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An Indirect Atomic Absorption Spectrometric Determination of Trifluoperazine Hydrochloride in Pharmaceutical Formulations Based on Chelate Formation with Palladium(II)

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Abstract: A new application of an indirect atomic absorption spectrometric (AAS) method was offered for the assay of low concentration of trifluoperazine hydrochloride (TFPH) in pure and pharmaceutical dosage form with good accuracy and precision. The method is depended on the formation of metal complex between the drug (TFPH) and palladium(II) to form orange-yellowish product extractable in organic solvent prior to its aspiration into an air-acetylene flame and indirectly determined by AAS. Using AA responses, all experimental parameters such as, pH, concentration of palladium, reaction time, extraction time and phase ratio which affect the complexation and extraction of TFPH-Pd(II), have been investigated. Under optimized conditions, linearity was observed in the range of 0.5-17 μg mL^{-1} with detection limit (S/N) of 0.038 μg mL^{-1}, precision in range of 1.18-1.92%, accuracy as the $\%E_{rel}$ of 2.4% and recoveries ranged from 101.7 to 104% with mean value of 102.4±0.135. The proposed method was applied for the determination of TFPH in the drug stelazine by both direct calibration and standard additions procedures and found to be 4.88 and 4.87 mg per unite, respectively compared with the stated value of 5 mg per unite. This method is also compared statistically with direct determination by using UV-Vis spectrophotometric technique which is preformed in our laboratory and found to be insignificant at 95% confidence level. All statistical calculations were implemented via the chemsoftware Minitab version 11.

Keywords: Trifluoperazine hydrochloride, Palladium(II), Chelate formation, Indirect AAS.

Introduction

Trifluoperazine hydrochloride (TFPH),chemically 10-[3-(4-methylpiperazin-1-yl)propyl]-2-(trifluoromethyl)phenothiazine hydrochloride (Figure 1), is a derivative of phenothiazine,

characterized by a tricyclic aromatic ring with sulfur and nitrogen atoms and substituents in the 2 and 10th positions[1]. It has been widely used in the treatment of psychotic patients for the neuroleptic and antidepressive action[2].

Due to the attractive features incorporated with the chemical structure of the phenothiazine derivatives from which trifluoperazine hydrochloride is belong to, analytical chemists have paid most of their interest in using these compounds as chemical reagents evenly for the determination of metal ions and organic compounds[3]. In parallel, owing to of their extensive use in psychiatry as tranquilizers and neuroleptics, many authors have also dedicated their efforts to develop a simple, rapid and sensitive analytical method for the assay of phenothiazine derivatives in pure, dosage form and biological samples. Generally, the assay of phenothiazine derivatives has previously been achieved by several analytical techniques such as, spectrophotometry[4-11], fluorimetry[12], flow injection analysis[13-14], HPLC[15-17], LC-ESI-MS[18] and potentiometry[19].There are few analytical methods available for the determination of TFPH alone in bulk, tablets and biological samples such us FIA[20] and HPLC[21-22]. However, a recent literature survey reveals that there has no work of using flame atomic absorption spectrometry (FAAS) for the determination of TFPH in pharmaceutical preparations so far. This encourages the authors to develop a simple, rapid, inexpensive and reliable method for the detection of TFPH as TFPH-Pd(II) complex in pharmaceutical samples in order to improve performance and exploitation of AAS in pharmaceutical analyses domain due to its availability in many laboratories.

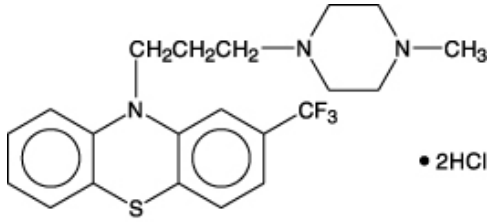

Figure 1. The chemical structure of trifluoperazine

In this work, an indirect FAAS method used for the determination of the drug TFPH in pure form and pharmaceutical sample (Stelazine). The method is based on the reaction of drug with palladium(II) in acidic medium to form stoichiometrically a yellowish-orange TFPH-Pd(II) complex at optimum conditions. The complex was extracted into benzyl alcohol and aspirated into air/acetylene flame for indirectly assay of TFPH via the measurement of AA signal of Pd in the formed complex. The proposed method was compared statistically with molecular spectrophotometric technique.

Experimental

Atomic absorption measurement were carried out on a GBC (933 plus) flame atomic absorption spectrophotometer equipped with background corrector GBC D_2 Lamp and palladium hallow cathode lamp under the following conditions: wavelength 247.6 nm, lamp current 10 mA, slit width 0.2 nm, air/acetylene flame (oxidant, lean). All the molecular absorption measurements were made using UV-Vis spectrophotometer type Shimadzu model UV-160 equipped with 10 mm matched quartz cell. Infrared spectrum for the produced complex was recorded on Shimadzu Fourier Transform Infrared model FT-IR8000. For pH measurement it is used a pH Meter Jenway 3020 with combined electrode.

All the chemicals used were of analytical reagent grade; deionized water was used for diluting the reagents and samples. A pure trifluoperazine hydrochloride and stelazine drug were denoted from the state company for drug industries and medical appliance, Sammara, Iraq. AA standard of palladium solution (1000 µg mL^{-1}), hydrochloric acid (36.4%) and Benzyl alcohol were purchased from BDH.

Trifluoperazine hydrochloride standard solution (1000 µg mL^{-1}) was prepared by dissolving 0.1 g of pure TFPH in sufficient water and diluted to 100 mL into a volumetric flask. A 100 µg $mL^{-1}$of working platinum standard was prepared by diluting of the stock solution in water.

General procedure and analytical curves

Direct calibration method

Aliquots (0.05-1.7 mL) of a stock standard solution of trifluoperazine hydrochloride (50 µg mL^{-1}) were transferred into 5 mL volumetric flask, then 0.4 mL of 50 µg Pd mL^{-1} was added to each flask followed by adjusting the pH of all solution to 1.9 using dilute HCl or NaOH solution. The solutions were set aside for 2 min, and then diluted to 5 mL with water. These solutions were corresponding to (0.5-17 µg TFPH mL^{-1}). Each solution was extracted with 1 mL of benzyl alcohol after shaking for 1 min. The organic layer for each solution was transferred into a test tube from which aspirated into air/acetylene flame and the AA signals were measured at 247.6 nm. The analytical curve was obtained by plotting absorbance (in mode of peak height) against TFPH concentration and the corresponding linear regression equation was used to convert absorbance into TFPH concentration, for all analyzed stelazine samples.

Preparation of drug stelazine tablets

20 Tablets of stelazine were crushed in a clean agate mortar, powdered and triturated well. A quantity of 0.4518 g of fine powder was dissolved in sufficient water with continuous shaking, then the content was filtered and the filtrate was transferred into 50 mL volumetric flask and dilutes to mark with water.

Standard additions method

Aliquots (2.5 mL) of the above prepared stelazine sample solution were pipetted into seven 5 mL calibrated flaks containing 0.000, 0.250, 0.35 and 0.45. 0.55, 0.65 and 0.75 mL of 100 µg TFPH mL^{-1}, then the same steps were followed according to the procedure previously mentioned.

Results and Discussion

UV-Vis spectra of the pure TFPH drug and its complex with Pd(II) were recorded using Shimadzu model UV-160 equipped with 10 mm matched quartz cell for recoding the spectra at 50 mg L^{-1} of TFPH standard solution and TFPH-Pd(II) in benzyl alcohol to verify of the formation of complex. It was shown that the pure drug gave two absorption maxima at 258 and 307 nm and palladium(II) solution gave one absorption maxima at 235 nm, while the spectrum of the chelate shows a new absorption maxima at 471 nm (Figure 2) indicating the formation of complex between the drug TFPH and Pd(II) solution in organic medium.

Optimum of Extraction Conditions

Effect of pH value

The effect of pH on the AA response for the formation of TFPH-Pd(II) complex at different pH values. Figure 3 showed the absorbance was at maximum value sharply at the pH of 1.9.

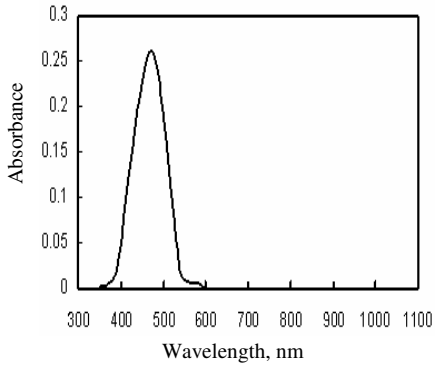

Figure 2. The absorption spectrum of TFPH-Pd(II)

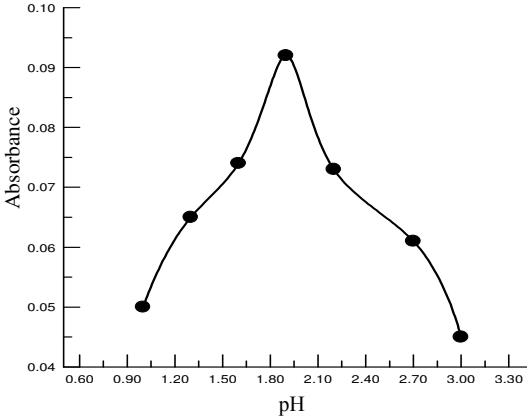

Figure 3. Effect of pH for the determination of TFPH with Pd(II)

Effect of concentration of Pd(II) solution

Different amounts of Pd(II) solution, 0.05-0.4 mL aliquots (100 µg Pd mL^{-1}) were added to 0.5 mL aliquots of 100 µg mL^{-1} TFPH. The maximum absorbance was attained at 0.2 mL amounts of 100 µg mL^{-1} of Pd(II) solution which correspond to 4 µg m L^{-1} (Figure 4). Thus, this concentration was employed to achieve a constant and maximum absorbance for complete formation of chelating complex.

Effect of phase ratio

This experiment was conducted to obtain the organic/aqueous ratio for the extraction of TFPH-Pd(II) complex, keeping the other variables were constant, *via* varying the volume of aqueous phase from 4-8 mL and keeping the volume of organic solvent at 1 mL. The results have shown that the AA signal was almost independent of A/O phase ratio from 4:1 to 5:1 (Figure 5). From the absorbance data, the percent extraction (%E) and distribution ratio (D) of the complex were also estimated and found to be 94.42% and 84.61 respectively, at one stage extraction.

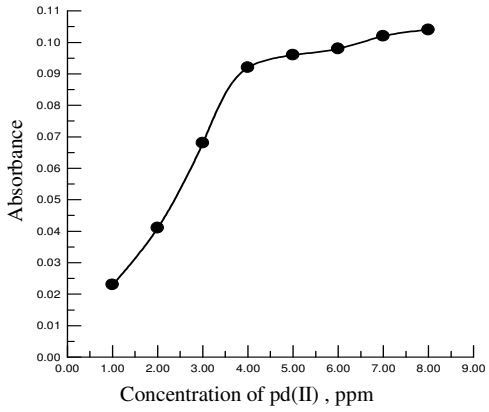

Figure 4. Effect of Concentration of palladium ion on the determination of TFPH

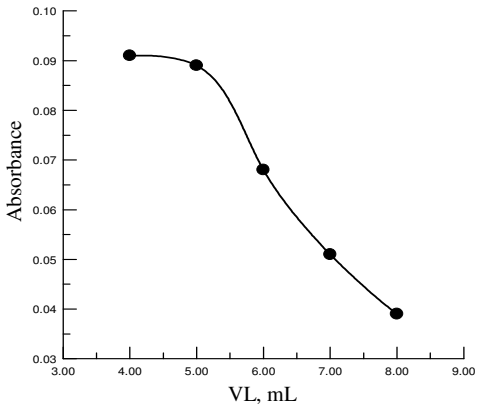

Figure 5. Effect of phase ratio on the determination of TFPH-Pd(II) complex

Effect of reaction time

Figure 6 shows the effect of reaction time on the formation of complex before the extraction process. It was shown that the absorbance increases rapidly with the reaction time up to 2 min and then reaches a plateau, which indicates that there is no advantages in going beyond 20 min, perhaps lead to partial dissociation of the complex with longer time in aqueous phase.

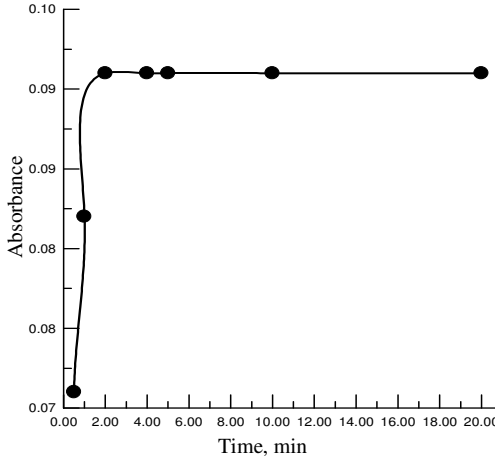

Figure 6. Effect of reaction time on the determination of TFPH-Pd(II)

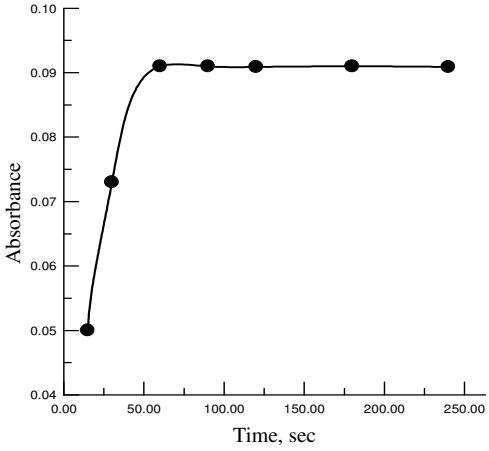

Figure 7. Effect of extraction time on the determination of TFPH-Pd(II) complex

Effect of extraction time

It was observed that the absorbance of the TFPH-Pd(II) complex increases readily with shaking time and reach a plateau, indicating the stability of the absorbance values with increasing shaking time, and hence a 1 min was selected as an optimal for complete extraction of the complex (Figure 7).

Selection of solvent

Since this procedure comprises the measurement of TFPH-Pd(II) complex in organic medium, it was necessary to use suitable solvent that will extract the complex alone, not excess of Pd(II) and free TFPH used. Consequently, the effect of different solvents, namely, *o*-xylene, toluene, carbon tetrachloride, 1-butanol, cyclohexanone, benzene, acetyl acetone, diethyl ether, benzyl alcohol, dichloromethane, petroleum ether was investigated. Experiments indicated that, benzyl alcohol was proved to be the most suitable solvent because for extraction of the complex at optimum conditions excluding other species in the extraction system and does not extract the blank but merely the complex. The other solvents were not suitable, because the complex formed in these solvents had low absorbance.

Several spectroscopic techniques, such as FTIR, FAAS and mole-ratio procedure preformed by UV-Vis spectrophotometry have been used to elucidate the probable structure of TFPH-Pd(II) complex produced at optimum conditions**.** Figure 8 shows that the mole ratio between TFPH and Pd(II) was 1:1 complex.

The stability constant was estimated by using the following equation [23]:

$$K = \frac{(A_1-A_3)(A_2-A_3)}{(A_2-A_1)^2 C}$$

Where K is stability constant, A_1, A_2, A_3 refers to the absorbances of intersect point of the two slopes, at constant absorbance, first point absorbance on the Figure 8, respectively and C is the molar concentration of complex *vs*. A_1. The stability constant was found to be $1.2x10^7$ M^{-1} at λ_{max} 471 nm.

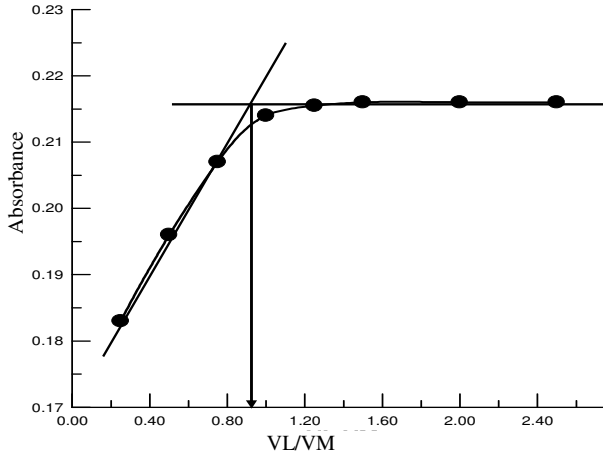

Figure 8. Mole ratio method for TFPH-Pd(II) complex

An FTIR spectrum of the chelate (Figure not shown) also reveals the shifting of aliphatic and aromatic (C-N) bands to 1020 and 1340 cm^{-1} respectively are indicating the formation of coordination with Pd ion, while the C-S-C band remains unchanged at 754 cm^{-1}. Also two bands appeared at 256 and 287 cm^{-1} which belong to (Pd-N), respectively**.** Consequently, we can propose the structure of the complex formed (Figure 9).

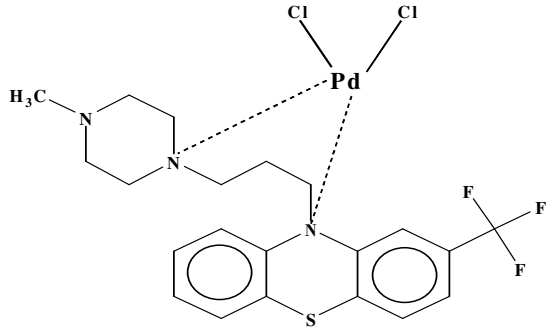

Figure 9. Structure of the complex

To ensure the stability of the complex in organic medium throughout measurements by AAS, we used the recovery percentage measurements with different time interval as a clue, for the complex containing 10 µg mL^{-1} of TFPH. Excellent recovery of 100.02± 2.88% as a mean was obtained up to 48 h duration time.

Analytical data

The proposed method was evaluated under the optimum conditions with regard to response linearity, detection limit, accuracy and precision. Beer's law was obeyed in the concentration range 0.5-17 µg mL^{-1} of TFPH. Linear regression analysis using least square method for calibration points (n=10) was made to evaluate the slope, intercept and

correlation coefficient .The regression calibration equation obtained was; $A=8.6x10^{-3}$ C $+3.81x10^{-3}$ (where A is the absorbance and C the TFPH concentration as µg L^{-1}) with a correlation coefficient of r= 0.9989 and the coefficient of determination (R^2) of 99.78% which suggests statistically valid. We use this fitted linear calibration model to estimate the TFPH concentration in the drug samples which appears justified, on statistical basis. The confidence limits of slope and intercept of the regression line were computed using the formulas b ± ts_b and a ± ts_a at 95% confidence level and found to be $8.6x10^{-3}\pm3x10^{-4}$ and $3.8x10^{-3}\pm2.7x10^{-3}$ respectively. Limit of detection was calculated on the statistical basis from the calibration graph data and found to 0.038 µg mL^{-1} which was 4-folds better than that obtained by Koupparis and Barcuchová[24] (0.14 µg mL^{-1}) using automated FIA and 26-folds better than that obtained by Basavaiah and Krishnamurthy[25] which was 0.21 µg mL^{-1} using spectrophotometric assay of some antipsychotropic and anticholinergic phenothiazine drugs with ammonium molybdate. The accuracy in term of recovery percent and precision were established by spiking of 2, 10 and 15 µg mL^{-1} using the recommended procedure previously mentioned. The results were shown in Table 1. These data indicate that the indirect FAAS determination of TFPH is not highly effected by the presence of other constituents in the drug sample.

Table 1. The accuracy and precision of the proposed method for the determination of TFPH in pharmaceutical preparation

Amount of TFPH taken, µg.mL^{-1}	Amount of TFPH found, µg.mL^{-1}	Rec, %	E_{rel}, %	RSD% n=5	Mean Rec%±S.D	Mean E_{rel}, %
2	1.92	96	-4.0	2.6	97±0.15	2.09
10	9.80	98	-2.0	1.8		
15	14.60	97	-2.6	1.4		

The proposed method was applied for the detection of TFPH in stelazine tablets with stated value of 5 mg per unite by using direct calibration and standard additions procedures under optimum conditions. The TFPH was determined through the atomization of the complex extracted as a result of the reaction of TFPH present in the pharmaceutical preparation with palladium(II) and found to be 4.88 and 4.78 mg / unit with relative error of (-2.4%) and (-2.6%) respectively. The results found by both procedures were agreed with stated concentration value and in a good agreement with results obtained by direct UV-Vis spectrophotometric method that was carried out in our laboratory under optimum conditions.

It can also be observed that the ratio of the slopes of the direct calibration and standard additions ($A=8.0x10^{-3}$ C $+3.81x10^{-2}$) is found to be one, which indicates that the interferences resulting from drug constituents are insignificant using the proposed procedure. Thus, it is possible to use direct calibration procedure for the determination of TFPH in drugs without need the standard additions method which requires more effort, more amount of sample and time-consuming. This finding is also support the specificity of the proposed method, indicating that the excipients did not interfere with the analysis of TFPH.

Since the majority of the determinations of TFPH drug have been performed by using UV-Vis spectrophotometric technique as intimated by literatures survey, this technique was also used in our laboratory for the detection of TFPH as TFPH-Pd(II) after taking into account all optimized conditions that were carried out with indirect FAAS, in an effort to compare it with the proposed method, to infer whether there is a significant difference in the results in term of systematic errors between two techniques at 95% confidence level. The figures of merit of two techniques were summarized in Table 2.

Table 2. Analytical statistics data for both indirect AAS and UV-Vis spectrophometry for the determination of TFPH as TFPH-Pd(II)

	Indirect AAS	UV-Vis spectrophotometry
Range of concentration, µg mL^{-1}	0.5–17	2-50
Detection limit, µg ml^{-1} for n=13	0.038	0.16
Regression line	y=0.0086x+ 0.0038	y=0.007x+0.006
Correlation coefficient, r	0.9989	0.9996
Coefficient of determination, R^2	99.78%	99.99%
C.L. for the slope($b\pm ts_b$) at 95%	0.0086±0.0003	0.007±0.0001
C.L. for the intercept($a\pm ts_a$) at 95%	0.0038±0.0037	0.006±0.0037
RSD%, n=5	1.09%	2.013%
Mean Recovery%	102.4±0.135	102.2±0.5
Molar absorptivity, L mol^{-1} cm^{-1}	-	5.96×10^3
Sandell's sensitivity, µg.cm^{-2}	-	0.0806
Extraction Efficiency, %E	94.42	97.34
Distribution ratio, D	84.61	60.98

To validate the proposed method with UV-Vis method, the regression line between two methods was constructed after taking into consideration the common concentrations of calibration range. The t-test for (r) was computed according to formula adapted by Miller and Miller[26]. It was found that the calculated value of t is 24.969 compared with tabulate (t=4.303) at 95% confidence level, using two-sided t-test and (N-2) degree of freedom, indicate that a significant correlation does exist between two methods at the cited concentrations range. This means that no discrepancy in the application of each method for the detection of TFPH in pharmaceutical preparations. Also, the precision of two methods was compared statistically using *F*-test for triplicate measurements of TFPH in pure form. The value of F was calculated and found to be 5.4 which was less than *F*-tabulated (9.0277) at 95% confidence level, indicating there is no significance difference in precision of both techniques. Finally, the amount of TFPH in pharmaceutical was determined by each method using direct calibration curves .It was shown that the indirect AAS gave 4.88 mg per unite with relative error of (-2.4%) compared with UV-Vis spectrophotometry which gave 4.91 mg per unit with relative error of (-1.8%).

Conclusion

An alternative indirect AAS method has been reported for the analysis of trifluoperazine hydrochloride in pure form and pharmaceuticals. To the best of our knowledge, no report has been considered the reaction between TFPH with palladium(II) despite of the importance this metal from the biological point of view, and determined the drug by FAAS. The proposed method is simple, accurate, precise and specific and can be used for routine quality control in both the pure form and pharmaceuticals without fear of interference that caused by the presence of excipients in pharmaceutical preparations. The results show that the quantity of TFPH in stelazine are in a good agreement with given labeled quantity. Furthermore, Due to its low detection limit, the indirect AAS method could be applied for the assay of TFPH in biological samples such as blood and urine.

Acknowledgment

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