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Determination of trace amount of Chlorpromazine hydrochloride in its pure form and in Pharmaceutical Preparations by using spectrophotometric analysis

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Abstract— A spectrophotometric analysis for valuing microgram quantities of Chlorpromazine hydrochloride drug in aqueous solution is defined that is simple, fast, and sensitive. The process is based on the formation of an intense red colored substance with maximum absorption at 530 nm from a transition metal complex between Chlorpromazine hydrochloride and Lead (IV) oxide (metal) in the existence of hydrochloride acid. With a Molar absorptivity of 2.9394 $x10^4$ $l.mol^{-1}.cm^{-1}$ and a Sandells sensitivity 0.014µg.Cm^{-2}, Beer's Law is followed over a concentration range of (1-20) µg.ml^{-2}. The planned process has been effectivelyuseful for assessment of Chlorpromazine hydrochloride in pharmaceutical preparations (Largactil drug)and bulk drug, and The optimum conditions for all colour production are defined. In this methodology, shared excipients and additives had no effect.

Keywords: Chlorpromazine hydrochloride, transition metal complex, Spectrophotometric Assessment.

Introduction

Phenothiazine derivatives are widely used as medicines to treat disorders of the stomach, intestines, and liver, as well as migraine headaches [1], psychiatry [2], epilepsy treatment [3], anti-dopamine receptors and tetanus treatment [4], a countermovement of ill dwelling, allergy counter and vomiting [5]. There are sixty-four derivatives in the phenothiazine group. They have rings that are heterogeneous. A nitrogen atom and a sulphur atom are present in rings. Chlorpromazine hydrochloride (CPZ) was in the center of the most common of these derivatives[6].Which was foundin the beginningof 1950s[7] ,and has the next structure and molecular weight of 355.33 g/mol, as well as the formula $C_{17}H_{19}ClN_2S.HCl$ and presented in Fig1

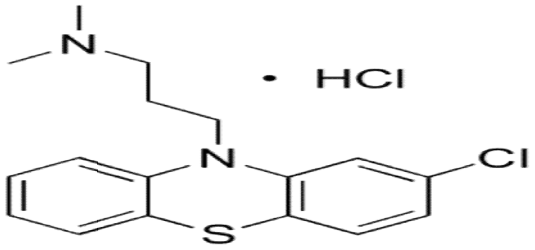


Figure 1: chlorpromazine hydrochloride structure (CPZ)

According to (IUPAC), the scientific name for (CPZ) was 3-(2-Chloro-10 H-phenothiazin-10-yl)-N,N-dimethylpropan-1- amine hydrochloride. In Europe, it was advertised as Largactil, while in the United States, it was advertised as Thorazine. It was a White crystal powder with a melting point of 196 C^o and strong solubility in ethanol and water, as well as the ability to degrade when exposed to air or light [9]. Injection, oral solution, and tablets were the pharmaceutical (CPZ) preparations. Because of its therapeutic value, many analytical chemists have invented different methods for evaluating it. It can be found in its purest form, as well as in body fluids and pharmaceutical preparations.Bestsignificant of these approximation methods are spectroscopic methods that use direct light. Which are based on the drug being oxidized to a radical Cation [10] and then measuring absorption with one of the oxidizing agents [11-18]. Some approaches have difficulties, such as a narrow range of the determination, use of heating, a lack of sensitivity , time-consuming and critical

working conditions [10, 15, 17]. ion association complex formation with a number of acidic Dyes, likeBromocresol green[10], eriochrome cyanine, chromeazurol S, amaranth and brilliant blue, and bromophenol blue [19-23], and charge-transfer complex formation with bromophenol blue [24]. For evaluating (CPZ) compound similarity, other analytical methods such as gas chromatography [25, 26], high-performance liquid chromatography[27-30][31,32] and flow injection with various forms of detection systems. In this paper, a rapid, quick, modern, sensitive method for determining the concentration of micrograms of Chlorpromazine Hydrochloride (CPZ) was identified, based on the transition metal complex with $PbCl_4$ and its reaction in the presence of a strong acid, with the aim of determining the best reaction conditions. The technique was applied to a variety of pharmaceutical preparations holding distilled water (CPZ) compound, and various doses and types were discovered with high precision and accuracy.

Reagents and Materials

Many of the chemicals used were not filtered and were of high purity further. They were made by the following:

Chlorpromazine HCl is a form of chlorpromazine. Dissolving (0.02) g of pure (CPZ) in (100)mL distilled water yields a standard solution of (CPZ) with a concentration of (200) g.ml-1. After saving far away from light, this solution is stable over a period a month. Pure powder was produced by the State Company for medical equipment and drug Industries, Iraq – samara(SDI)

Hydrochloride acid (1M) wassupplied byBDH Chemicals Ltd,a laboratory reagent company, at a percentage (percentage 98) and was used to prepare (1M) solution.

Lead(IV) oxide (0.02) M, it was supplied byBDH Chemicals Ltd, Laboratory reagent company and prepared by dissolving (0.239)g of pure material in 50 mL of distilled water.

Experimental

Apparatus

Both absorbance measurements and spectral were accepted on the applied UV-VIS (UV-9200) single beam recording spectrometer and a pH meter, Shimadzu water bath, and Sensitive balance. Double-beam UV-VIS (UV-1650 Pc) recording spectrometer

Procedure Suggested

In a sequence of 20mL volumetric flasks, aliquotsNormal chlorpromazine hydrochloride solutionswith concentrations of (1-20) $\mu g.ml^{-1}$.The final volume was separately inserted, followed by1mLof lead tetrachloride .After that, the content of 1mLof hydrochloride acid (1 M). They were diluted to the mark with a sequence of (CPZ)Water that's distilled. The mixture were left in water bath for 20 minutes at 10 ° C was modified and the absorption wasMeasured at (530 nm) versusmetalBlank and constructed a calibration curve

Tablets Procedure [9]

A total of ten pills were weighed and thinly powdered from every kind of tablet. A powder section that is precisely measured and equal to (0.020)g of CPZ It is based on the type of tablet used. 5 mL ethanol and 5 mL HCl are dissolved in (5M). After heating and filtering, hydrochloric acid is obtained. To separate the elements, which will then be redissolved. Then one, then the other. Transported to a 100mL measured flask and diluted to the last quantity with distilled water. It was then monitored by taking a sufficient quantity of each best solution and treating it in the same states

that were used in the simple working method of concentrating on a concentration centered on a calibration curve.

Injection Procedure [8]

One millilitre of CPZ (50 mg/mL) was moved to 100mL volumetric flask and diluted to the spot concentration with distilled water. The concentration was then measured using the steady calibration curve as a reference.

Results and discussion

Test the optimal reaction conditions: - Various conditions affecting the absorbance of the product yield were explored in order to enhance it.

Acid Effect

The existence of acid has been found to rise the strength of product, so some acids like, HNO_3, CH_3COOH, HCl, H_2SO_4 have been tested. Each of these acids were found to absorb the color product, HCl was chosen. It was discovered that 2mL of HCl has the highest sensitivity, which was chosen in several experiments.

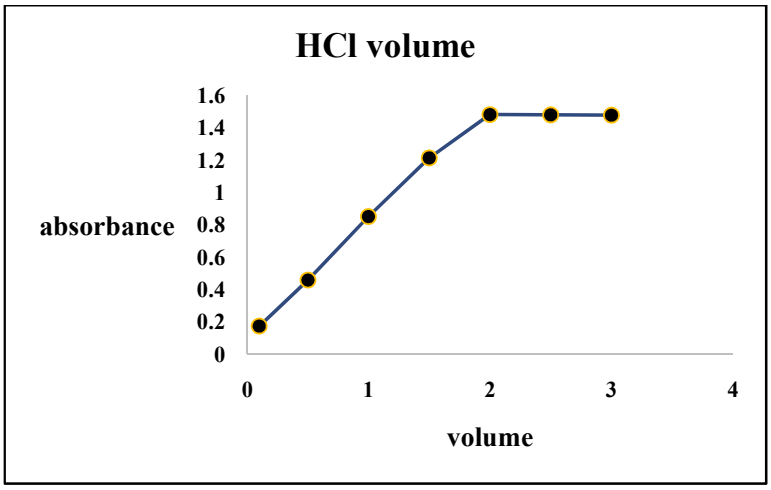


Figure 2: effect of HCl volume

Addition Order Effect

The best addition order that provides the maximum absorption (D+M +A)where (M= metal, D= drug content, and A= acidic solution) was chosen in followingtests was found.

Temperature Effect

The end result of the intended method was tested at various temperatures. The results show that values of the absorbance are approximately constant over a large temperature range (0-60^{o}C), but they decrease at higher temperatures, suggesting that the material dissociates when heated for long periods of time. The coloured product was kept at the same temperature (10^{o}C) throughout, resulting in optimum absorption.

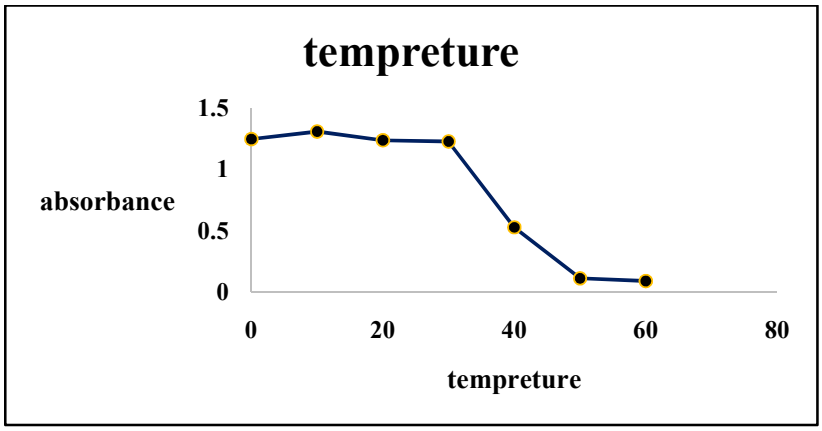


Figure 3: effect of temperature

Reaction Time Effect

The drug (CPZ) was reacted straight with metalin exist of HCl, the colour strength appears to be its maximum and after 20 minutes, the acid solution became stable. Therefore, in the general method, 20 minutes of development time was chosen as optimal.

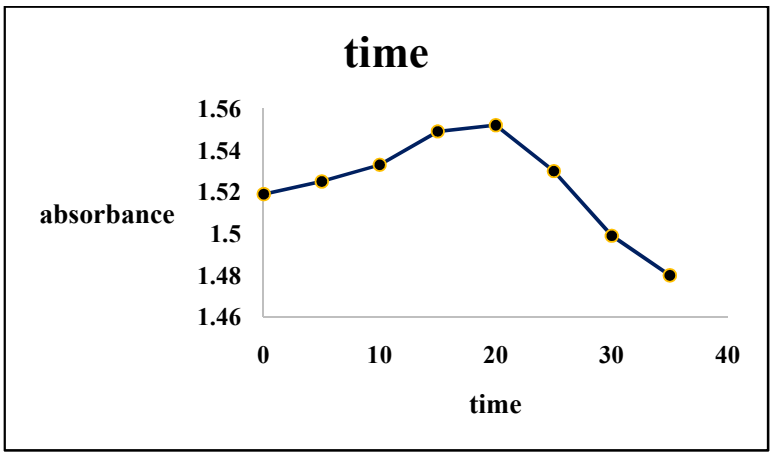


Figure 4: Effect of time

MetalVolume Effect

The impact of the Pb (IV) concentration was examined by measuring the arrangements containing (1 mL) of CPZ and different sums of lead (0.1-3 ml). The absorbance of the CPZPb (IV) complex at first expanded directly as the concentration of the Pb (IV) particle expanded, and after that tapered off (Fig. 5). The ideal volume of Pb (IV) was1.5 mLand this was chosen for total complex formation in ensuing tests

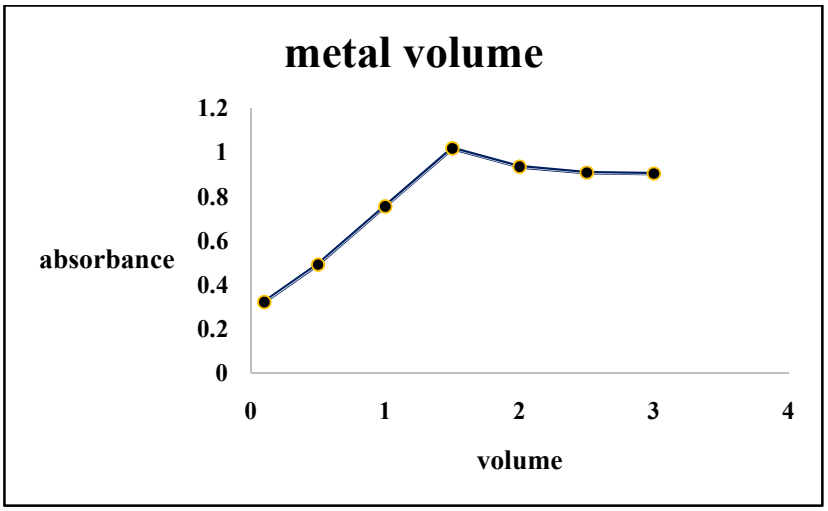


Figure 5: Effect of Metal volume

Absorption Spectra

After fitting the optimal conditions for reaction versus a blank solution containing metal and acid, the scan of Spectral was shown to achieve better wavelength absorption of the resulting compound.

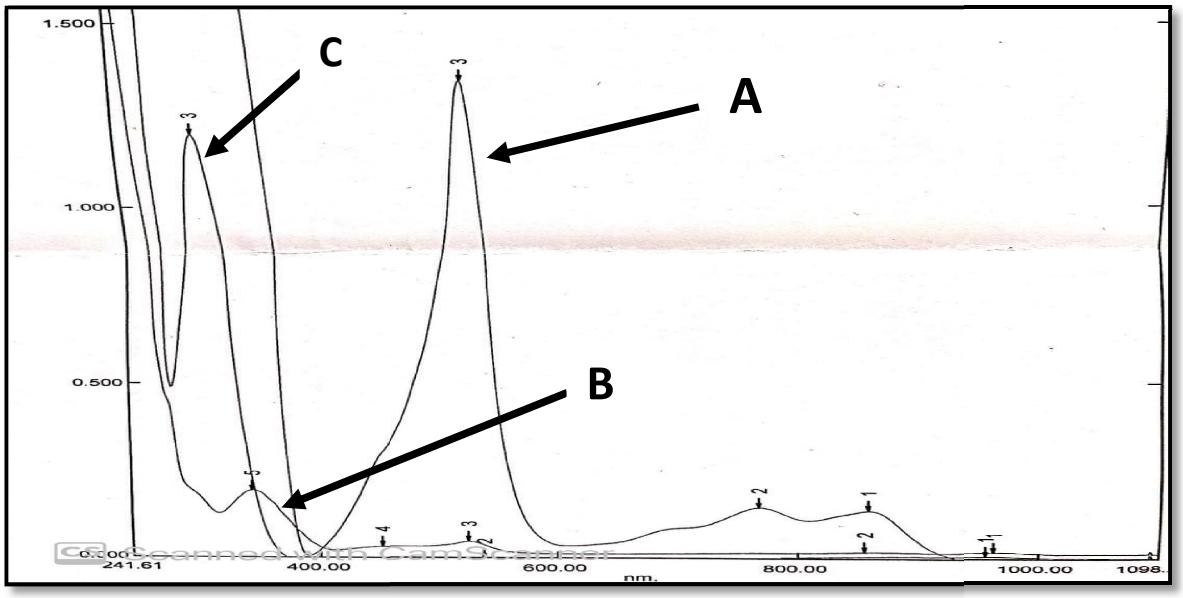


Figure6 The product's spectrum (A) and the blank solution's spectrum (B). (C) Pure drug spectrum

Calibration curve

A linear calibration curve for CPZ is found using the conditions labeled in the procedure, showing that Beer's Law is obeyed over the concentration spectrum of (1– 20)µg.ml^{-1} with a coefficient of correlation 0.9992 and a slope of 0.0828 and an intercept of 0.0773. The red substance produced had a subjunctive molar absorptive of 2.9394 x10^{4} L.mol^{-1}.cm^{-1}. The sensitivity of the Sandells method was 0.014(µg.cm^{-2}), the limit of quantization (LOQ) was 0.124 µg.ml^{-1}, and the detection limit (LOD) was 0.037 µg.ml^{-1}.

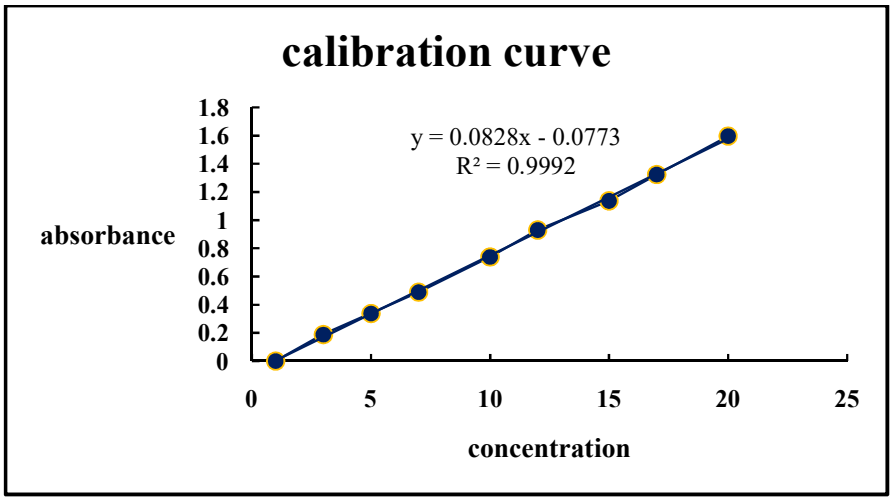


Figure 7: calibration curve

Table1: Analytical Parameter for Determining (CPZ)

Parameters	Values
Beer's Law Limit (µg/mL)	(1-20)
Molar Absorptivity (L / mol.cm)	$2.9394x10^4$
Sandell's sensitivity (µg/cm2)	0.014
Limit of Detection (LOD) (µg/mL)	0.037
Limit of Quantitation (LOQ) µg/mL	0.124
R.S.D%	0.326
Correlation Coefficient	0.9992
Slope	0.0828
Intercept	0.0773

Precision and accuracy

The CPZ was used to test the method's accuracy and precision. At three levels of concentration. Table 2 demonstrates that the procedure is appropriate, with a high degree of precision and accuracy.

Table 2: The expected method's accuracy and precision

Conc. of(CPZ)µg.ml^{-1}	% Error	% Recovery	% R.S.D
3	+1.33	100.013	0.8
10	-0.1	99.9	0.093
15	-0.4	99.6	0.086

Stoichiometry of reaction

Job's method and the mole ratio method were used to investigate the ratio of the reaction between CPZ and metal; the results showed that a 1:1 metal to drug complex was developed at 530nm, as presented in Figure4. The resulting products were water soluble. The color stability constant was determined by Comparison of the absorbance for a solution consist ofstoichiometric concentrations of CPZ and thus the metal to that of a solution consist ofthe optimal volume (1ml of 2.42610^{-6} M) and an alternative metal solution by five times the first concentration. Under stated experimental conditions, color product's standard provisional stability constant in water was 7.128 X 10^6 l.mol^{-1}

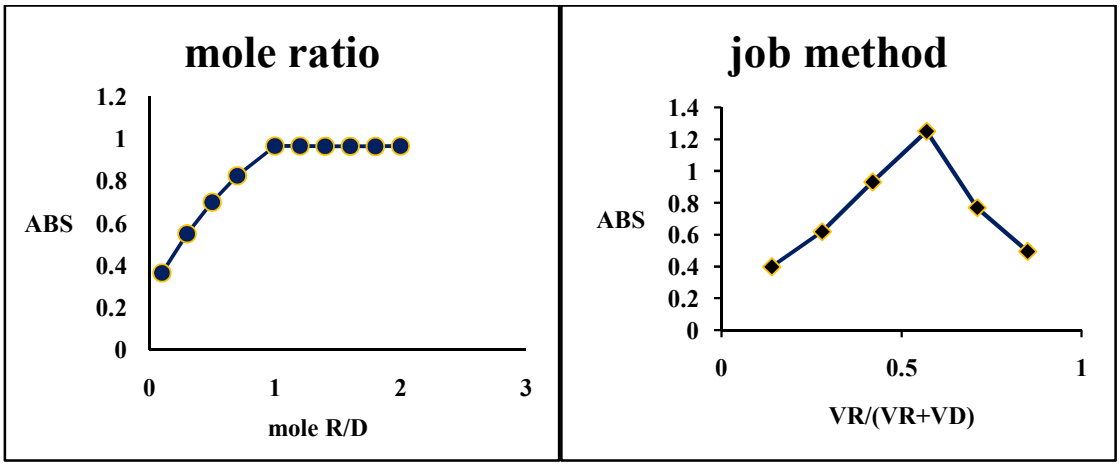
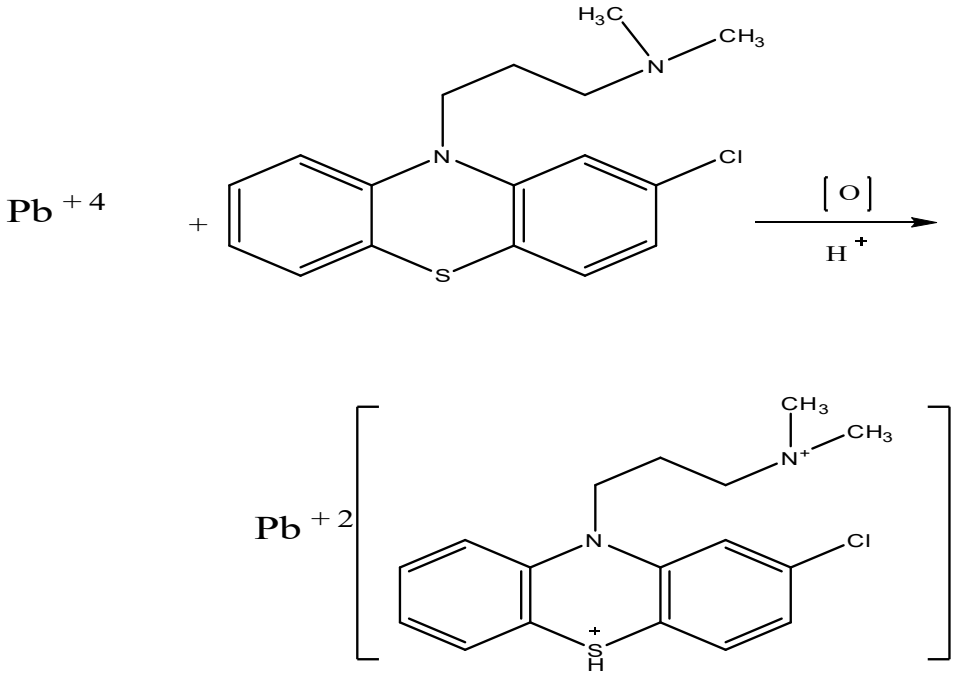


Figure 8: Plots for the reaction of (CPZ) with metal in the existence of HCl using the mole ratio and job methods.

Suggested mechanism

According to the reaction scheme, the colored substance formation between CPZ and reagents in the existence of HCl most likely occurs as follows:



Scheme 1 .The suggested mechanism of reaction for the proposed method

Interference:

The identified excipients were, fructose, ascorbic acid , benzoic acid , starch , urea , $CaCl_2$, talc , cellulose , spartam , cholesterol , sucrose , lactose , NaCl , sodium sulphateand sodium succinate . The solution containing (CPZ) was used for this analysis under the same procedure, each of excipients was measured alone at ten times concentrations higher than CPZ in the calibration curve. 1mL of (200) ppm drug solution and 1mL of every excipient were taken for interference analysis and dilution to the spot of a (20ml) volumetric flask. If the error was less than 2% as compared to the expected amount,

the level of interference was considered reasonable. There was no intervention found in CPZ determination of in the life of the excipients evaluated (average of three determinations), Table 3.

Table 3: Determination of 10ppmChlorpromazine hydrochloridein the Existence of excipients

Interference	**%Error**	**%Recovery**
fructose	0.8	100.8
ascorbic acid	-1.9	98.1
benzoic acid	-1.5	98.5
starch	-1.3	98.7
urea	2	102
$CaCl_2$	0.1	100.1
talc	1.7	101.7
cellulose	1	101
spartam	1.6	101.6
cholesterol	-0.4	99.6
sucrose	0.2	100.2
lactose	1.8	101.8
NaCl	2	102
sodium sulphate	-1.6	98.4
sodium succinate	-0.1	100.2

Chlorpromazine HClinPharmaceutical Formulations Assay Method.

A variety of preparations having (CPZ) as an active Component (Largactil) were examined, and the next were found:

Largactil tablets (100 mg) were given by the company (Ruhsat Sahibin- turkey, Istanbul) under license by Aventis Pharma-France.

Under license from Aventis Laboratory in France, LargactilTablets (100 mg) were given by (Oubari Pharma - Aleppo, Syria).

Under license from Aventis pharma France, argactil injections (50mg/5ml) were supplied by (ruhsatsahibin- turkey, Istanbul).

Table 4: Chlorpromazine Hydrochloride Assay in Pharmaceutical Preparations

Preparations Largactil consist of (CPZ)	Concentration of chlorpromazine hydrochloride (ppm)	Relative Error %	Recovery %	R.S.D%
Largactil tablets (100)mg turkey	3	-2	98	0.424
	10	-3.8	96.2	0.138
	15	-2	98	0.061
Largactil tablets (100)mg Syria	3	-3.6	96.33	0.451
	10	-4.4	95.6	0.097
	15	-2.6	97.4	0.088
Largactilinjections(50)mg	3	-4.33	95.67	0.434
	10	-4	96	0.097
	15	-2.33	97.66	0.061

Table 5: Optimization of conditions for the proposed method

Parameter	Investigation condition	Condition in procedure
λ_{max} (nm)	380-760	526
Effect of acid (ml)	0.1-3	2
Effect of temperature (^{0}C)	0-60	10
Incubation time(min.)	0-40	20
Effect of metal (ml)	(0.1-3)	1.5

Conclusion

Based on its transition metal complex with lead (IV) oxide in the presence of Hydrochloride acid, a precise, rapid, simple, sensitive spectrophotometric technique has been established for the valuation of trace quantities of Chlorpromazine HClat aqueous Solution. The planned approach does not involve a solvent extraction phase; it was effective in determining small quantities of profitable (CPZ) drug.

References

[1] Robinson, O.P.W., J.Med. Postgard,"Spectrophotometric Determination of chlorpromazine Hydrochloride in Pharmaceutical Preparations by Using Oxidative coupling reaction"**1973**,4,77
[2] Tarasiewicz, H. P.; Kuzmicka, L.; Karpinska, J. &Lukasiewicz, K.M., Anal. Sci.,"Modern spectrophotometric approach for assessment chlorpromazine hydrochloride drug"**2005**, 21, 1149.
[3] Diaz, J. N. J. Prentice Hall,"aBlood-Based Screening Tool for Alzheimer's Disease That Spans Serum and Plasma": Findings from TARC and ADNI**1997**, 285.
[4] Healy, D., "Explorations in a New World the Creation of Psychopharmacology", Harvard University Press. **2004**, 77.
[5] Gordon, M., "Psychopharmacological Agents", Vol. II, Academic Press, New York, **1964**, 178.
[6] The Merck Index on CD-Rom" 12th ed., copy right by Merck Co., Inc. Whiteho., **2000**.
[7] Karpinska, J.; Starczewska, B.; Puzanowska, H. Anal.Sci.,Analytical Properties of 2- and 10-Disubstituted Phenothiazine Derivatives**1996**, 12(2), 161.
[8] British Pharmacopoeia, Her Majesty's Stationary Office, London, **2009**, 1292-1293, 8319-8324.
[9] US Pharmacopoeia XXIIth Rev., US Pharmacopoeia Convention, Rockville, MD, **2007**, 294-295.
[10] Basavaiah, K.; Krishnamurthy, G. Anal. Lett."Spectrophotometric Assay of Some Antipsychotropic and Anticholinergic Phenothiazine Drugs Using Ammonium Molybdate"**1998**, 31, 1037-1046.
[11] Basavaiah, K.; Swamy, J. M., Anal. Sci.,"newspectrophotometricmethodfordeterminationchlor promazinehydrochlorideinpharmaceuticalpreparationsbyusingoxidativecouplingreaction" 2001, 17,963-976.
[12] Revanasiddappa, H. D.; Veena, M. A. Zh. Analit. Khim,**2008**, 63,157-161.
[13] Basavaiah, K.; Swamy, J. M. Chem. Anal. (Warsaw),"Spectrophotometric Determination of chlorpromazine Hydrochloride in Pharmaceutical Preparations by Oxidative coupling reaction"**2002**, 47,139-164
[14] Misiuik, W.; Tarasiewicz M., Pharmazie, "Efficacy of a drug composed of herbal extracts on postoperative discomfort after surgical removal of impacted mandibular third molar: a randomized, triple-blind, controlled clinical trial"**1993**, 48, 66-67.
[15] Taha, A. M.; El-Rabbat, N. A.; El-Kommos, M. E.; Refat, I. H, Analyst,"Spectrophotometric Determination of some Phenothiazines Using NChlorosuccinimide"**1983**,108,1500-1505.
[16] Misiuik, W.; Tarasiewicz, M., Pharmazie,"A Highly Sensitive Spectrophotometric Method for the Determination of Some Phenothiazine Antipsychotics Using Chloramine-T and Indigocarmine"**1996**, 51, 62.

[17] Hassan, S. M.; Belal F.; Ibrahim, F.; Aly, F. A., Anal.Lett."Colorimetric Determination of Some N-Substituted Phenothiazine Derivatives Using 2-Iodoxybenzoate"**1989**, 22, 1485-1498.
[18] Murthy, K.C.S.; Seetharamappa, J., Indian J. Pharm. Sci., **2000**, 62,273-276.
[19] Basavaiah, K.; Swamy, J.M.; Krishnamurthy, G.Chem.Anal.Warsaw, "Spectrophotometric Determination of Chlorpromazine Hydrochloride Using Oxidation Reduction Method based on Reaction of Iron (II) with 2, 2` -Bipyridyl Reagent"**1999**, 44, 1049-1054.
[20] El-Kerdawy, M. M.; Moustafa M. A.; El-Ashry, S. M. ; El-Wasee, D. R., Anal.Lett.,"Spectrophotometric Determination of Certain Phenothiazines and Their Dosage Forms Using Bromophenol Blue"**1993**, 26, 1669- 1680.
[21] Starczewska, B.;Karpinska, J., Anal. Lett.“Application of Eriochrome Cyanine R to the Extractive -Spectrophotometric Determination of Chlorpromazine"**1996**, 29, 2475-2486.
[22] Bhongade, S.L.; Kasture, A.V, Indian J. Pharm. Sci.,"Spectrophotometric Determination of some Phenothiazines Using N-Chlorosuccinimide"**1993**, 55, 151-154.
[23] Bhongade, S. L.; Kasture, A. V., Talanta,"Extractive spectrophotometric determinations of some phenothiazine derivatives in pharmaceutical preparations"**1993**, 40, 1525-1528.
[24] Basavaiah, K., Il Farmaco,"Determination of some psychotropic phenothiazine drugs by charge-transfer complexation reaction with chloranilicacid“**2004**, 59, 315-321.
[25] Gruenke, L. D., Craig, J. C., Klein, F. D., Nguyen, T. L, Hitzemann, B. A., Holaday, J. W.mass spectrom.,**1985**,12,707-713.
[26] Qi, F.; Shao, Y.; Zhan, J.; Liu,Y.YaoxueTongbao,"Spectrophotometric Determination of chlorpromazine Hydrochloride in Pharmaceutical Preparations by Using Oxidative coupling reaction"**1985**,6, 346-348.
[27] Ohkubo, T., Shimoyama. R. and Sugawara, K., J.Chromatogr.,"Determination of chlorpromazine in human breast milk and serum by high-performance liquid chromatography"**1993**, 614, 328-332.
[28] Chagonda, L. F. S.; Millership, J. S. Analyst (London),“Sequential injection technique for the determination of chlorpromazine hydrochloride in pure form and pharmaceutical formulations"**1988**, 113(2), 233-237.
[29] Tamai, G.; Yoshida, H.; J. Chromatogr., **1987**, 423,163-168.
[30] Zhu, J. P.; Chen, H. W.; Fang, Q. J. FenexIHuaxue,"Spectrophotometric Determination of chlorpromazine Hydrochloride in Pharmaceutical Preparations by Using Oxidative coupling reaction "**1997**,5,573-575.
[31] Kojlo,A. , Anal. Lett,"Indirect Potentiometric Determination of Chlorpromazine with an Oxidative Column in a Flow Injection System"**1997**, 13, 2353-2363.
[32] AL-Ward, H. S. Journal of Um-Salama for Science 2:“Spectrophotometric micro determination of promethazine hydrochloride in pharmaceutical preparations via oxidative coupling reaction with sulphanilamide and in the presence of ferric chloride".**2005**, 110-119.
[33] Nina, A. & Zahra, R. J. Chil. Chem. Soc.57 (2):"Extractive Spectrophotometric determination of Ketoconazole, Clotrimazole AND Fluconazole by ion –pair complex formation with bromothymol blue and picric acid.”**2012,** 1104-1111.