

Spectrophotometric Method for The Microdetermination of Chlorpromazine Hydrochloride in Pure and Pharmaceutical Dosage Forms Using Charge Transfer Complex

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Abstract

This study was aimed to find out a Simple, sensitive and rapid spectrophotometric method for determination of chlorpromazine hydrochloride (CPZH). The suggested method was based on the charge transfer (CT) formation complex reaction with O-Chloranil as π - acceptor. The formed violet colour of the reaction product was measured at a maximum absorption wavelength of 543 nm against the blank solution. It was obeyed to Beer-Lambert's law over the concentration ranged of 4–36 $\mu\text{g/ml}$ with a molar absorptivity of. 2309. 645 $\text{L mol}^{-1}.\text{cm}^{-1}$ and the lower of detection limit 0.3024 $\mu\text{g.ml}^{-1}$ The method revealed high sensitivity for determination of the selected drug .

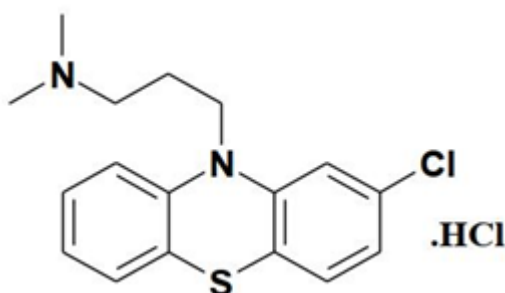
Keywords:

charge transfer; spectrophotometric; O-Chloranil ; chlorpromazine hydrochloride

Introduction

Drug chlorpromazine hydrochloride(CPZH) , is one of the most important derivatives of phenothiazines, Derivatives of phenothiazines has low ionization energy, also electron-donors, And the drug CPZH is a white powder, readily soluble in water and alcohol and partially dissolves in the ether and disintegrate when exposed to air and light ⁽¹⁾, the molecular formula for him $\text{C}_{17}\text{H}_{19}\text{ClN}_2\text{S}.\text{HCl}$, the degree of melting 196°C , $\text{M.wt}=355.33 \text{ g.mol}^{-1}$, and the scientific name

of chlorpromazine hydrochloride according to the IUPAC system is: 2-Chloro-10 (dimethyl amino propyl) phenothiazine hydrochloride ⁽²⁾.



Figure(1) Structural formula of chlorpromazine HCl.

And pharmaceutical drug are Tablet and injections, and has several names, according to Manufacturers ^(3,4) : Largactil , Taroctyl , Chloractil , Thorazine , Hepanil , Marazine .

Different analytical methods were used to estimate the Chlorpromazine hydrochloride (CPZH) include the Spectral methods⁽⁵⁻¹³⁾, chromatographic methods⁽¹⁴⁻¹⁷⁾, electrochemical method⁽¹⁸⁻²¹⁾, and flow-injection techniques⁽²²⁻²⁵⁾.

Experimental

Apparatus:

1-A shimadzu Uv-vis 1800 spectrometer Japan equipped with a quartz cell of 1.0 cm width used for determination and all absorbance measurements .

2- Sensitive Balance Kern Abs 120-4N .

3- Labtech water bath manufacture of lab institute .

Reagents and Materials:

All chemicals and analytical reagents are high purity shown in the Table (1)

Table (1) Reagents and materials chemistry used

Chemicals name	Chemical structure	Company
Orthochloranil	$C_6Cl_4O_2$	SIGMA CHEM.
Acetonitril	CH_3CN	SIGMA CHEM.
Chlorpromazine, HCl	$C_{17}H_{19}ClN_2S.HCl$	SDI
Sodium carbonate	Na_2CO_3	BDH

Preparation of solutions

- **Standard Chlorpromazine Solution, (100 µg/ml)**

prepared by dissolving 0.0100g of CPZH in 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.

- **O-Chloranil reagent Solution (0.005M)**

prepared by dissolving 0.123g of ortho chloranil in 100 ml of acetonitrile

- **Sodium carbonate solution (approximate, 0.1 M)**

prepared by dissolving 1.06 g of pure Sodium carbonate in 100 ml of distilled water .

- **Surface active substances solution (0.1 %)**

Prepared by dissolving 0.100 g of each of Surface active substances compounds (SDS, CTAB, Triton X-100) in a suitable solvents then the volume is completed to 100 ml in a volumetric flask.

- **Interference solutions (1000 µg/ml)**

Prepared by dissolving 0.100 g of each foreign compounds in distilled water then the volume is completed to 100 ml in a volumetric flask .

- **Solution of CPZH tablets formulation (100 µg/ml)**

Largactil CPZH (40 mg), Oubari Pharma - Aleppo-Syrie, every tablet contains 40 mg CPZH the solution is prepared as follows :

Ten tablets are weighed 4.122g and powdered well then a weight 0.4122g is dissolved in distilled water and filtered by paper filtration , the volume is completed with distilled water in volumetric flask of 100 ml which gives the conc. 400 µg/ml, We then take 25 ml of this solution and put it in

a volumetric flask and completed with distilled water in volumetric flask of 100ml which gives the conc.100 $\mu\text{g/ml}$.

Results and Discussion

Optimization conditions

Various parameters which affect the spectrophotometric intensity were studied and the reaction conditions were improved. Subsequent, all experiments were performed in a volumetric flask of 5 mL using 0.4 mL of 0.005 M of O-chloranil, 1mL of 100 $\mu\text{g/ml}$ of CPZH and 0.6 mL of 0.1 M of sodium carbonate. All spectrophotometric measurements were recorded at a maximum absorption wavelength of 543 nm against the blank solution.

Effect of bases solution

Different bases solution were prepared of concentration of 0.1M, Added constant volume of 0.6 ml of these solutions to the Chlorpromazine, HCl and measured absorption at the 543 nm the results showing in table (2) .

Table (2): Effect of base types

Type of base	Abs.
Na_2CO_3	0.07
NaOH	0.02
KOH	0.03

Form the above table it was found that . Sodium carbonate gave maximum color intensity for Chlorpromazine. HCl there for it was recommended for subsequent experiments .

Effect of Order of addition

In order to illustrate the effect of sequence addition on the absorbance of the violet product there were three sequence method of addition are described in Table(3).

Table (3): Effect of Order of Addition

Order of Addition	Abs.
Drug + Reag. + Na ₂ CO ₃	0.070
Drug + Na ₂ CO ₃ + Reag.	0.065
Reag. + Na ₂ CO ₃ + Drug	0.062

Effect of Sodium carbonate volume

The effect of the volume of Na₂CO₃ was studied by adding different volumes (0.4-1.6) ml to volumetric flasks containing 1.0 ml of CPZH (100µg/ml) and 0.4 ml of the reagent solution (5×10⁻³M) and the volume is completed to 5.0 ml with distilled water .

Table (4): Effect of Sodium carbonate volume

Vol (mL) Na ₂ CO ₃	0.4	0.6	0.8	1.0	1.2	1.4	1.6
Abs.	0.053	0.07	0.094	0.103	0.087	0.084	0.073

The volume of 1.0 ml of Na₂CO₃ 1×10⁻¹M (PH=11.25) is the optimum amount because it gave the highest absorption So it is adopted in subsequent experiments .

Effect of Orto- Chloranil reagent amount

The effect of the amount of Orto-Chloranil reagent was studied by adding different volume (0.2- 2.0) ml of reagent (5×10⁻³M) to volumetric flasks containing 1.0 ml of CPZH (100µg/ml), then addition of 0.6 ml of (0.1M) Na₂CO₃ and the volume was completed to 5.0 ml with distilled water, the results are shown in Table (5) .

Table (5): Effect of the amount Orto-Chloranil reagent

Vol. reagent(ml)	0.2	0.4	0.6	0.8	1.0	1.2	1.4	1.6	1.8	2.0
Abs.	0.02	0.07	0.94	0.107	0.113	0.124	0.135	0.127	0.115	0.114

The volume of 1.4 ml of reagent (5×10⁻³M) is the optimum amount because it gave the highest absorption So it is adopted in subsequent experiments .

Effect Of Surface active substances.

Effect of the Surfactant active substances studied on the intensity absorption of Chlorpromazine HCl. (CPZH) -Orto- Chloranil complexes, including sodium dodecyl sulphate (SDS), Triton x-100 and cetyl trimethyl ammonium bromide (CTAB). It was found that these surfactants decreased the absorbance of solution, so that did not depend in subsequent experiments as shown in the table (6).

Table (6): Effect of Surface active substances

Surfactant 0.1% (1mL)	Abs.
Without Surfactant	0.134
SDS	0.127
Triton x-100	Turbid
CTAB	Turbid

Effect of Temperature

At optimum condition, the effect of temperature (5–55 °C) on the Charge Transfer complex reaction was studied. The results have shown that the better absorbance was at a temperature of 30 °C and it is used in subsequent experiments (Table 7).

Table (7): Effect of Temperature

Temp. (°C)	15	20	25	30	35	40	45	50	55
Abs.	0.102	0.118	0.125	0.135	0.131	0.129	0.125	0.114	0.109

Effect of reaction time:

The effect of time on the stability period of the formed colored complex under optimum experimental condition after mixing the components of the reaction and the absorbance of colored species remained constant for at least 40 min.

Table (8): Effect of Time

T (min)	1.0	5.0	10	15	20	25	30	35	40	45
Abs.	0.116	0.135	0.136	0.136	0.136	0.135	0.135	0.135	0.135	0.129

Final absorption spectrum

The spectrum of the formed colored product by coupling (8 $\mu\text{g/ml}$) of CPZH with OrtoChloranil reagent ($5 \times 10^{-3}\text{M}$) in the presence of Na_2CO_3 ($1 \times 10^{-1}\text{M}$) in basic medium (11.25) and temperature 30°C against its corresponding reagent blank show $\lambda_{\text{max}} = 543.0\text{ nm}$

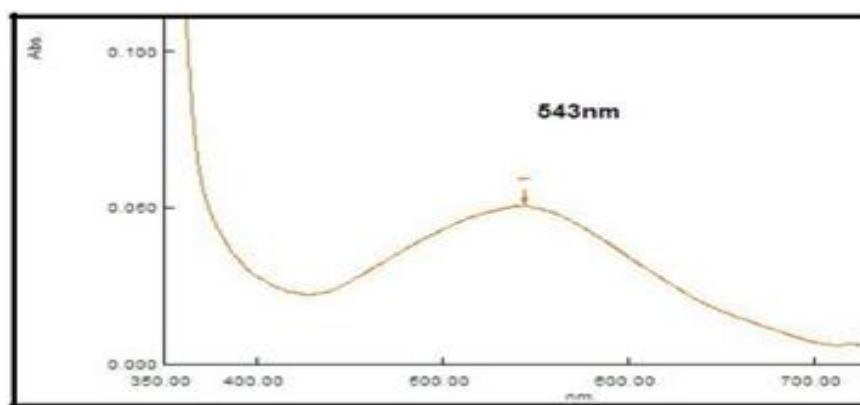


Fig.(2): Absorption spectrum of CPZH - Orto -Chloranil complexes.

Procedure for construction of calibration curve

To a series of solutions containing increasing volume (0.1-2.0) ml of CPZH (100 $\mu\text{g/ml}$) to 5.0 ml volumetric flask containing 1.4 ml of 0.005M o-CA, and 1ml 0.1M of Na_2CO_3 than complete the volume to the mark distilled water and measure the absorption of all solution versus Blank solution at 543.0 nm, linear calibration curve for CPZH with concentration (4.0-36) $\mu\text{g/ml}$,

($R^2=0.9965$), Molar absorption coefficient 1847.87 L/mol. cm, sandel's Index $0.19231\text{ }\mu\text{g/cm}^2$.

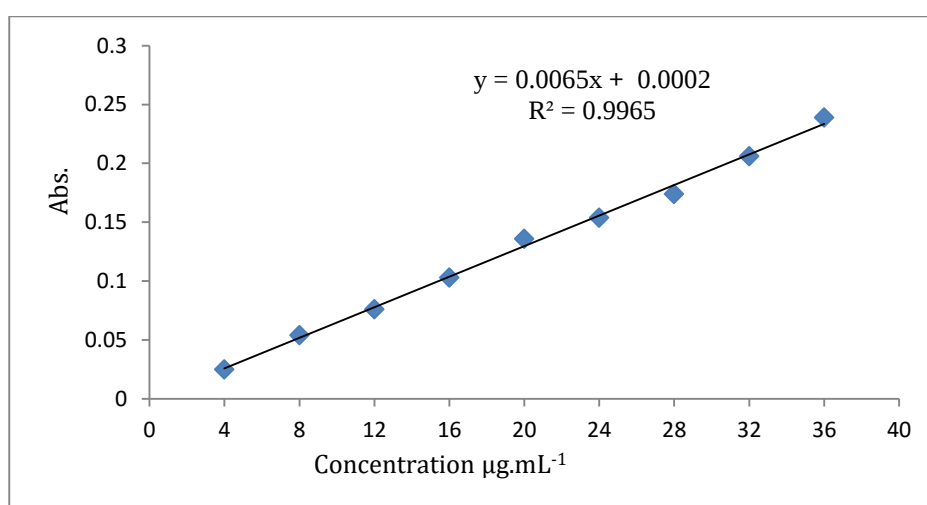


Fig. (3):- Calibration curve for the determination of chlorpromazine

Accuracy and precision

The accuracy and precision of calibration curve measured by determination three different concentration of 100 µg/ml CPZH the product were show in Table (9) which indicate good thoroughness and agreement.

Table (9) precision and accuracy.

Conc. taken µg/ml	Abs.	Conc.found µg/ml	Ave. Of Rec. %	RSD%
8	0.054	8.276	100.416	1.057
16	0.103	15.815		1.288
32	0.206	31.661		1.516

* Average of five determinations

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

The limit of detection (LOD) was calculated by measuring the absorption for the lowest concentration (4 µg/ml) in the calibration curve at the optimum condition The results of LOD and LOQ of the proposed method are summarized in table (10).

Table (10) optical Characteristic and validation data Spectrophotometric method.

No	Parameters	data
1	λ max (nm)	543.0
2	Beers Law limit (µg/ml)	4.0 - 36
3	Colour	violet
4	Correlation Coefficient	0.9965
5	Sandells sensitivity(µg/cm ²)	0.1538
6	Molar absorptivity (L/ mol.cm)	2309.645
7	% Relative standard Deviation	1.22
	(average of five determination)	
8	LOD (µg/ml)	0.3024
9	LOQ (µg/ml)	1.008

Stoichiometry of reaction

The stoichiometry of reaction between CPZH and ortho-chloranil Job's method and molar ratio method were applied the concentration of drug and reagent equal 5×10^{-3} M, in Job's method, we take series of volumetric flasks (5.0 ml), and we put volumes of the drug solution ranging from

(0.1-0.9 ml) and different volumes (0.9-0.1 ml) of reagent solution and added 1.0 ml of Na_2CO_3 (0.1M) and volumes were completed to the mark with distilled water. and absorbance measured at 543.0 nm against the blank reagent. The results fig.(4) show the ratio is 1:1.

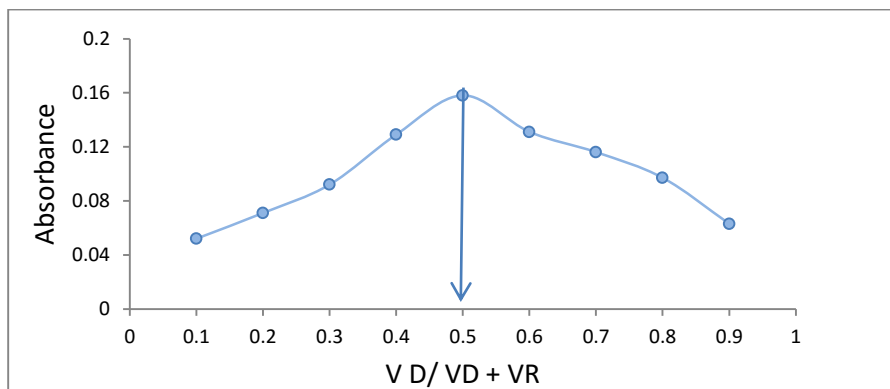


Fig. (4) Job methods

While molar ratio method, 0.4 ml of standard CPZH solution in a series of volumetric flasks 5.0 ml. and added different volumes (0.1-1.0) ml of reagent solution and 1.0 ml of Na_2CO_3 (0.1M) and volumes were completed to the mark with distilled waterd and absorbance measured at 543.0 nm against the blank reagent. The results fig.(5) show the ratio is 1:1.

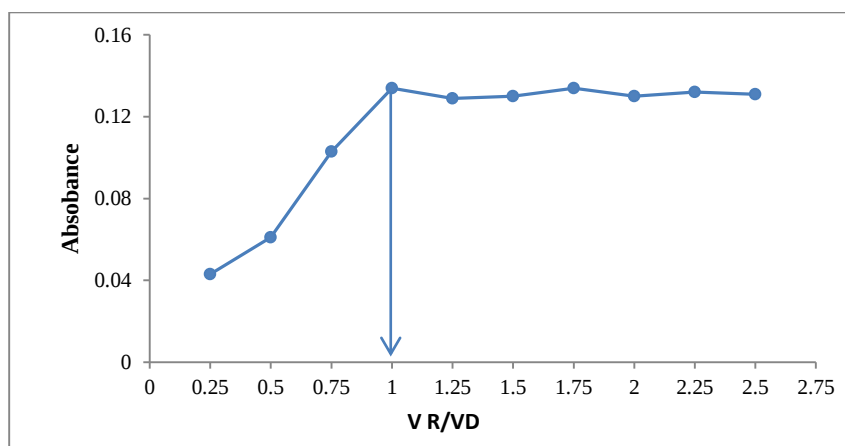
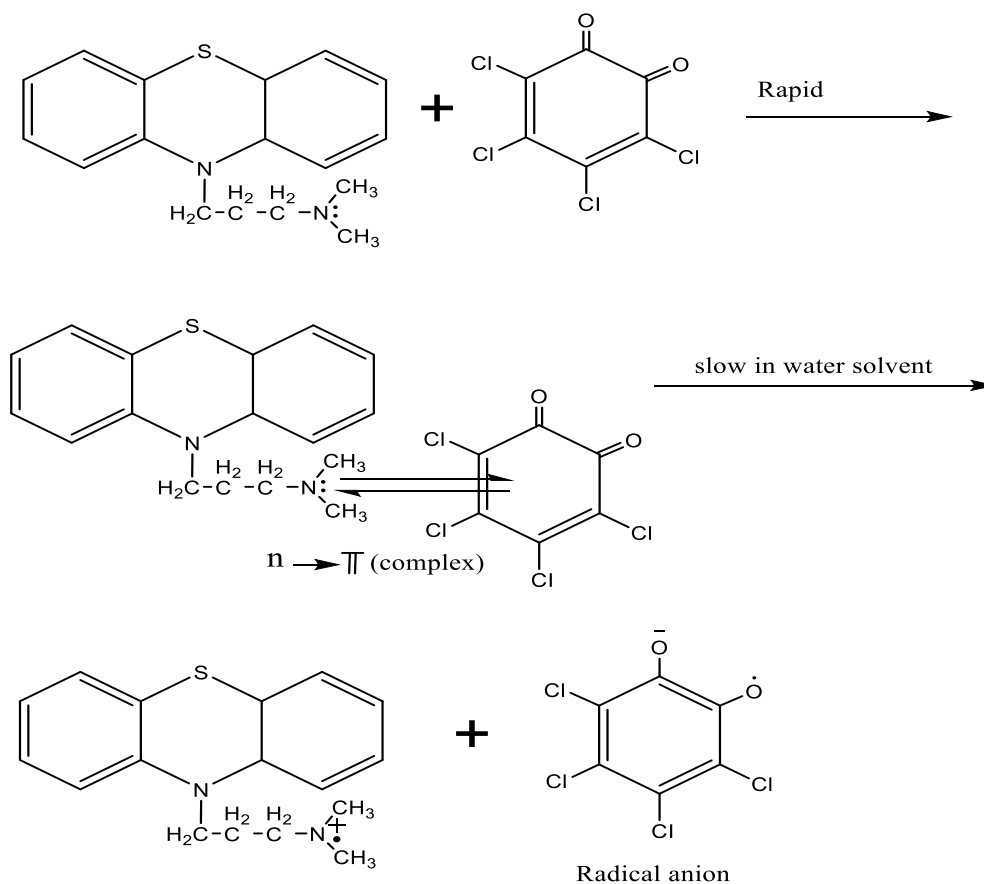


Figure (5) molar ratio method

The proposed mechanism for reaction can be written as follows:



Applications

The method was applied to pharmaceutical preparations containing CPZH Largactil (40mg/Tablet) .

• Direct method

Three different concentration were taken (16,20,24) $\mu\text{g.mL}^{-1}$ the solution treated with the same steps as the calibration curve and measured at 543.0 nm, the result show in Table (11) which indicate to success the suggested method in Assessment CPZH in pharmaceutical preparation .

Table (11) Direct Method.

Drug	Taken ($\mu\text{g.mL}^{-1}$)	Abs.	Found ($\mu\text{g.mL}^{-1}$)	Ave. of Rec%	RSD%
LARGACTIL	16	0.105	16.123		1.095
Tablets	20	0.127	19.507	99.379	1.168
(40 mg)	24	0.156	23.969		1.442

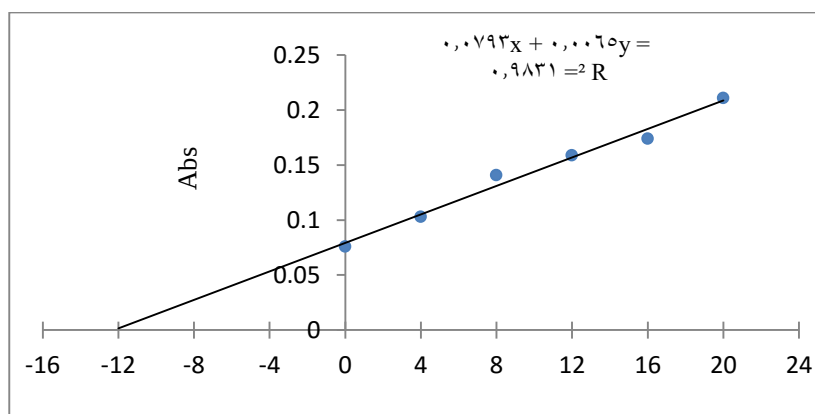
* Average of five determinations

• standard additions method

Apply the standard additions method it based on concentration of the drug by taking 0.6 ml (100 $\mu\text{g/ml}$) solution of CPZH to six 5.0 ml volumetric flasks, then adding increasing volume of standard solution CPZH (0.2-1.0) ml with the 6 bottles remaining without addition. then treated in the same way as the calibration curve and then measured at 543.0 nm. Figure 6 and Table 12 show the results obtained when applying the standard addition method.

Table (12) Accuracy of standard addition method

LARGACTIL Tablets(40 mg)	
Taken($\mu\text{g.mL}^{-1}$)	12
Absorbance	0.077
Found ($\mu\text{g.mL}^{-1}$)	11.8
Recovery%	98.333
RSD%	1.163

**Figure (6) standard addition method**

Conclusions

A fast and accurate method for assessment Chlorpromazine hydrochloride was developed by using charge transfer complex reaction based on the method of reduction CPZH with O-Chloranil and Na_2CO_3 (0.1M). and then complex formation violet color soluble in water and stable for a

period of time of at least 40 minutes maximum absorption at a wavelength of 543nm. The standard calibration curve shows that the linear rang 4-36 $\mu\text{g/ml}$, the recovery is 99.56%, the value of the standard deviation was less than the mean 1.22%, molar absorptivity 2309.645 $\text{L.mol}^{-1}\text{.cm}^{-1}$, and Sandell Index 0.1538 $\mu\text{g.cm}^{-2}$.

The References

- 1- Kojlo A, Karpinska J, Kuzmicka L, Misiuk W, Puzanowska-Tarasiewicz H, Tarasiewicz M. Analytical study of the reaction of phenothiazines with some oxidants, metal ions, and organic substances. Journal of trace and microprobe techniques. 2001 Mar 28;19(1):45-70.
- 2-Al-kaffiji M, Al-anbakey AM, new chromogenic reagent for the spectrophotometric determination chlorpromazine HCl in aqueous solution and pharmaceutical formulations. International journal of pharmacy and pharmaceutical sciences. 2013;5(3).
- 3- Abdine H, Korany MA, Wahbi AM, El-Yazbi F. Colorimetric determination of some sulphonamides with phenothiazine. Talanta. 1979 Nov 1;26(11):1046-8.
- 4-Pharmacopeia B. The Requirements of the 5th Ed. of the European Pharmacopoeia,(2005). CD Rom .
- 5- SK. Jaffar, "Appliction of mbth/ FeCl_3 : A Reliable and coast Effective Analytical Methodology for Routine pharmaceutical Determination of chlorpromazine hydrochloride", International Journal of research and Rrvies in pharmacy and Appled sciences, 2011, 202-206.
- 6- Ahmed AM, Baker MH, Hussein NA. Spectrophotometric determination of chlorpromazine HCl by oxidative coupling method in pharmaceutical formulations. Tikrit Journal of Pure Science. 2017 Aug 5;22(6).
- 7- Dikran SB, Mohammed AK, Hammodi AS. Spectrophotometric Determination of Chlorpromazine–HCl Using Potassium Permanganate. Ibn AL-Haitham Journal For Pure and Applied Science. 2017 Mar 16;28(1):100-12.
- 8- Al-Rufaie MM, Al-Sharefy AN. Spectrophotometric Determination of chlorpromazine Hydrochloride in Pharmaceutical Preparations by Using Oxidative coupling reaction. Iraqi National Journal of Chemistry. 2013(51):338-47.

- 9-** Alwan W, Jasim F, AL-Ayash AS. Spectrophotometric determination of Chlorpromazine Hydrochloride in Pharmaceutical preparations. Iraqi National Journal Of Chemistry. 2009(33):42-53.
- 10-** Al Shatti LA. Method development and validation of assay of chlorpromazine hydrochloride tablet formulation using ultra violet visible spectrophotometry. J. Anal. 2014 Mar 1;2-4.
- 11-**Anwar SM. Spectrophotometric Determination of Chlorpromazine Hydrochloride in Pharmaceutical Preparations by Oxidative Coupling reaction. kirkuk university journal for scientific studies. 2018;13(3):23-36.
- 12-** Humeidy IT. Spectrophotometric determination of Chlorpromazine Hydrochloride by oxidative coupling reaction with P-Bromo aniline using Ammonium Ceric Sulphate Dihydrate. kirkuk university journal for scientific studies. 2016;11(1):1-9.
- 13-** Aljabar RA. Spectrophotometric Determination Of Chlorpromazine Hydrochloride By Oxidative Coupling Reaction With Picric Acid Using Sodium Periodate. journal of kerbala university. 2017;15(1):244-52.
- 14-** Dhabab, Jameel M. "Simultaneous Determination of Chlorpromazine and Trifluo-perazine in Pharmaceutical Preparations Using High Performance Liquid Chromatography." Al-Mustansiriyah Journal of Science 22, no. 2 (2011): 123-128 .
- 15-** Shetti, P., and A. Venkatachalam. "Stability indicating HPLC method for simultaneous quantification of trihexyphenidyl hydrochloride, trifluoperazine hydrochloride and chlorpromazine hydrochloride from tablet formulation." Journal of Chemistry 7.S1 (2010): S299-S313.
- 16-** Zhang G, Terry Jr AV, Bartlett MG. Sensitive liquid chromatography/tandem mass spectrometry method for the determination of the lipophilic antipsychotic drug chlorpromazine in rat plasma and brain tissue. Journal of Chromatography B. 2007 Jul 1;854(1-2):68-76.
- 17-** Zhang G, Terry Jr AV, Bartlett MG. Simultaneous determination of five antipsychotic drugs in rat plasma by high performance liquid chromatography with ultraviolet detection. Journal of Chromatography B. 2007 Sep 1;856(1-2):20-8.

- 18-** Mahmood AR. Indirect Determination of Chlorpromazine Hydrochloride by Square Wave Voltammetry of Sodium Nitroprusside: Application to Pharmaceutical Formulations. Rafidain journal of science. 2013;24(3E):66-75.
- 19-** Frag EY, Zayed MA, Omar MM, Elashery SE, Mohamed GG. Potentiometric determination of chlorpromazine HCl using carbon paste electrode in pure and pharmaceutical preparations. Int. J. Electrochem. Sci. 2012 Jan 1;7:650-62.
- 20-** Sales MG, Tomás JF, Lavandeira SR. Flow injection potentiometric determination of chlorpromazine. Journal of pharmaceutical and biomedical analysis. 2006 Jun 16;41(4):1280-6.
- 21-** Ni Y, Wang L, Kokot S. Voltammetric determination of chlorpromazine hydrochloride and promethazine hydrochloride with the use of multivariate calibration. Analytica Chimica Acta. 2001 Jul 17;439(1):159-68.
- 22-** I. A. Shakir and M. K. Hammood, "New Turbidity metric – Continuous Flow Injection Analysis Method for The Determination of Chlorpromazine HCl in Pharmaceutical Preparation Using Linear Array Ayah 5SXI-T-ID-CFI Analyser", Iraqi Journal of Science, 2015, 55(2) 594-605.
- 23-** Feng S, Li C, Fan J, Chen X. Sequential injection technique for the determination of chlorpromazine hydrochloride in pure form and pharmaceutical formulations. Journal of Analytical Chemistry. 2007 Mar 1;62(3):233-7.
- 24-** S. M Sultan, and F. O. Sulima, " Application of Super Modified Simplex Optimization to The Flow-Injection Spectrophotometric Determination of Promethazine Hydrochloride in Drug Formulations", Anal. Sci., 1992, 8(6), 841 - 843.
- 25-** Al-Hashimi IM, Jassim Hamzah Al-Kaffije M. New approach development for determination of chlorpromazine HCl in pure and pharmaceutical forms using homemade wave length selector flow injection photometer. Karbala Journal of Pharmaceutical Sciences