The effect of concentration of picric acid $C_6H_2(NO_3)_3OH$

The optimum concentration of the reagent was obtained by study different volumes from 0.2 to 3 ml of picric acid of 0.001M solution.; it was found that 1.0 mL of reagent (1×10^{-3} M) was suitable to develop the maximum intensity of the formed complex. Hence, it was considered as the optimum concentration of the reagent for the further investigation. The Fig(3) show the result.

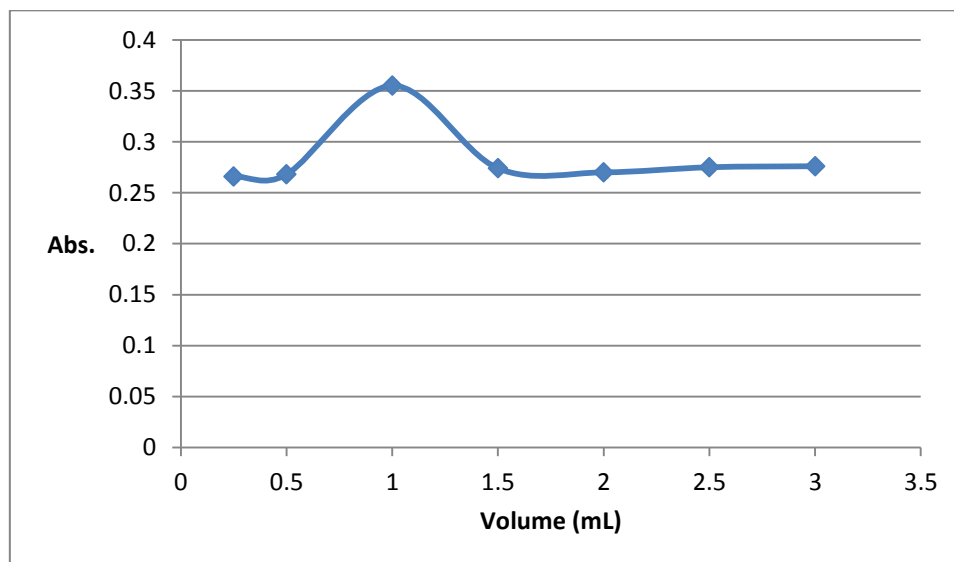


Figure (3): Effect of picric acid volume

The effect of amount of sodium periodate

The effect of sodium periodate concentration on the intensity absorbance was studied in the range of (0.5- 5) mL of a 0.01M of sodium periodate. The results shown that 0.5mL of sodium periodate gave the highest absorbance according to the figure (4). So it was used in subsequent experiments.

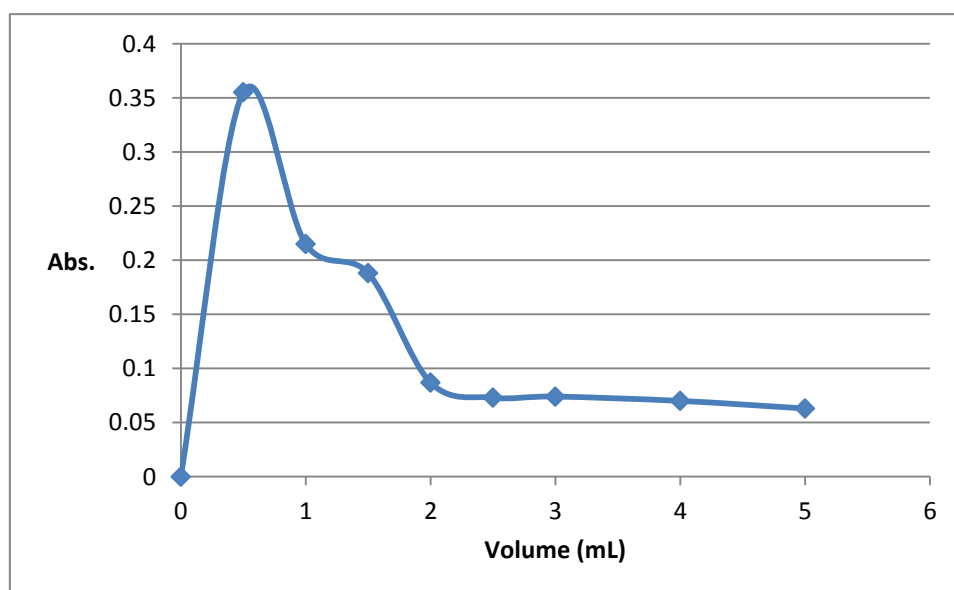


Figure (4): Effect of sodium periodate concentration.

Effect of amount of acid

It was found that the presence of acid (such as H₂SO₄ and HCl) led to increase the intensity of the produced product. A 1.5 mL of a 1.0M Hydrochloric acid was selected because it was found the acid give high absorbance than sulfuric acid.

Effect of order of addition

In order to illustrate the effect of sequence addition on the absorbance of the red product there were three sequence method of addition are described in Table(1).

Table(1) Effect of order of addition

Order of addition	Absorbance
C ₆ H ₂ (NO ₃) ₃ OH +drug+NaIO ₄ +HCl	0.355
drug + C ₆ H ₂ (NO ₃) ₃ OH + NaIO ₄ +HCl	0.348
NaIO ₄ +drug+ C ₆ H ₂ (NO ₃) ₃ OH +HCl	0.302

The three sequence of addition effected on the absorbance of the product. The first sequence of addition which selected in subsequent experiments shows the higher absorbance than the other.

Effect of Temperature:

The effect of temperature on the color intensity of the product was studied. In practice the same absorbance or very closed was obtained when the color was developed at room temperature (25C⁰) .Therefore, it is recommended that the reaction should be carried out at room temperature as shown in table(2), because at higher temperatures the absorbance value decrease indicating the dissociation of the product on prolonged heating.

Table(2) Effect of temperature:

Temperature (°C)	Absorbance
25°C	0.355
40 °C	0.338
50 °C	0.273

Effect of reaction time:

The effect of time on the development and stability period of the formed colored dye was investigated under optimum experimental conditions describe before. The formation of colored dye being complete after mixing the components of the reaction and the absorbance of colored species remained constant for at least 20 minutes.

Calibration Curve

The calibration curve was constructed according to the general procedure under the optimum condition. The result is shown in Fig.(5).

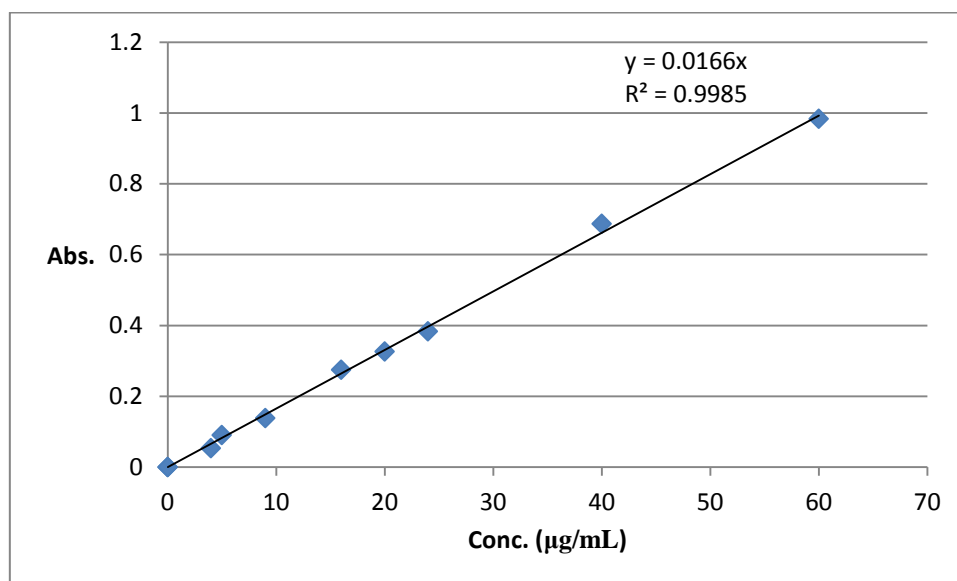


Figure (5):- Calibration curve for the determination of chlorpromazine

A liner relationship had been obtained by plotting between the absorption and concentration for chlorpromazine. The figure (6) shows that Beer’s law is obeyed over the concentration rang of (4-60) $\mu\text{g.ml}^{-1}$ with correlation coefficient of 0.9985. The slope of curve was 0.0166. The molar absorptivity of the red product was $(0.6 \times 10^4 \text{ L.mol}^{-1} . \text{cm}^{-1})$.

Accuracy and precision

The competence of the method was statistically evaluated by measuring accuracy and precision of the proposed methods by measuring the relative error percentage (E%), Recovery and Relative standard deviation (R.S.D) the results are shown in Table (3).The obtained results were satisfactory and indicate that the proposed methods have a good accuracy and precision.

Table(3):Accuracy and Precision of the method

Con.($\mu\text{g.ml}^{-1}$)	S	R.S.D	Error%	Recovery%
3.00	0.0028	5.49	2.28%	102.33%
7.00	0.00179	0.154	-0.28%	99.71%

Limit of Quantification (LOQ) and limit of detection (LOD)

The limit of quantification (LOQ) was determined by establishing the lowest concentration that could be measured according to ICH Q2(R1) recommendation (international conference on harmonization of technical requirements for regression of pharmaceutical for human use . Below which the calibration graph is non linear ($\text{LOQ}=10\sigma/\text{S}$) where S is the slope and σ is the standard deviation of the intercept of regression line of calibration curve. the limit of detection (LOD) was determined by evaluation the lowest concentration of the analyte that can be detected ($\text{LOQ}=3.3 \sigma/\text{S}$) . The results of LOD and LOQ of the proposed method are summarized in table (4).

Table(4): optical Characteristic and validation data Spectrophotometric method.

No	Parameters	data
1	λ_{max}	526 nm
2	Beers Law limit ($\mu\text{g ml}^{-1}$)	4-60
3	Molar absorptivity ($\text{L mol}^{-1}\text{cm}^{-1}$)	0.5×10^4
4	Sandells sensitivity ($\mu\text{g cm}^{-2}$)	0.0592
5	Regression Equation ($y=bx$) b slop	$y=0.0166x$
6	Correlation Coefficient (r)	0.9985
7	% Relative standard Deviation (R.S.D) (average of five determination)	0.154
8	Colour	red
9	LOQ	1.078
10	LOD	0.355

Stoichiometry of reaction

The stoichiometry of reaction between (CPZ) and the picric acid was investigated using job's method^[31]. From the results in figure (6) obtained that 1:1 drug to reagent.

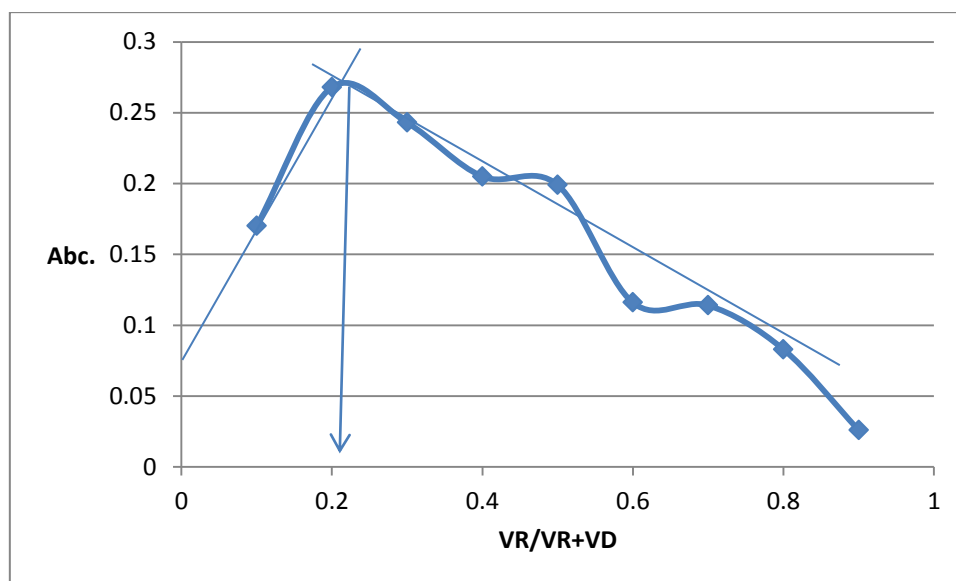


Figure (6): Job's method plot for reaction of (CPZ) with reagent in the presence of NaIO_4 and HCL.

The reaction between (CPZ) and the reagent in presence of HCl and NaIO₄ to provide red product was suggested at the reaction in the following equation in figure (7).

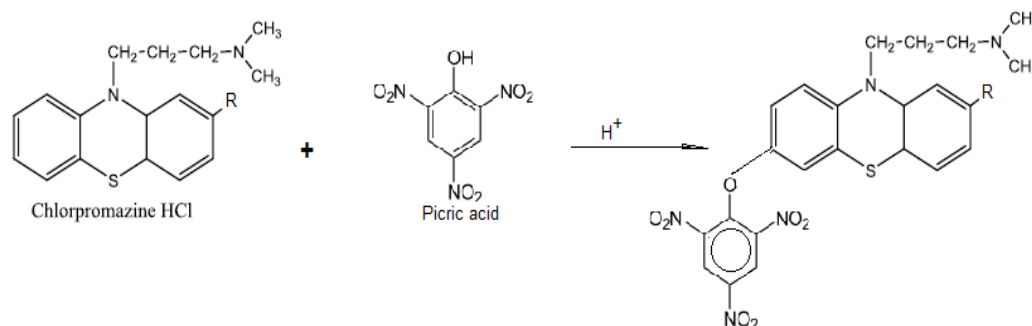


Figure (7):- The expected equation of the reaction between (CPZ) and the reagent.

Pharmaceutical Application

Appropriate aliquots of drug solution were taken. The individual assay procedure was carried out for the estimation of drug contents in tablets. The concentration of the drug in the tablets was calculated using calibration curve. The recovery experiment was carried out by standard addition method. The values of analysis are given in table (5)

Table (5) Application of the method for determination of in pharmaceutical tablets

Con. Of FAM($\mu\text{g.ml}^{-1}$)		R.S.D	Error%	Recovery%
Taken	Found			
4.00	4.05	2.98	1.2	101.25
8.00	7.94	2.73	- 0.75	99.52

Conclusions:

The high recovery and low relative standard deviation reflect the high accuracy and precision of the described spectrophotometric. The proposed methods are found to be reproducible, precise and accurate and can be applied for quality control analysis of CPZ in raw samples as well as in pharmaceutical preparations. Also this validated method is suitable for the routine analysis of drug. The main benefit of this method is cost effective and some laboratories in poor countries cannot afford to run HPLC and other advanced techniques. The method for the estimation of raw drug and tablet dosage form has been developed. Therefore, the proposed method concludes that much time and money can be saved. Moreover, the methods are simple, precise, applicable to a wide range of concentration, besides being less time consuming and depending on simple and available reagents thus offering economic and acceptable methods for the routine determination of CPZ in pharmaceutical formulations. The comparative study of the molar absorptivity indicated good sensitivity of the proposed method.

Referance:-

- 1- T. Lambert and D. Castle, Schizophrenia MJA 178 (2003) 57.
- 2- K. Mahadik, B.Kuchekar and K.Deshmukh, "Concise Organic Pharmaceutical" (1991),10-20
- 3- R.Glenon and R.Young "Drug Discrimination Application to Medicinal Chemistry and Drug Studies" (2011),303-305.
- 4- J.Swazey "Chloropromazine in psychiatry" (1974),82.
- 5- S.Dikran, A.Mohammed and A.Hammodi, (2015) Ibn Al-Haitham J. for Pure & Appl. Sci., 28 (1)101-112.
- 6- M.Al-Kafajy and A. Al-Anbaky (2013) International Journal of Pharmacy and Pharmaceutical Science 6,606-612.
- 7- A. AL-Ayash , F. Jasim and W. Alwan (2009)National Journal of Chemistry,33, 42- 53.
- 8- M. AbdulLatif and A. Mhammed, (2008) Ibn Al-Haitham J. for Pure & Appl. Sci.,21(4).
- 9- M.AL-Rufaie, A. Al-Sharefy and K.Kadim, (2013)Iraqi national Journal of chemistry 51,338-347
- 10- K.Basavaiah and J.Swamy (2001) IL Farmaco 56,579-585
- 11- K.Basavaiah, P.Nagegowda, H.Prameela and B.Somashekar, (2005)Indian Journal of Chemical Technology,12,25-29
- 12- A.Miftode , A. Stefanache, A. Spac and V. Dorneanu (2013) Rev. Med. Chir. Soc. Med. Nat., Iași,117, 3.
- 13- W. Abd Al Cader (2011) Rafidain Journal of science, 2,22,79-93.
- 14- Y.Yamini and M.farajy (2014),Journal of Pharmaceutical Analysis;4(4)279–285
- 15- J.Dhabab, (2011) Al- Mustansiriya Journal of science, 22(2)124-128
- 16- L. Zhang, W. Huang and X. Jiang, (2015)Journal of Chinese Pharmaceutical Sciences, 24 (10)690–694
- 17- L.Zhang, P.Wu, Y.Zhang Q. Jin, D. Yang, L.Wang and J. Zhang, (2014) Journal of Analytical Methods,2(6) 503-508
- 18- M. Karimi, A.Mehrjardi, M.Ardakani, R.Ardakani, M.Mashhadizadeh, and S.Sargazi Russian (2011) Journal of Electrochemistry, 47(1) 34–41.
- 19- M.Parvin, M.Goliv , M. Najafi and S.Shariaty (2012) Journal of electroanalytical chemistry 683,31–36
- 20- E.Frag, M.Zayed, M.Omar, S.Elashery and G.Mohamed (2012) International Journal of Electrochemical Science 7, 650-662
- 21- M.Saraji, A. Bidgoli, A.Ensafi, E.Bafrooei and B.Farajmand, (2013) Journal of Analytical Methods, 5(19)5024-5030.
- 22- F. Liu, J. Shao and Y. Zhao (2014) Journal of Analytical Methods,16 (6)6483-6487.
- 23- A. Abounassif, M. Hefnawy, M. Hassanien, M. Mostafa, A. Gamal (2012)Sensor Letters, 10(8)966-973
- 24- A. Mahmood (2013) Rafidain Journal of science, 24(3)66 -75,.
- 25- Z.Zaho, L.Wang Y.Peng and X.Zhang (1996) Journal of West China University of Medical Sciences27(4)428-431
- 26- M. Hassouna, A. Adawi and E. Ali (2012) Egyptian Journal of Forensic Sciences 2,62–68.
- 27- A. Mohamed, O. Abdelmageed, H. Salemc, D. Nagyd and M. Omar, (2013)Luminescence 28,345–354.
- 28- S. Wen-Jia, S. Yu-Dong, S. Yuan-Ming, L. Hong-Tao, W. Hong, Z. Dao-Pin,Y.Jin-Yi(2013) Chinese Journal of Analytical Chemistry40(9)1397-1402.
- 29- I. Shakir and M. Hammood, (2014)Iraqi Journal of Science, No.2B, (55)594-605.
- 30- I.Shakir and M.hamzah,(2012)Kerbala Journal of Pharmaceutical Sciences,3,86-97.
- 31- P.Atkins, Physical Chemistry, 5th ed, Oxford University Press, UK, 109(2006).