Iranian Journal of Organic Chemistry Vol. 9, No. 3(2017) 2161-2167

Modern spectrophotometric approach for assessment chlorpromazine hydrochloride drug

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Received: May 2017; Revised: July 2017; Accepted: July 2017

Abstract: A rapid,simple, and sensitive spectrophotometric approach for theassessment of microgram amounts of chlorpromazine hydrochloride drug in aqueous solution is described. The method is based on the oxidative coupling reaction between chlorpromazinehydrochloride and N-methyl-p-hydroxy aniline (metol)in thepresence of sodium periodate andhydrochloride acid to form an intense redcolored product withmaximum absorption at 526 nm. Beer's law is obeyed over the concentrationrange of(1-20)µg.ml^{-1} with molar absorptivity of 1.597x10^{4}l.mol^{-1}.cm^{-1} and Sandell`s sensitivity of 0.022µg.cm^{-2}. The approach does not resort totemperature control or to solvent extraction. Theoptimum conditions for all color development are described and the proposedmethod has been successfully applied for the assessment of chlorpromazinehydrochloride in bulk drug and pharmaceutical preparations(Largactil drug). The commonexcipients and additives did not interfere in this approach .

Keywords: Chlorpromazine hydrochloride, Oxidative coupling, Spectrophotometric Assessment.

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,counterof allergy and vomiting [4], tetanus treatment and anti dopamine receptors [5]. Phenothiazine group has sixty four derivatives. Theyinvolved 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 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] shown in Figure **1**.

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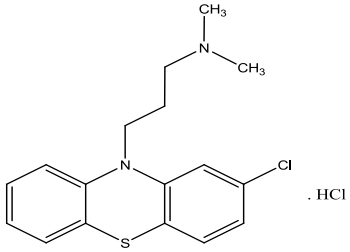

Figure 1: The chemical structure of chlorpromazine hydrochloride(CPZ)

The scientific name of (CPZ) According to (IUPAC) was3-(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 are 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, a newly, simple, rapid and sensitive procedure for the assessed of micrograms amounts of chlorpromazine hydrochloride (CPZ) was describeddepend on the oxidative coupling reaction (N-methyl-p-hydroxy anilinereaction to the color generator) and through its reaction reagent (in the presence of sodium periodate as oxidant in the midt of a strong acid and study the optimum conditions for this reaction. The application of the approach on some different types of pharmaceutical preparations which is containingdistilled water (CPZ) compound was obtained by different doses and forms with highaccuracy and precision.

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.

Effect of Reagent volume:

The effect of reagent volume on the absorbance was studied. It was taken from (0.2 – 3)mL of the reagent(0.01M) with N-methyl-p-hydroxy aniline in presence 1mL of theoxidizing agent and 1ml 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.

Effect of oxidizing agent volume:

The effect of oxidizing agent volume on the intensity absorption was studied. It was taken from (0.2–2)mLof sodium periodate at concentration (0.1M) in presence1 mL of the reagent and 1mL from acidic solution. It was found that 1mL is the best volume of the oxidizing agent, that gives the highest absorption, which was used in the following experiments.

Effect of acid:

It was found that the presence of acid led toincrease the intensity of the produced product, therefore some acids suchas HCl, CH_3COOH,$H_2SO_4$and HNO_3 are examined. It was found that allthese acids give the absorbance of the color product,soHCl was selected whichwas found that 1mL of this acid gives high sensitivity which selected insubsequent experiments.

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.

Effect of Temperature:

The resulting product of the proposed method was 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 valuedecrease, indicating the dissociation of the product on prolongedheating. The colored product was stable at temperature (10ºC) which was giving the highest absorbance.

Effect of Reaction Time:

The color intensity appears its maximum after the drug (CPZ) had been reacted immediately with the reagent in the presence of sodium periodates and acidic solution became stable after 5 minutes. Therefore 5 minutes development time was selected as optimum in the general procedure. The color 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 color product formed and of the reagent blank, the maximum absorption at 526 nm where (A) spectrum represents compound product

from the reaction and (B) is giving the spectrum of blank and (C) spectrum of pure drug.

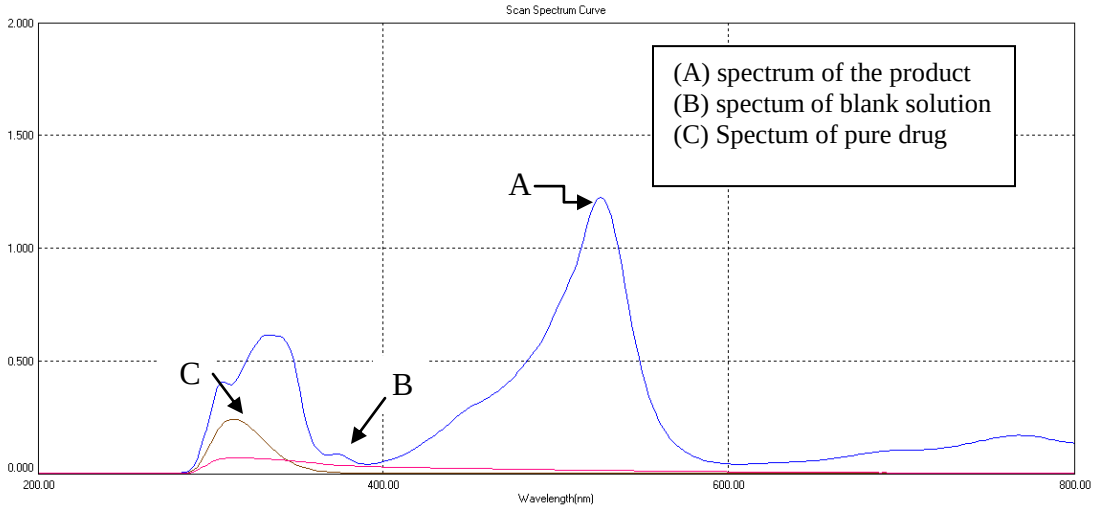

Figure 2: Spectra of the product formed at(10ppm) of (CPZ)(A) and of the blank(B)at (0.01M) of reagent and oxidant and (1M)Hydrochloride acid (C) solution of (CPZ) as pure drug.

Calibration curve:

Employing the conditions described in the procedure, a linear calibration curve for CPZ is obtained (Figure **3**), which shows that Beer's law is obeyed over the concentration range of (1– 20)µg.ml^{-1} with correlation coefficient of 0.9994 and an intercept of 0.045. The slope of curve was 0.015.The conditional molar absorptive of the red product formed was foundto be 1.597x10^{4} L.mol^{-1}.cm^{-1}.TheSandell's sensitivity was 0.022(µg.cm^{-2}), the detection limit (LOD) was 0.252 µg.ml^{-1} and limit of quantization (LOQ) was 0.891 µg.ml^{-1}.

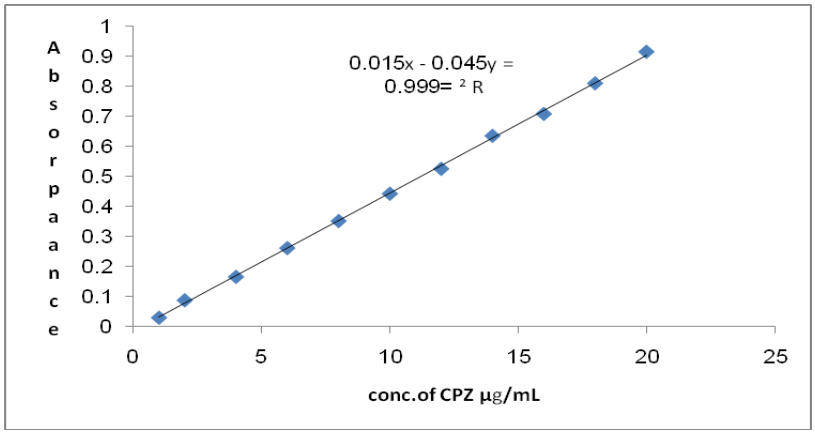

Figure 3: Calibration curve of (CPZ).

Accuracy and precision:

The accuracy and precision of the method were checked by determining the CPZ 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)µg.ml^{-1}	**% Error**	**% Recovery**	**% R.S.D**
2	+ 0.065	100.065	0.043
10	- 0.007	99.993	0.064
18	+ 0.091	100.091	0.124

Stoichiometry of reaction:

The stoichiometry of the reaction between CPZ 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 526nm shown in Figure **4**. The product formed was soluble in water.The stability constant of the color was calculated by comparing the absorbance of a solution containing stoichiometric amount of CPZ and the reagent with that of solution containing the optimum amount (1ml of2.816×10^{-5} M) and other solution reagent solution at five times the concentration of the original concentration. The average conditional stability constant of the color product in water under the described experimental conditions was $3.398\times10^{7}l^{1}.mol^{-1}$.

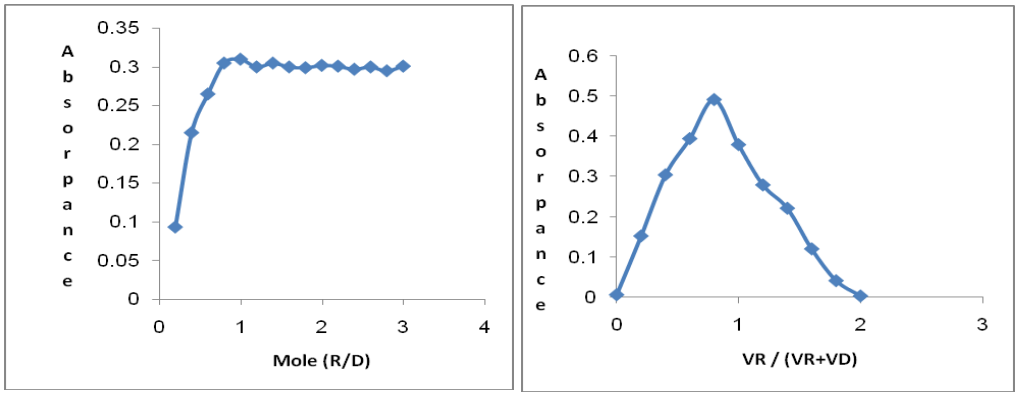

Figure 4: Mole ratio and jobmethods plots for reaction of (CPZ)with reagent in the presence of NaIO4 and HCl.

The formation of thecolored product between CPZand reagent in presence of HClwas suggestedat the scheme of reaction probably occurs as the following [32].

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 (250)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 **2**.

Application of the approach:

The applicability of the approach for the assay of pharmaceutical formulation was examined. The result of assay for available formulations of CPZ drugs are summarized in Table **3**.

Where the average of three assessments and the standard approach were taken from British Pharmacopoeia (2013). The results were reproducible and the assay of formulations was cross checked by the Standard method.

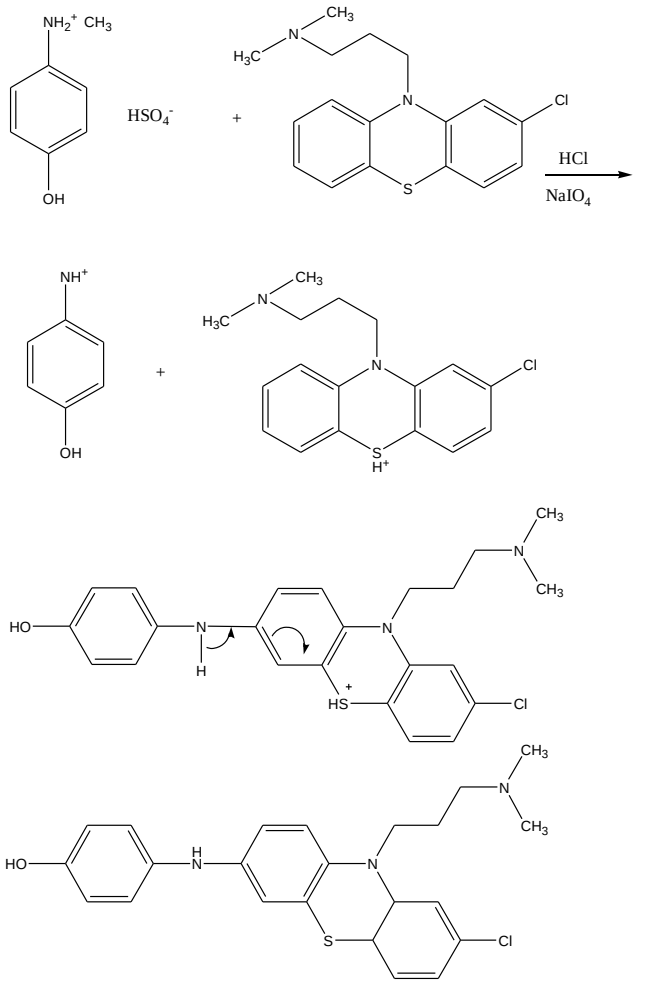

Figure 5: Scheme of the oxidative coupling reaction

Conclusion

A simple, rapid, precise and sensitive spectrophotometric approach has been developed for the assessment of trace amounts of chlorpromazine hydrochloride in aqueous solution based on its oxidative coupling reaction with N-methyl-p-hydroxy aniline and sodium periodate in the presence of Hydrochloride acid. The proposed approach does not require the solvent extraction step; the approach was applied,successfully for the determined of small amouts commercial (CPZ)drug.

Experimental

Apparatus

All spectral and absorbance measurements were carried out on applied UV-vis(UV-1650 Pc) double - beam recording spectrometer and UV-vis (UV-9200) single beam recording spectrometer . pH meter , Shimadzu. Sensitive 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:

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 (250) µg.ml^{-1} is prepared by dissolving (0.025)g of pure material in(100)mL distilled water. This solution is stable for at least a month after saving well away from the light.

Sodium periodate$NaIO_4$ (0.1) M, it was provided from BDH Chemicals Ltd, Laboratory reagent company and prepared by dissolving (1.075)g of pure material in(50)mL distilled water.

Hydrochloride acid (1M),it was provided fromBDH Chemicals Ltd, Laboratory reagent company at percentge (%98) and used for preparation (1M)solution.

N-methyl-p-hydroxy aniline (0.01) M, it was provided from BDH Chemicals Ltd, Laboratory reagent company and prepared by dissolving (0.061)g of pure material in 50 mL ethanol absolute.

Recommended Procedure

Into a series of volumetric flasks of 25mL, aliquots of standard solutions of chlorpromazine hydrochloride with concentrations of (1-20) µg.ml^{-1}, respectively in final volume were added separately, followed byaddition of 1mLN-methyl-p-hydroxy aniline(0.01) Mand 1 mL of sodium periodate(0.1) M,then addition after that 1mLof hydrochloride acid (1 M), the contents were in aseries of (CPZ) diluted to the mark with distilled water. The solutions were left for 5minutes in a water bath adjusted at 10°C and the absorbance was measured at (526 nm), respectively against reagent blank and a calibrationcurve was constructed.

Procedure for Assay of chlorpromazine hydrochloride in pharmaceutical preparations.

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

Largactil tablets (100)mg, were supplied from (oubari pharma-aleppo-syria) company under license from Aventis Laboratory-France.

Table 2: Determination of (10ppm) chlorpromazine hydrochloridein the presence of excipients.

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

Table 3: Assay of CPZin bulk and dosage forms

Preparations Largactil containing (CPZ)	Average recovery %	
	Proposed approach	Standard approach[8]
Pure (CPZ)	100.049	99.996
Largactil tablets (100)mg Syria	99.976	100.981
Largactil tablets (100)mg turkey	100.005	100.380
Largactilinjections(25)mg	99.732	99.859
Largactil tablets (25)mg Syria	100.015	100.820
Largactilsyrup (40)mg	100.02	100.846

Largactil tablets (100)mg,were supplied from(ruhsat sahibin- tukey,istanbul) company under license from Aventis pharma-France.

Largactil syrup (40)mg,were supplied fromthe state fabricado sob licenca from Aventis Laboratory-Turky. Largactil tablets (25)mg,were supplied from(oubari pharma-aleppo-syria) company under license from Aventis Laboratory-France.

Largactilinjections(25mg/5ml), were supplied from(oubari pharma-aleppo-syria) company under license 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(0.025)g 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 thenon-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 Syrup:

Thesyrup containing (40 mg/mL) of CPZ takes (0.625mL) it was transferred into 100 mL volumetric flasks and diluted up to the mark with distilled water. Then the concentrationwascalculated depending on the standard calibration curve.

Procedure for Injection [8]:

One milliliter from ampoule containing (25 mg/mL) of CPZ was transferred into 100 mL volumetric flasks and diluted up to the mark with distilled water. Then the concentrationwascalculated depending on the standard calibration curve.

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