ISSN 0975-2366
DOI:https://doi.org/10.31838/ijpr/2020.12.01.044

Research Article

Determination of Chlorpromazine Hydrochloride in its Pure and Dosage Forms by Diazotization Reaction and Coupling with Diazotized Sulfanilic Acid

SAHAR RIHAN FADHEL[1*], ABBAS SHEBEEB AL-KADUMI[2] AND WADHAH HILAL ABDULLAH[1]
[1] College of science - Diyala University/Iraq.
[2] College of pharmacy – Al - Nahrain University/Iraq.
Corresponding author:
Sahar Rihan Fadhel
E-mail: saharchemst2011@yahoo.com
Received: 16.10.19, Revised: 17.11.19, Accepted: 22.12.19

ABSTRACT

A simple and sensitive spectrophotometric method for determination trace amount of Chlorpromazine Hydrochloride (CLPZ) in tablet pharmaceutical preparations were described. The method was based on the coupling reaction of drug with (0.3 mole.L^{-1}) diazonium salt (prepared from reaction of sulphanilic acid with (12.07 mole.L^{-1}) hydrochloric acid and sodium nitrite at (0-5) °C in basic medium of sodium hydroxide (0.5 mole.L^{-1}) to produce pink color azo dye compound can be absorbed at 526nm, the optimum reaction conditions and other analytical parameters were evaluated. The high accurate and precise results obtained with RSD%, Recovery%, Ere% and D.L were 0.9333, 101.045, 1.0457, and 0.1114 µg.ml^{-1} respectively, the linearity of rang 2.0-100.0 µg.mL^{-1}. The proposed method was successfully applied to the determination of CLPZ in pharmaceutical formulations without any effect of interference of chemical materials in pharmaceuticals.

Key words: Chlorpromazine Hydrochloride, spectrophotometry, sulphanilic acid, azo dye.

INTRODUCTION

Chlorpromazine is 10-(3-dimethylaminopropyl)-2-chlorphenothiazine, a dimethylamine derivative of phenothiazine [1], figure (1). It is present in oral and injectable forms as the hydrochloride salt, and in the suppositories as the base [2].

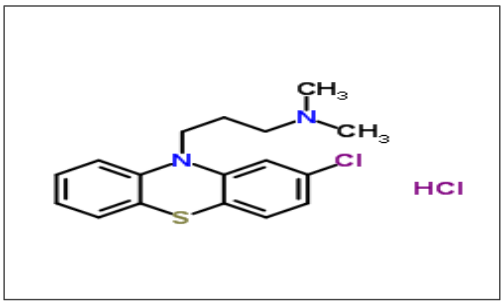

Figure (1): Chemical structure of chlorpromazine hydrochloride.[1]

CLPZ marketed under the trade names Thorazine and Largactil among others, is an antipsychotic medication. It is primarily used to treat psychotic disorders such as schizophrenia. Other uses include the treatment of bipolar disorder, attention deficit hyperactivity disorder, nausea and vomiting, anxiety before surgery, and hiccups that do not improve following other measure. It can be given by mouth, by injection into a muscle, or into a vein [2]. Many analytical methods are used for determination of chlorpromazine included spectrophotometry [3-11], chromatography [12-15], electro analytical methods [16, 17], and flow injection analysis method [18, 19] .The proposed method involved determination of chlorpromazine hydrochloride after reaction with diazotized sulphanilic acid as a colorimetric reagent.

Experimental

Instrumentation

UV-Visible double beam spectrophotometer equipped (JASCO V-650, Japan) with 10 mm quartz cell. Sensitive balance ± 0.0001 g, Sartorius BL 210 S Scientific balance (Gottingen – Germany). Hot plate (Labtech, Germany)

REAGENTS AND CHEMICAL MATERIALS

All chemicals used were of analytical reagent grade and CLPZ standard material were provided from state company for drug industries and medical appliance (SDI) Samarra-Iraq ,while Largapromactil® 50mg/ tablet (SDI/ Iraq Ltd) and largactil® 25mg/5mL (sanofi Aventis- France) from local market.

Standard Chlorpromazine hydrochloride solution (1000µg.mL^{-1})

100 milligram of CLPZ standard material is dissolution in suitable volume of distilled water and complete to 100ml in standard flask. Working standard solutions of CLPZ were freshly prepared

Sodium hydroxide solution (0.5M)

2 gram of sodium hydroxide was dissolution in suitable volume of distilled water and complete to100ml in standard flask.

Diazoated sulphanilic acid (Diazonium salt) 0.3M

was prepared by dissolving 5.196 gram from sulphanilic acid in 30ml of distilled water with stirring and heating ,five milliliters of 11.8M hydrochloric acid solution was added gradually with stirring in ice path (0-5)Cº, after transferred to 100ml brown standard flask, added 2.069 gram of sodium nitrite with stirring after five minutes the solution was diluted to the mark, this solution was keep in refrigerator.

Determination of chlorpromazine HCl in pharmaceutical preparations

a- tablet

Ten tablets labeled to contain (50mg) of chlorpromazine HCl were weighed and grounded into fine powder. An amount of powder equivalent to about (0.3544g) equivalent to (500μg.ml^{-1}) of the standard pure drug was weighed. The powder was dissolved in 10 mL distilled water with stirring and the total volume of the formed solution was made to 100 mL in a standard flask with distilled water to obtain 500μg.mL^{-1} CLPZ solution. The solution was filtered by using Whatman filter paper No.41. Working tablet solutions of CLPZ were freshly prepared.

b- Ampoule

Each 5mL of the injection ampoule contains 25mg of chlorpromazine. An accurately measured volume 2mL was transferred into a 10 mL volumetric flask and diluted to the mark with distilled water to get 1000μg.mL^{-1} CLPZ solution. Working solutions were freshly prepared.

Preliminary investigations: 1mL of prepared diazonium salt with 0.3M concentration transferred to 10 ml volumetric flask contained one milliliter of (100μg.ml^{-1}) chlorpromazine hydrochloride solution with stirring, 1mL of 0.5M sodium hydroxide solution and diluted to the mark with distilled water, the absorbance spectrum was recorded.

Recommended procedure and construction of CLPZ calibration curve Transfer 1mL from (0.3M) diazonium salt in to a series of 10mL volumetric flasks contained 1ml of (2.0-100) μg.mL^{-1} of drug with stirring then added 1mL from 0.5M of sodium hydroxide solution, leave the solution for 5 minutes in dark place, after diluted to the mark with distilled water, the absorbance of pink dye was recorded at 526nm against blank solution after 5minutes against the reagent blank. The unknown concentration of CLPZ was read from the calibration graph or computed from the regression equation derived using Beer's law data.

RESULT AND DISCUSSION

Primary absorption spectra

The uv-vis spectra of the pink azo product by the reaction between CLPZ and diazotized sulfanilic acid was recorded and gives maximum absorption at 526nm as in figure (2).

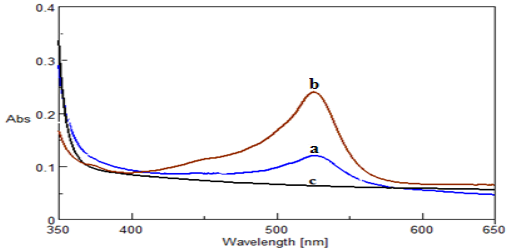

Figure (2): Absorption spectra (a) Azo dye formed of (10µg.mL^{-1}) CLPZ with diazonium salt vs reagent blank under primary conditions, (b) Azo dye formed of (10µg.mL^{-1}) CLPZ with diazonium salt vs reagent blank under optimum conditions, (c) reagent blank vs distilled water.

Optimization of experimental variable

Effect of reagent concentration

The influence of reagent was tested by using different concentrations (0.1–0.6) M of the diazotized Sulphanilic acid solution. The results showed in figure (3) that adding 1mL of 0.3M of reagent is sufficient for production of maximum and reproducible color intensity.

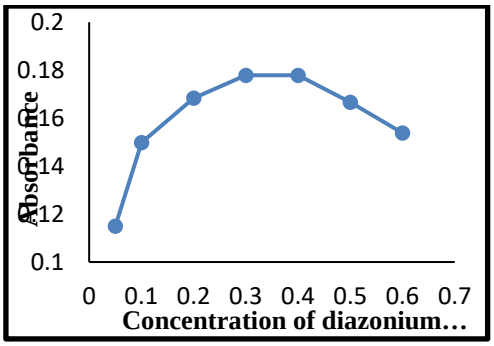

Figure (3): Effect of reagent concentrations on the absorption of (10µg.mL^{-1}) chlorpromazine HCl.

Effect of different concentration of sodium hydroxide

The addition effect of 1mL of different sodium hydroxide concentrations on the absorption of azo dye formed, the results in Figure (4) show that 1mL of 0.5M NaOH solution was optimum and it was recommended for the subsequent experiment.

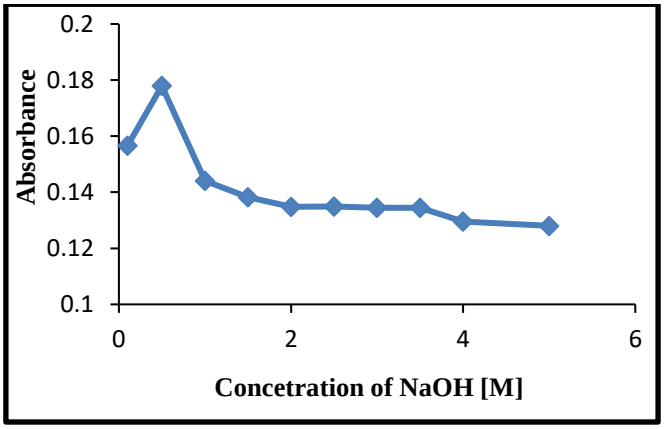

Figure (4): Effect of different concentration of sodium hydroxide on the absorption of (10µg.mL^{-1}) chlorpromazine HCl.

Effect of reaction time

The optimum time after mixing CLPZ with diazonium salt was determined at different time periods. The results showed that maximum absorbance occurred after 5 minutes after adding the base, Figure (5).

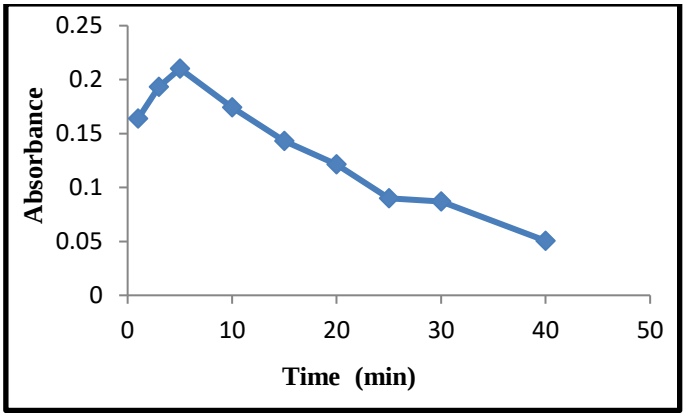

Figure (5): Effect of reaction time on the absorption of dye.

Effect of different type of basic medium

After experimentation of basic medium in order to increase intensity of the reaction, the experiments indicated that the alkaline medium is necessary for developing a more intense dye color. Accordingly, different base solutions of 0.5M were examined such as NaOH, KOH, NH_4OH and Na_2CO_3 with regard to Table (1). It was clear that the sodium hydroxide was appropriate for a maximum absorbance and used in all next experiments.

Table (1): Effect of 0.5M of different basic mediums on dye absorption.

Type of Base	Absorbance
NaOH	0.2101
KOH	0.1882
NH_4OH	0.1513
Na_2CO_3	0.1451

Effect of order of addition

The mixing process of chlorpromazine HCl, sulphanilic acid and sodium hydroxide in different addition orders on the absorption of dye formed. It was found that the addition of drug solution to the reagent solution followed by adding the base solution (order 1 in Table 2) gave the maximum absorbance. Therefore, order I was recommended for the subsequent experiments.

Table (2): Effect of different addition order of (10µg.mL^{-1})chlorpromazine HCl, 1mL (0.3M) diazotized sulphanilicacid and 1mL (0.5M) NaOH on the absorbance.

Order No.	Order of mixing			Absorbance
	1	2	3	
1	Drug	Reagent	Base	0.2101
2	Drug	Base	Reagent	0.2010
3	Reagent	Base	Drug	0.2013
4	Reagent	Drug	Base	0.2016

Study of stability of the formed azo dye

The effect of time on the azo dye product was investigated by allowing the reaction to proceed for varying times. The results showed that the azo-dye reached maximum absorbance after 5 minutes and remained stable at room temperature for at least 60 minutes, Figure (6).

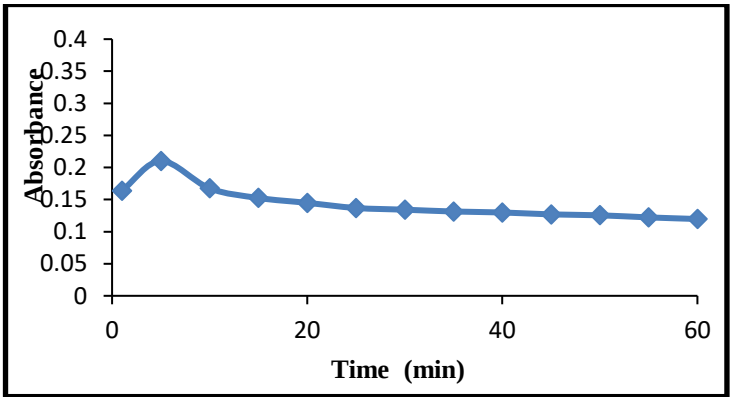

Figure (6): The time effect on stability of (10µg.mL^{-1}) chlorpromazine.

Final absorption spectrum

After adjusting optimum conditions. we obtained the final absorption spectrum for azo dye formed against blank solution at optimum conditions as in figure (2).

Calibration curve for chlorpromazine HCl

After estimation of optimum conditions, calibration curve was obtained by plotting the measured absorbance versus varying concentration of chlorpromazine HCl solutions, the figure (7) showed the relationship obeyed Beer Lambert law at (2.0-100) μg.mL^{-1} and above that values appeared negative deviation. Other statistical parameters namely: intercept (b), molar absorptivity and Sandell's sensitivity values are calculated as well and given in Table (3).

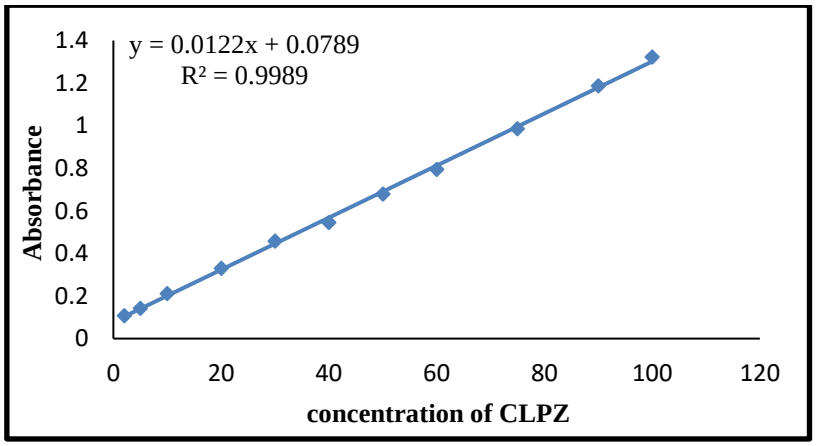

Figure (7): Calibration curve for chlorpromazine.HCl.

Table (3): analytical values obtained for chlorpromazine HCl at optimum conditions.

parameter	Value
λ_{max} (nm)	526
Color	pink
Linearity range (μg.mL^{-1})	2.0 – 100
Molar absorptivity (L.mol^{-1}.cm^{-1})	4334.904
Regression equation	A=0.0122[CLPZ.μg.mL^{-1}]-0.0789
Calibration Sensitivity(L.mg^{-1})	0.0122
Sandals Sensitivity (μg.cm^{-2})	0.0819
Correlation of Linearity (R^2)	0.9989
Correlation coefficient (r)	0.9994
Detection limit (μg.mL^{-1})	0.1114
Quantification limit (μg.mL^{-1})	0.3713

Accuracy and Precision of the proposed method

Five repetition for three concentrations (10, 30 and 50) μg.mL^{-1} were used for calculation precision and accuracy the results in table (4) show a good accuracy and precision.

Table (4): Accuracy and precision for analysis of chlorpromazine HCl.

CLPZ Conc. (μg.ml^{-1})		Relative Error %	Reco. %	Average Reco. %	S.D	R.S.D%*
Taken	Found*					
10	10.0174	0.1740	100.1740	101.0450	0.0935	0.9333
30	30.7250	2.4160	102.4160		0.3785	1.2318
50	50.2737	0.5470	100.5470		0.6430	1.2789

*Average of five determinations

Interference effect

The effect of different materials likely found in chlorpromazine.HCl tablet such as glucose, sucrose, starch and magnesium stearate at concentration 1000μg.mL^{-1} were studied, the result showed in table (4) that there was no interference from excipients for the experimental method.

Table (4): Interference effect of different excipients likely found in chlorpromazine.HCl tablet.

Excipients	Con.of excipients. Taken(μg.mL^{-1})	CPZ. Conc.Taken 10μg.mL^{-1}	
		Conc. found* μg.mL^{-1}	Recovery%
glucose	1000	10.1327	101.327
Sucrose		9.9426	99.426
Lactose		10.1530	101.530
Starch		10.2459	102.459
Mg-Citrate		9.9344	99.344

*Average of five determinations

Determination of chlorpromazine. HCl in pharmaceutical preparations

For verifying the efficiency of the proposed method, it was applied on a real samples with known contents of CLPZ, tablet (containing 50 mg CLPZ/tablet) and ampoule (containing 25 mg CLPZ/ 5 mL). The results of the application of the proposed method that are given in Table (5) were satisfactory. The recovery was ranged from (98.660- 100.750) % for the analysis of Largapromactil tablets and from (99.235-100.267%) for the analysis of ampoule.

Table (5): Determination of chlorpromazine HCl in pharmaceutical preparations.

Pharmaceutical	Assay		Con. μg.mL^{-1}		*Reco. %	Avarg Reco. %	S.D*	RSD*
	Spiked	*Found*	*Taken*	*Found**				
Largapromactil 50 mg/tablet	50.000	50.376	20.000	20.150	100.750	99.570	0.0891	0.044
		49.3	40.0	39.46	98.660		0.231	0.022
		49.6	60.0	59.59	99.310		0.602	0.018
largactil 25mg/5mL ampule	25.000	24.8	20.0	19.84	99.235	99.755	0.063	0.319
		25.0	40.0	40.10	100.26		0.379	0.945
		24.9	60.0	59.85	99.765		0.586	0.979

*Average of five determinations

CONCLUSION

Although CLPZ has been determined by a variety of techniques, the method described here were simple, accurate, rapid, sensitive, and don't require special working conditions, unlike many other reagents. Moreover, owing to the good stability of azo dye in the solution.

REFERENCES

1. British Pharmacopeia, (2013) CD-ROM Her Majesty, Stationary office, London.
2. P. Seeman (1981) "Brain dopamine receptors" Pharmacol.Rev.32 229–313.
3. AL-kaffiji, M. J. H. and AL-anbakey, A. M. S. (2013). "new chromogenic reagent for the spectrophotometric determination of chlorpromazine .HCL in aqueous solutions and pharmaceutical formulations" International journal of pharmacy and pharmaceutical sciences, 5(3).
4. Ayash, A., S., Jasim, F. and Alwan, W.(2013) "Spectrophotometric determination of Chlorpromazine Hydrochloride in Pharmaceutical preparations" , National Journal of Chemistry: 33, 42-53.
5. Al-Rufaie, M., M. (2013). "Spectrophotometric Determination of chlorpromazine Hydrochloride in Pharmaceutical Preparations by Using Oxidative coupling reaction, Iraqi National Journal of Chemistry, 51:338-347.
6. Dikran, S. B., Mohammed, A., K. and Hammodi, A. S. (2017). "Spectrophotometric

Determination of Chlorpromazine–HCl Using Potassium Permanganate" , Ibn AL-Haitham Journal For Pure and Applied Science , 28 (1):100-112.

7. Humeidy, I., T.(2016)." Spectrophotometric determination of Chlorpromazine Hydrochloride by oxidative coupling reaction with P-Bromo aniline using Ammonium Ceric Sulphate Dihydrate" , Kirkuk University Journal /Scientific Studies , 11(1) :PP1-19.
8. Anwar, S., M., Khalil, A., I and Hussein, K., S. (2016). "Spectrophotometric Determination of chlorpromazine Hydrochloride in Pharmaceutical Preparations by Oxidative coupling reaction" , Kirkuk University Journal /Scientific Studies ,11(4) :297-313.
9. Ali, S., M. and Kadhim, K., H. (2016). "Spectrophotometric Determination of Chlorpromazine Hydrochloride in Pure and Pharmaceutical formulation by Using The Organic Reagent 2-5 dimethoxyaniline". RESEARCH JOURNAL OF PHARMACEUTICAL BIOLOGICAL AND CHEMICAL SCIENCES, 7(5) : 640-650.
10. Ahmed, A., M. K. , Baker, M., H. and Hussein, N., A. (2017). "Spectrophotometric Determination of Chlorpromazine HCl by Oxidative Coupling Method in Pharmaceutical formulations". Tikrit Journal of Pure Science, 22(6).
11. Khanfous, S., N. , Nasser, N., A. H. and AL-Rufaie, M., M. (2017)." Modern spectrophotometric approach for assessment chlorpromazine hydrochloride drug" , Iranian Journal of Organic Chemistry , 9(3) : 2161-2167.
12. Fadhel, S. R., Khalil, S. I. (2018). "Simultaneous Estimation of Chlorpromazine hydrochloride and Carvedilol in Bulk and Pharmaceutical Dosage Forms Using HPLC". J Biochem Tech (2018) 9(3): 5-9.
13. Kumar, M., B., Ramachandran, S. and G, N., S. (2010). "HPLC METHOD DEVELOPMENT,VALIDATION AND ITS APPLICATION TO STABILITY STUDIES OF CHLORPROMAZINE HYDROCHLORIDE TABLETS" , Venkatesh S et al.IRJP , 1(1) :225-232.
14. Dhabab, J., M. (2011). "Simultaneous determination of chlorpromazine and trifluoperazine in pharmaceutical preparations using high performance liquid chromatography", Al-Mustansiriya J. Sci, 22(2):pp123-128.
15. Trefi, S. (2016). " ASSAY OF FOUR PSYCHOTROPIC DRUGS CHLORPROMAZINE, CLOMIPRAMINE, AMITRIPTYLINE AND NORTRIPTYLINE IN TABLETS BY A SINGLE HPLC METHOD". International Journal of Pharmacy and Pharmaceutical Sciences,8(8): 0975-1491.
16. Frag, E., Y. , Zayed, M., A. , Omar, M., M. , Elashery, S., E. and Mohamed, G., G. (2012). "Potentiometric determination of chlorpromazine HCl using carbon paste electrode in pure and pharmaceutical preparations", Int. J. Electrochem. Sci, 7: 650-662.
17. Mahmood, A., I. (2013)." Indirect Determination of Chlorpromazine Hydrochloride by Square Wave Voltammetry of Sodium Nitroprusside: Application to Pharmaceutical Formulations", Raf. J. Sci.,24(3) : 66-75
18. Al-Hashimi, I., M. S. and Al-Kaffije, M., J. H. (2012)." New approach development for determination of chlorpromazine HCl in pure and pharmaceutical forms using homemade wavelength selector flow injection photometer",Karbala Journal of Pharmaceutical Science, 3: 86-97.
19. Shakir, I., M. and Hammood, M., K. (2014). "New turbidimetric-continuous flow injection analysis method for the determination of chlorpromazine HCl in pharmaceutical preparation using linear array ayah 5SX1-T-1D-CFI analyser " , Iraqi Journal of Science, 55 (2): 594, 605.
20. Elmiawati Latifah, Susi Ari Kristina, Sri Suryawati, Satibi. "Overview of Drug Availability and Influencing Factors in Several Low, Lower and Upper- Middle Countries: A Systematic Review." Systematic Reviews in Pharmacy 10.1 (2019), 67-72. Print. doi:10.5530/srp.2019.1.11