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NEW SPECTROPHOTOMETRIC METHOD FOR DETERMINATION CHLORPROMAZINE HYDROCHLORIDE IN PHARMACEUTICAL PREPARATIONS BY USING OXIDATIVE COUPLING REACTION

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KEYWORDS:

Chlorpromazine Hydrochloride, Oxidative coupling Spectrophotometric, Determination.

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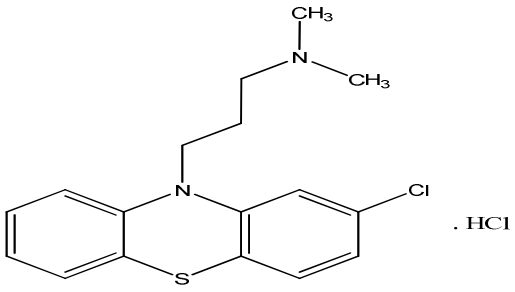
ABSTRACT

A simple, rapid and sensitive spectrophotometric method for the determination of microgram amounts of chlorpromazine Hydrochloride drug in aqueous solution is described. The method is based on the Oxidative coupling reaction between chlorpromazine hydrochloride and para tolidene in the presence of sodium persulphate and hydrochloride acid to form an intense colored product with maximum absorption at 514 nm. Beer's law is obeyed over the concentration range of(0.2 – 15.2) ppm with molar absorptivity of 4.0433 $x10^4$ l/mol/cm.and Sandell`s sensitivity of 0.008 µg.cm^{-2} . The method does not resort to temperature control or to solvent extraction. The optimum conditions for all colour development are described and the proposed method has been successfully applied for the determination of chlorpromazine hydrochloride in bulk drug and pharmaceutical Preparations (Largactil drug). The common excipients and additives did not interfere in this method.

INTRODUCTION:

phenothiazine derivatives are widely used as drugs in the psychiatry [1],treatment of epilepsy [2], Diseases of the stomach, liver, intestines , migraine headaches [3], a counter-movement of ill-dwelling, counter- of Allergy and vomiting [4], tetanus treatment and anti dopamine receptors [5]. Phenothiazine group has sixty four derivatives. They involved in being contain heterogeneous rings.these rings have a sulfur atom and a nitrogen atom. Among the most important of these derivatives was chlorpromazine hydrochloride(CPZ) [6]. Which was discovered in in the early 1950s [7]. And which has the following structure and its structure formula was $C_{17}H_{19}ClN_2S$, HCl and a molecular weight of 355.33 g / mol [8] showen in figure(1).



Figure(1) The chemical structure of chlorpromazine hydrochloride(CPZ)

Where the scientific name of (CPZ) According to (IUPAC) was 3-(2-Chloro-10*H*-phenothiazin-10-yl)-*N*,*N*-dimethylpropan-1-amine hydrochloride. It commercially marketed in Europe as Largactil In the United States on behalf of thorazine. It was a white crystalline powder has melting point 196 C^o with high solubility in water and ethanol, also disintegrate when exposed to light or air [9].The Pharmaceutical Preparations of (CPZ) were tablets , oral Solution and Injection. Due to its therapeutic importance. Many workers in the field of analytical chemistry have made many ways for determination Whether in its pure form or in pharmaceutical Preparations or in body fluids. The most important of these estimation methods is the direct spectroscopic methods. Which depend on the oxidation of drug to the radical Cations [10] and then subsequent measurement of absorption using one of the various oxidizing agents [11-18]. Some of these methods suffer from some disadvantages such as the use of heating , lack of sensitivity , narrow range of the determination , critical working conditions and time-consuming [10, 15, 17]. Procedures based on charge-transfer complex formation [19]. and ion-association complex formation with many acidic dyes such as bromocresol green [10], chrome azurol S, bromophenol blue, eriochrome cyanine, amaranth and brilliant blue [20-24]. The other analytical methods are used for determination (CPZ)compound like high-performance liquid chromatography [25-27], Gas chromatography [28-29] and flow injection with different types of detection system [30-31]. In this paper described a

newly, simple, rapid and sensitive procedure for the determined of micrograms amounts of chlorpromazine hydrochloride(CPZ) depending on the oxidative coupling reaction (reaction to the color generator). and through its reaction reagent (Para toluene in the presence of sodium persulphate as oxidant in the mid of a strong acid and study the optimum conditions for this reaction .the application of the method on some different types of pharmaceutical Preparations which is containing distilled water (CPZ) compound was obtained by different doses and forms with high accuracy and precision.

Experimental

Apparatus : All spectral and absorbance measurements were carried out on applied UV-Visible 160 digital double - beam recording spectrometer , pH meter , Jenway 3020. Sencetive balance ,water bath.

Material and reagents

All Chemicals used were of high degree purity and used without further purification they were prepared by the following:

1- Chlorpromazine: HCl standard powder was provided from the state company for drug industries and medical appliances Samara –Iraq (SDI). The standard stock solution of(CPZ) at a concentration (100) ppm is prepared by dissolving (0.01)gm of pure material in(100)ml Distilled water. This solution is stable for at least a month after saving well away from the light.

2- Sodium persulphate $Na_2S_2O_8$ (0.01) M, It was provided from (BDH Chemicals Ltd, Laboratory reagent) company by dissolving (0.214) gm of pure material in(100)ml Distilled water.

3- Hydrochloride acid (1M): It was provided from (GCC) at percentage (%98) company and used for preparation (1M) solution.

4- Para toludine (0.01) M: it was provided from (BDH Chemicals Ltd, Laboratory reagent) company by dissolving (0.053) gm of pure material in(50 ml) ethanol abselute from(BDH Chemicals Ltd,%99.9) .

Recommended Procedure: In a series of volumetric flasks of (25ml), aliquots of standard solutions of, chlorpromazine hydrochloride with concentrations of (0.2- 15.2) ppm respectively in final volume were added separately, followed by addition of (1ml) Para tolidene (0.01) M and 2 ml of Sodium persulphate (0.01) M, then addition after that(2ml)of Hydrochloride acid (1 M), the contents were in a series of (CPZ) diluted to the mark with distilled water, The solutions were left for 10 minutes in a water bath adjusted at 30°C and the absorbance was measured at (498 nm), respectively against reagent blank and a calibration curve was constructed.

Procedure for Assay of chlorpromazine Hydrochloride in Pharmaceutical Preparations.

a number of preparations Largactil containing (CPZ) as active ingredient were taken and it included the following:-

1- Largactil tablets (100) mg :- they were supplied from (oubari pharma-aleppo-syria) company under licence from Aventis Laboratory-France.
2- Largactil tablets (100)mg :- they were supplied from (ruhsat sahibin- tukey,istanbul) company under licence from Aventis pharma-France.
3- Largactil tablets (50)mg :- they were supplied from the state company for drug industries and medical appliances Samara –Iraq (SDI).
4- Largactil tablets (25)mg :- they were supplied from (oubari pharma-aleppo-syria) company under licence from Aventis Laboratory-France.
5- Largactil injections(25mg/5ml):- they were supplied from (oubari pharma-aleppo-syria) company under licence from: sanofi- Aventis -France.

Procedure for Tablets [9]:

Ten tablets were weighed and finely powdered from each type of tablets separately. An accurately weighed portion of the powder equivalent to(0.01)gm of (CPZ) which depends on the type of tablets that be used, It was dissolved in(5 ml) of ethanol and (5 ml) of (5M) hydrochloric acid with heating and after that filtering to separate the non-dissolved components. Then transferred into a (100ml) calibrated flask and diluted to the final volume with distilled water followed take the suitable amount of each record solution and treated in the same conditions that were used in the based way of working was to find a concentration depending on a calibration curve.

Procedure for Injection [8]:

(2 ml) from ampoule containing (25 mg/5ml) of Chlorpromazine HCl was transferred into 100 ml volumetric flasks and diluted up to the mark with distilled water. Then we calculated the concentration depending on the standard calibration curve.

RESULTS AND DISCUSSION;-

Study the optimum conditions for reaction: Different conditions were studied which are affecting the absorbance of the product formed so as to in order to improve it.

1 – Effect of Reagent volume:

The effect of Reagent volume on the absorbance were studied .It was taken from (0.5 – 4) ml of the reagent Para tolidene (0.01M) with Presence(2ml)of the oxidizing agent and (2 ml)from acidic solution (1 M). It was found that (1 mL) is the best volume of the reagent, that gives the highest absorption, which was used in the following experiments .

2 - Effect of oxidizing agent volume :-

The effect of oxidizing agent volume on the intensity absorption were studied. .it was taken from (0.5 – 6)ml of Sodium persulphate at concentration (0.01M). with Presence(1ml)of the reagent and (2ml)from acidic solution. It was found that (2 mL) is the best volume of the oxidizing agent, that gives the highest absorption, which was used in the following experiments.

3- Effect of acid:-

It was found that the presence of acid led to increase the intensity of the produced product, therefore some acids such as HCl, CH_3COOH,$H_2SO_4$and HNO_3 are examined it was found that all these acids gave the absorbance the color product, so; HCl was selected which was found that(2 ml) of this acid give high sensitivity which selected in subsequent experiments.

4- Effect of Order of Addition :-

It was found that the best order of addition that gives the highest absorption(R+D+O+A)where (R= Reagent, D=drug substance ,O= oxidizing agent and A=acidic solution) which selected in subsequent experiments.

5- **Effect of Temperature:**-

The resulting product of the proposed method were studied at different temperatures. The results indicate that the absorbance values remain nearly constant in the temperature range (0-70ºC), whereas, at higher temperatures the absorbance value decrease, indicating the dissociation of the product on prolonged heating. The coloured product was stable at temperature (30ºC) which was giving the highest absorbance. The room temperature was selected in this method.

6- Effect of Reaction Time:-

The colour intensity appear its maximum after the drug (CPZ) had been reacted immediately with the reagent in the presence of sodium persulphate and acidic solution became stable after 10 minutes. Therefore 10 minutes development time was selected as optimum in the general procedure. The colour obtained was stable at 65 minutes.

7- Absorption Spectra:-

The spectral scan was conducted to obtain the greater wavelength absorption of resulting compound resulting after installing the optimum conditions for reaction against blank solution that was containing the reagent , oxidizing agent and the acid .

Figure (2) shows the spectra of colour product formed and of the reagent blank, the maximum absorption spectra at 514 nm where (A) spectrum represents compound product from the reaction and (B) is giving the spectrum of blank.

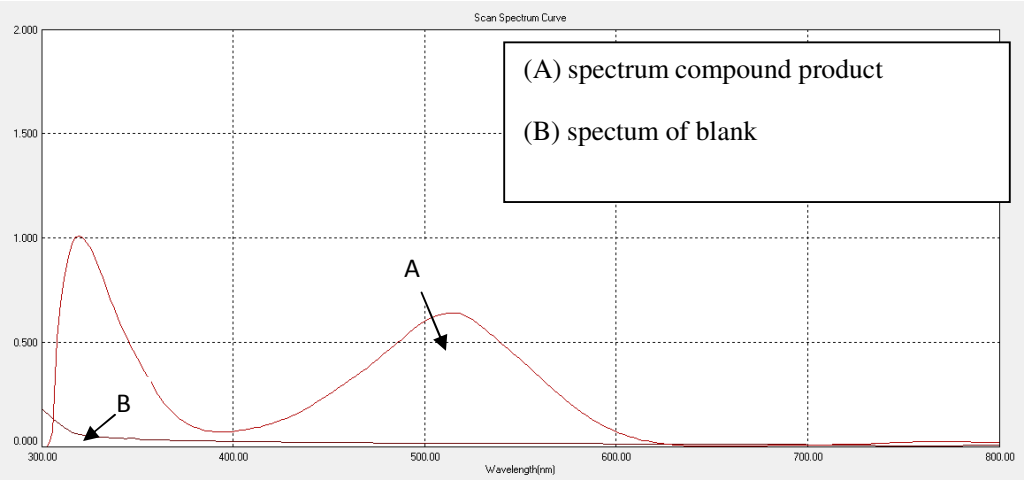
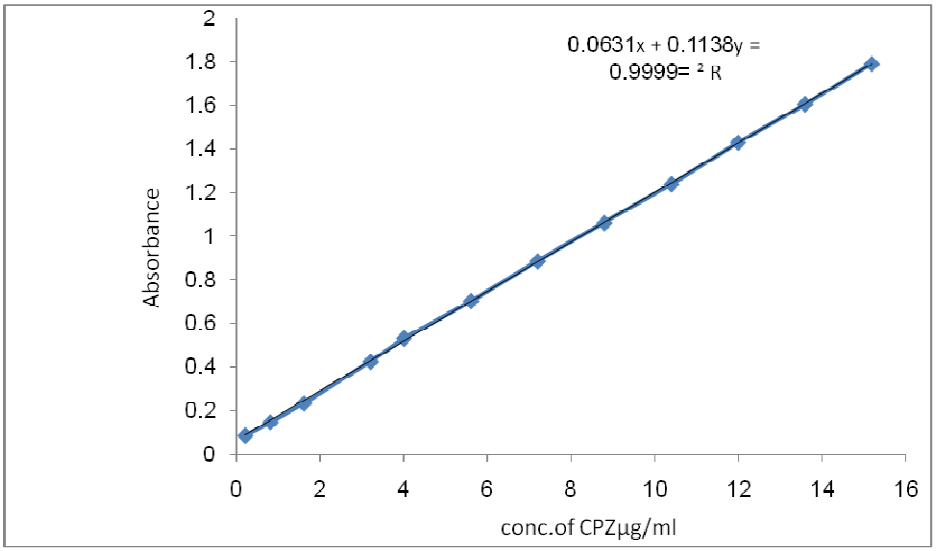


Figure (2) shows the spectra of red product formed at(4ppm) of (CPZ) (A) and of the blank(B)at (0.01M) of reagent and oxidant and (1M) Hydrochloride acid.

8- Calibration curve:-

Employing the conditions described in the procedure, a linear calibration curve for Chlorpromazine – HCl is obtained (Figure 3), which shows that Beer's law is obeyed over the concentration range of (0.2 – 15.2) ppm with correlation coefficient of 0.9999 and an intercept of 0.0631. the slope of curve was 0.1138.The conditional molar absorptivity of the red product formed was found to be 4.0433 x10^4 L.mol^{-1}.cm^{-1}. The Sandell's sensitivity was 0.008 (µg.cm^{-2}). the detection limit (LOD) was 0.581 µg/ml^{-1} . LOQ was 0.281 µg/ml^{-1}.



Figure(3) shows the Calibration curve of (CPZ)

9- Accuracy and precision:-

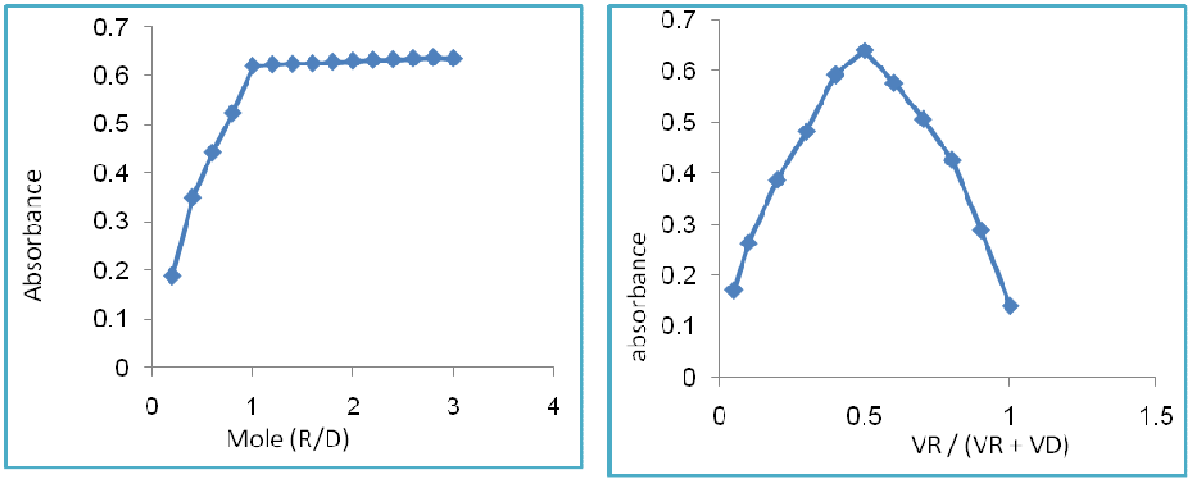
The accuracy and precision of the method, were checked by determining the Chlorpromazine – HCl at three different concentrations. The results represented in Table (1) indicate that the method is satisfactory. and have high accuracy and precision.

Table (1) Accuracy and precision of the proposed method.

Conc. Of (CPZ) ppm	% Error	% Recovery	% R.S.D
1.6	- 1.50	98.50	0.397
3.2	+ 0.84	100.84	0.307
8	+ 0.23	100.23	0.193

10 – Stoicheiometry of reaction :-

The stoicheiometry of the reaction between Chlorpromazine – HCl and the reagent was investigated using Job's method and mole ratio method; the results obtained that 1:1 drug to reagent complex was formed at 498 nm shown (Figure 4). The product formed was soluble in water, The stability constant of the colour was calculated by comparing the absorbance of a solution containing stoicheiometric amount of Chlorpromazine – HCl and the reagent with that of solution containing the optimum amount (1ml of 2.8×10^{-3} M).and other solution reagent solution at five times the concentration of the original concentration. The average conditional stability constant of the colour product in water under the described experimental conditions was 1.40 $\times10^{7}$ $l^{1}.mol^{-1}$.



Figure(4)mole ratio and job methods plots for reaction of (CPZ)with reagent in the presence of NaS_2O_8 and HCl.

The formation of the colour product between(CPZ)and reagent in presence of HCl was suggested at the scheme of reaction probably occurs as the following equation[32] Fig (5):

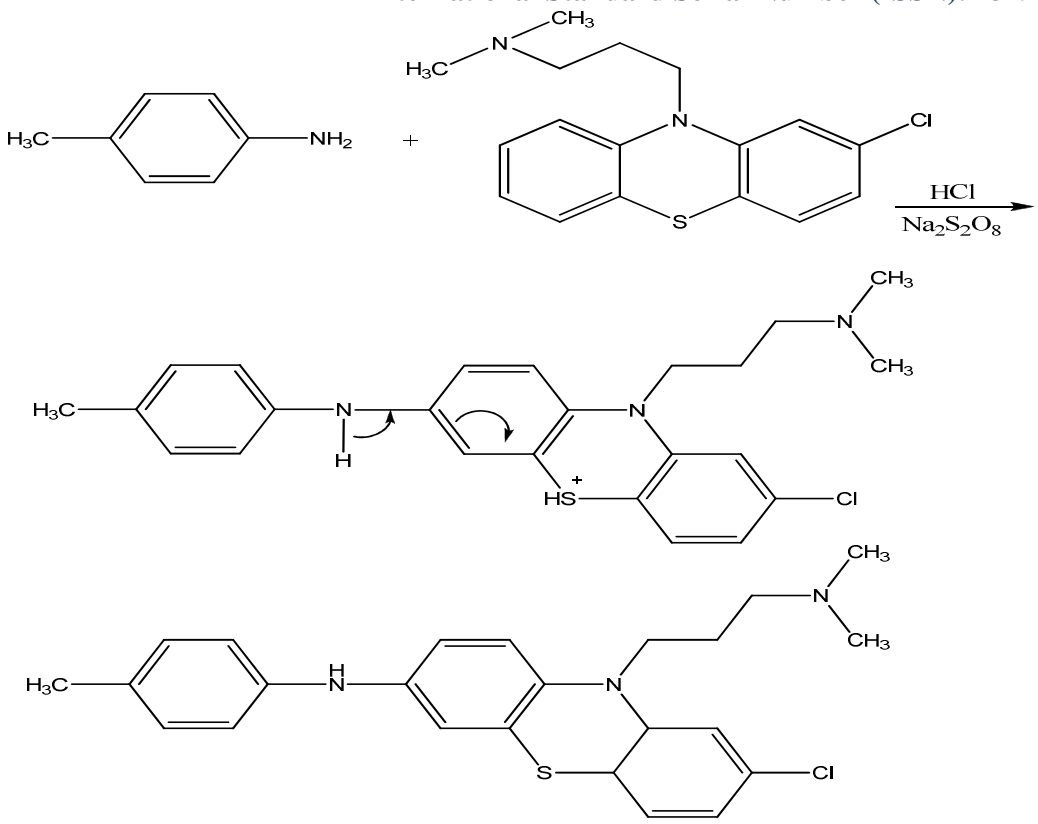


Figure (5) scheme of the oxidative coupling reaction

11- Effect of organic solvents:-

The spectrophotometric characteristics of the colour product in various organic solvents are given in Table (2). Water is shown to be the best medium from the point view of sensitivity and economy.(solvent used in dilution to the mark of (25ml) conical flask.

Table (2): Spectrophotometric characteristics of the colour product in various organic solvents

Solvent	**λ_{max} ,nm**	**ε ,L.mol^{-1}.cm^{-1}**
Acetone	522	2.453×10^3
chloroform	-	Turbid
2- propanol	530	2.195×10^3
Acetic acid	522	1.73×10^4
Dimethyl sulphoxide	-	Turbid
CCl_4	530	1.371×10^3
Dioxane	522	3.085×10^3
Dimethyl formamide	528	2.325×10^3
Ethanol	544	2.007×10^3
Benzene	-	Two layers
Methanol	530	1.660×10^3
Teri butyl alcohol	528	4.417×10^3
Formic acid	-	Turbid
Pyridine	-	Turbid
Di ethyl ether	-	2.453×10^3

12- Interferences:-

The excipients studied were, lactose, talc, starch**,** Acacia, Sucrose, Glucose, magnesium stearate, and polyvinylpirrolidone (PVP). For this study, solution was containing (CPZ) and each one of the excipients was taken separately in concentrations ten-times greater than that of(CPZ) were analyzed under the same procedure in the Calibration curve.(1ml) of (100)ppm solution of drug and (1ml) of each excipients was taken for interferences study and dilution to the mark of (25ml) conical flask . level of interference was considered to be acceptable if the error was not higher than ± 2% relative to the expected No interferences were observed in the determination of (CPZ) in the presence of the excipients studied(Average of three determinations). Table (4)

Table(4)Determination of (4ppm)chlorpromazine hydrochloride in the presence of excipients.

Interference	**% Error**	**% Recovery**
lactose	- 0.125	99.875
Talc	- 0.350	99.650
starch	+ 0.275	100.275
Acacia	- 0.325	99.675
Sucrose	- 0.175	99.225
Glucose	- 0.225	99.775
magnesium stearate	+ 0.4	100.400
PVP	+ 0.550	100.550

13- Application of the method

The applicability of the method for the assay of pharmaceutical formulation was examined. The result of assay for available formulations of Chlorpromazine – HCl drugs are summarized in Table (5) .

Table (5) : Assay of Chlorpromazine – HCl in bulk and dosage forms .

preparations Largactil containing (CPZ)	Average recovery %	
	Proposed method	Standard method[8]
Pure (CPZ)	99.856	100.102
Largactil tablets (100)mg Syria	100.002	99.323
Largactil tablets (100)mg turkey	99.710	99.765
Largactil tablets (50)mg (SDI)	99.252	99.188
Largactil tablets (25)mg Syria	100.099	99.661
Largactil injections(25mg/5ml) Syria	100.027	100.011

Where the average of three determinations. and the standard method were taken from British Pharmacopoeia (2009). The results were reproducible and the assay of formulations was cross checked by the Standard method.

CONCLUSION: A simple, rapid, precise and sensitive spectrophotometric method has been developed for the determination of trace amounts of chlorpromazine hydrochloride in aqueous solution based on its oxidative coupling reaction with para tolidene and sodium persulphate in the

presence of Hydrochloride acid. The proposed method does not require temperature control or the solvent extraction step; the method was applied, successfully for the determined of small amouts commercial (CPZ)drug.

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