ISSN:2523-0522
Volume 6: issue 2, April 2023
ISRAA UNIVERSITY JOURNAL OF APPLIED SCIENCE (IUJAS)

ORIGINAL ARTICLE

Development of a New Analytical Method for Estimation of Trifluoperazine-HCl in Pharmaceutical Formulation

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Received: 13/10/2022 ***Accepted:25/12/2022*** ***Published:01/04/2023***

OPEN ACCESS

Doi:
https://doi.org/10.52865/rwic5362

Competing Interests: The authors declare that this manuscript was approved by all authors in its form and that no competing interest exists.

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ABSTRACT:

The estimation of trifluoperazine hydrochloride in pure and dosage forms has been developed using a simple spectrophotometric method. The method is based on using an oxidation-reduction reaction with 4,7diphenyl 1,10-phenanthroline in the presence of Ferric(III) ion solution to produce a red-colored product complex of Fe(II)- 4,7diphenyl 1,10phenanthroline with maximum absorption at 533nm. The molar absorptivity is 0.44x104 L. mole -1.cm-1, Beer's law is followed over a concentration range of 5-100 µg. ml-1.Various parameters that influence the development and stability of the color product were thoroughly researched and optimized, and a reaction pathway proposal was offered. The proposed method was successfully used to determine trifluoperazine hydrochloride in tablet form.

KEYWORDS: Trifluoperazine- hydrochloride; 4,7-diphenyl 1,10-phenanthroline ;Spectrophotometry ;Oxidation-reduction.

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INTRODUCTION:

In recent years, many chemists have tried to find various methods that have been used to determine Chemicals in pharmaceutical preparations ; it should be sensitive, accurate and simple.(Nejres A. and Najem M.,2022). This is important in light of the increasing of global consumption of medicines. For example, in developing countries, about 20% to 50% of health budgets are spent on medicines (Elhabil M.,2022).

Trifluoperazine hydrochloride is a white-colored powder that is odorless and highly dissolved in water and alcohol, partially dissolved in diethyl ether, and kept isolated from the light in dark containers (British Pharmacopoeia,2001). The scientific name of trifluoperazine hydrochloride is 10-[3-(4-methyl-1-piperazinyl) propyl] trifluoperazine hydrochloride-2-trifluoro-methyl phenothiazine di-hydrochloride), it has the following chemical structure as shown Figure1.

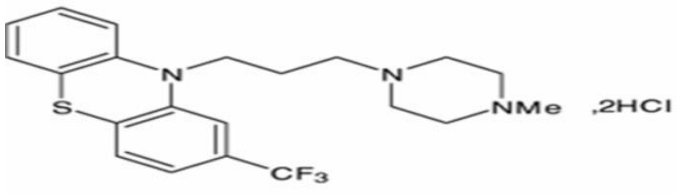

Figure 1: Chemical structure of Trifluoperazine- HCl

It has been known that to induce QT prolongation and ventricular tachycardia, which can lead to by sudden death (Se-Young et al., 2005), and is therefore used in the treatment of various mental diseases like schizophrenia. The drug is used in the treatment of depressive diseases (Walash et al., 1983). It was estimated via various methods including electrochemical using electrodes made of carbon. (Aveen et al.,,2019), Various spectrophotometric methods used these methods including oxidative coupling reaction (Mohammad et al., 2017, Al-Rufaie and Kathem,2014; Marwan,2020, Maadh and Kamal,2016; AI-Rashidy et al., 2018; Jalal, 2020). Ultraviolet Spectrophotometric (Nief,2014). Also, other types of techniques have been used the indirect atomic absorption method (Ameen et al.,2011). Voltammetric method) Stankovi´c et al.,2015). Potentiometric sensors (Ahmed et al.,2009). Electrochemical Sensing (Sura,2022) . Flow injection analysis (Moath, 2017; Kamal and Maadh,2017), RP-HPLC (Bhadani and Ekta,2015; Suman,2015), HPLC and thin layer chromatographic densitometric (El-Gindy et al., 2002).

This paper proposes a spectrophotometric method for determining trifluoperazine hydrochloride,

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which depends on its oxidation-reduction reaction using 4,7-diphenyl 1,10-phenanthroline in the presence of Ferric) III). The proposed method was used to determine trifluoperazine hydrochloride in its tablet formulations.

Experimental

Apparatus

All Spectral measurements and absorption readings were carried out using a JASCO-360 (Japan) spectrophotometer. Cells of glass and quartz with a light path of 1 cm were used. The pH was measured using a BP3001 pH meter and a BEL-sensitive balance was used to carry out the required weighing operations.

Reagents and Solutions

The reagents used in this research were pure (from Fluka and, BDH companies) and the trifluoperazine-HCl in its pure form will be brought from the State Company for Pharmaceutical Industry Samarra – Iraq.

Trifluoperazine hydrochloride (500 µg/ml) solution was prepared by weighting 0.0500 g of the pure trifluoperazine-HCl and dissolved it in distilled water and complete the volume to the mark of 100 ml and keep in an opaque flask.

Ferric (III) solution (2 x 10-3) M solution was prepared by dissolving 0.0799 g of anhydrous ferric sulfate (Fluka company) in 4 ml of sulfuric acid at a concentration of 0.25 M. then completed the volume to the mark of 100 ml volumetric flask with distilled water.

4, 7 diphenyl 1,10-phenanthroline (2×10-3) M was prepared by dissolving 0.0664 g of pure reagent (BDH) in 100 ml of ethanol, and this solution was kept in an opaque flask , this solution is stable for one day.

Preparation of pharmaceutical preparation

5 tablets for (5mg/tablet, S.D.I) , were carefully weighed and after being crushed and mixed well, the amount of the powder equivalent to 0.0500 g of pure TFPH was weighed and dissolved in distilled water then filtered into a volumetric bottle of 20ml and supplemented with distilled water up to the

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mark.

10 tablets for (1mg/tablet, S.D.I) , were carefully weighed and after crushed and mixing well, an amount of the powder equivalent to 0.0500 g of pure TFPH was weighed and dissolved in distilled water then filtered into a volumetric bottle of 20 ml and supplemented with distilled water up to the mark.

Primary Experiment.

In this research, an oxidation-reduction reaction is carried out between the Ferric(III) ions and trifluoperazine hydrochloride, where the Ferric(III) ions are reduced to iron(II) as a result of the oxidation of trifluoperazine hydrochloride in a water bath cited at 50 °C and with standing time for 15 minutes, then the solution was left for 10 minutes at room temperature, after that the absorption of the solution was done against the blank solution. The absorption depends indirectly on the amount of trifluoperazine hydrochloride that is already present in the solution and the temperature The formation of a colored product gives the highest absorption at the wavelength of 533nm.

Results &Discussion

The Optimum Conditions

All factors that affected the intensity of the colored product were studied, and the optimal of each parameter was selected

Effect of Acid

When adding any acid, there was a decrease in the absorbance of the colored complex, so it was not recommended to add any type of acid (Table 1).

Table1: The effect of various acids on absorbance.

Type of Acid (1M,1ml)	With out	HCl	HNO_3	H_2SO_4	CH_3COOH
Absorbance	0.5349	0.4981	0.4229	0.3573	0.3165

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The results in Table 1 indicated that the acids play a reverse role by re-oxidizing the iron (II) to the (III) iron, so the absorbance was decreased.

Effect of Ferric(III) Ion Solution Amount.

The effect of the various volume of the Ferric(III) ion solution(2 x 10-3 M) on the absorbance of colored complex resulted from different concentrations(5-75 µg/ml) of trifluoperazine hydrochloride(TFPH) was studied, different volumes of 1-1.5ml were added and the result is illustrated in Table 2.

Table2: The effect of the amount of Ferric sulphate solution

Ferric sulphate solution (ml ,2×10-3M)	Absorbance / µg TFPH						
	5	12.5	25	37.5	50	75	R^2
1	0.048	0.1184	0.2253	0.3391	0.4480	0.6418	0.9988
1.25	0.0548	0.1433	0.2834	0.4201	0.5411	0.8185	0.9995
1.5	0.036	0.1086	0.2187	0.3132	0.4085	0.6043	0.9986

The results in Table 2 indicated that 1.25 ml of ferric sulfate solution was optimal, it gave the highest absorbance and highest value of determination coefficient (R^2). Iron(III) is a good oxidizing agent that oxidizes the compound that enters the reaction with it and suffers reduction to iron(II).

Effect of the Amount of 4,7-Diphenyl -1,10-phenanthroline

The effect of the quantity of the reagent, on the intensity of colored complex, was studied by adding to a series of flasks different volumes of 1-2.5 ml of the reagent 4,7- diphenyl -1,10-phenanthroline with a concentration of 2x10-3 M to different amounts of TFPH (5-75 µg). The results are shown in Table 3.

From the results above, it is noted that the volume of 2 ml of the reagent 4,7 diphenyl 1,10-phenanthroline gave the highest absorbance of the formed complex and the highest value of the

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determination coefficient so 2 ml was adopted in subsequent experiments. We used the reagent 4,7-Diphenyl-1,10-phenanthroline because it is a selective reagent for iron (II).

Table 3: The effect of 4,7- Diphenyl- 1,10-phenanthroline amount on absorbance

4,7 Diphenyl-1,10-Phenanthroline solution (ml, 2×10-3M)	Absorbance / µg of TFPH						
	5	12.5	25	37.5	50	75	R2
1	0.025	0.1042	0.1885	0.2926	0.3361	0.5210	0.9909
1.5	0.038	0.1095	0.2143	0.3053	0.4518	0.6670	0.9974
2	0.0526	0.1347	0.2783	0.3917	0.5423	0.8112	0.9994
2.5	0.033	0.1025	0.2163	0.3185	0.3980	0.5893	0.9967

Effect of Temperature

The effect of different temperatures on the absorbance of the complex result from the reaction of 500 µg of TFPH and 1.25 ml of Ferric(III) ion solution. and 2 ml of the reagent 4,7 diphenyl 1,10phenanthroline at a concentration of (2x10-3 M). The solutions were diluted to a volume of 10 ml with distilled water and heated by placing them in a water- bath at different temperatures for 15 minutes , then the flasks were standing for 15 minutes at room temperature before measuring the absorbance of each solution against its blank solution . The results are shown in Table 4.

Table4: Effect of temperature on absorbance

Temperature (C°)	10	25	40	50	60
Absorbance of 25µg TFPH	No .R	0.1985	0.246	0.289	0.271
Absorbance of 50 µg TFPH	No .R	0.374	0.428	0.537	0.511

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From the results shown in Table 4, the highest absorbance of the complex formed at a temperature of 50°C, and after this degree led to a decrease in the intensity of the complex, so 50°C was chosen in the subsequent experiments. We note that at the temperature of 50, it was the highest absorbance because the heat accelerated the rate of the reaction and therefore when it was raised to the temperature of 60°C it had a negative effect that worked to destroy the resulting-colored complex.

The Optimal Time of Completed Oxidation-reduction reaction

The time required to complete the process was studied, as the reduction of the Fe+3 ion to Fe+2 ion and oxidation of TFPH.

The solutions containing TFPH, Ferric (III) ion solutions, and the reagent 4,7 diphenyl 1,10-phenanthroline were left for periods in a water bath at a temperature of 50°C, and the absorbance of the formed complex was measured against its blank solutions. The results are shown in Table 5.

Table 5: Effect of time on oxidation–reduction reaction.

Time, minutes	5	10	15	20	25	30
Absorbance	0.004	0.2062	0.5418	0.5328	0.5162	0.5151

It is noted from the results in Table 5 that the best time to complete the oxidation-reduction process was 15 minutes at a temperature of 50°C. It was noted that the intensity of complex after 25 minutes is approximately constant. Therefore, 15 minutes was chosen as the best time to complete the process and was adopted in subsequent experiments.

Effect Order of Addition

To make sure that an optimal additional sequence was added, different sequences of addition were checked, and the best sequence was No.1(Table 6), and it was the same that used in the preliminary study, another order of addition a loss in absorbance.

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Absorption Spectrum

The absorption spectrum was taken for the colored product formed from the reaction of 500 µg of TFPH with Ferric(III) ion solution (2 x 10-3 M) in the presence of 4,7 diphenyl-- 1,10phenanthroline in 10 ml final volume. The formation of a colored product gives the highest absorption at the wavelength of 533 nm, under the conditions in Table 7.

Table 6 : Order of addition. Trifluoperazine-HCl (TFPH) , Fe2(SO4)3.,(O) , 4,7 diphenyl - 1,10phenanthroline (R)

Reaction component	Order number	Absorbance
TFPH + O + R	I	0.5408
TFPH + R + O	II	0.1987
R + O + TFPH	III	0.4876

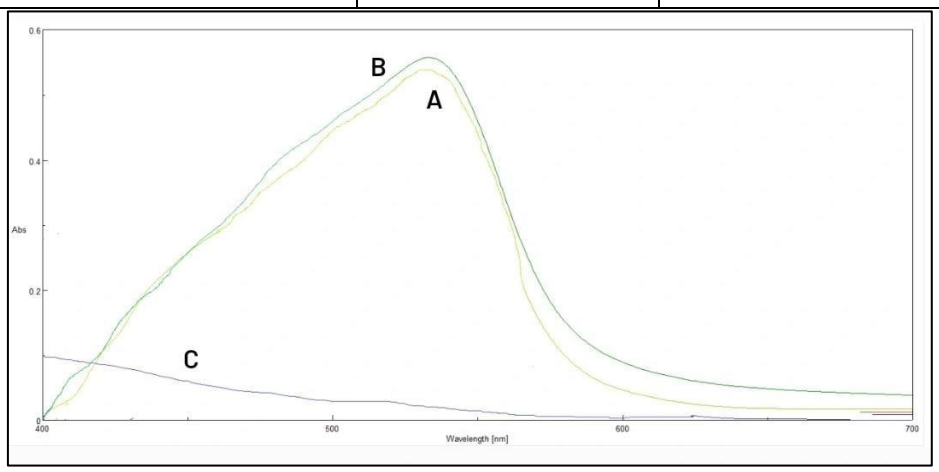

Figure 2: Absorption spectra (A) 50µg/ ml TFPH proceed as mentioned before against distilled water(b)50 µg/ml TFPH versus blank solution and (c) blank solution versus distilled water

Calibration Graph

A linear calibration graph for TFPH (Figure 3) is obtained using the optimum conditions illustrated in Table 7. Beer's law is obeyed over the concentration range of 5–100 µg/ml with a determination coefficient of 0.9993 and. The colored product generated had a conditional molar absorptivity of 0.44×10^{4} L..mol^{-1}.cm^{-1}. The calibration curve shows that the range limits from 5 to 100 µg/ml, and above 100 µg/ml a negative deviation from Beer's law (deviation from linearity) have been shown.

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Table 7: The optimal conditions.

Variable	Optimal
Amount of Fe^{+3}(ml,M)	1.25ml,(2x10-3M)
Amount of 4,7diphenyl-1,10phenanthroline(ml,M)	2ml , (2x10-3M)
Temperature(°C)	50
Standing time in water bath (minutes)	15

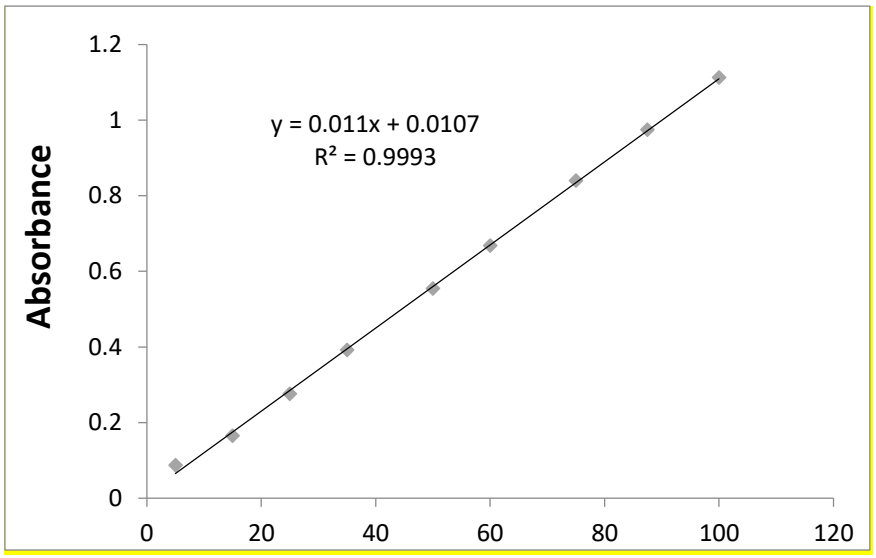

Figure 3: Calibration graph for determination of TFPH.

Effect of organic solvents.

The effect of some of organic solvents on the spectral properties of the formed colored complex was studied and the results are shown in Figure 4 and Table 8.

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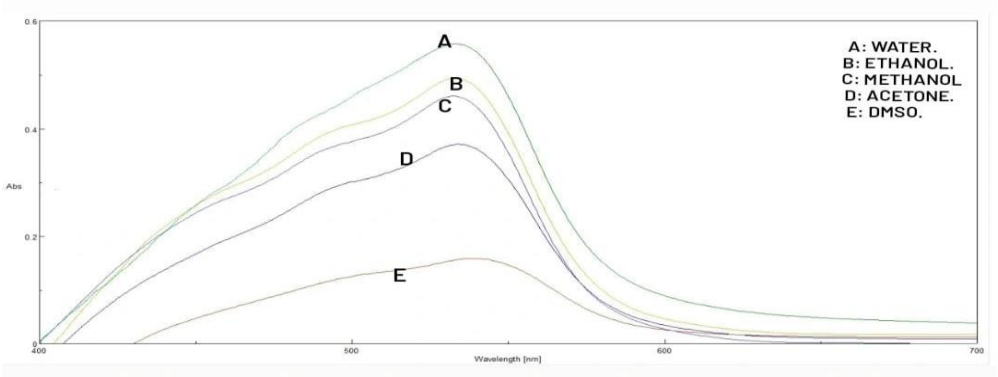

Figure 4: Effect of some solvents on the absorption spectrum of the resulting complex

Table 8: Effect of the spectral properties of the complex formed in different solvents

Solvent	Maximum wavelength, nm	ε, l.mol-1.cm-1
Methanol	532	0.3746×104
Dimethylsulphoxide	539	0.1291×104
Acetone	534	0.3020×104
Ethanol	533	0.4021×104
Water	533	0.4512×104

From the results shown in Figure (4) and Table (8) , it is noted that water is the best solvent as it gives the highest absorption intensity, while the rest of the solvents except for acetone and dimethyl sulfoxide (which give a low absorption intensity compared to water).

The Stoichiometry of Colored Complex

The colored complex formed from the reaction of Fe(II) with4,7 diphenyl-- 1,10phenanthroline. The complexity ratio is known and proven in the literature (Unnisa et al., 2011) with 1 [Fe(II)] to 3 [4,7 diphenyl-- 1,10phenanthroline]. Figure 5 shows the chemical structure of the formed colored complex.

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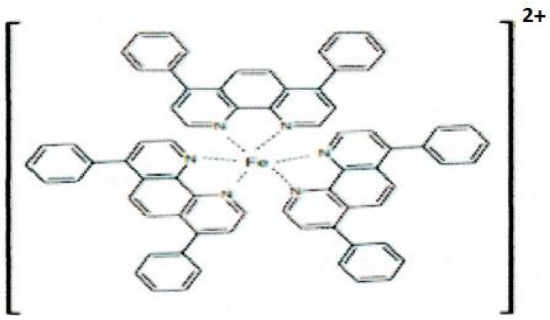

Figure 5: The chemical structure of colored complex.

Standard Addition Method

The standard addition method was used to determine 30 and 50 µg/ ml of two types of tablet solution (S.D.I.,1 and 5 mg). The obtained results were cited in Figures (6 and 7) and illustrated in Table 9.

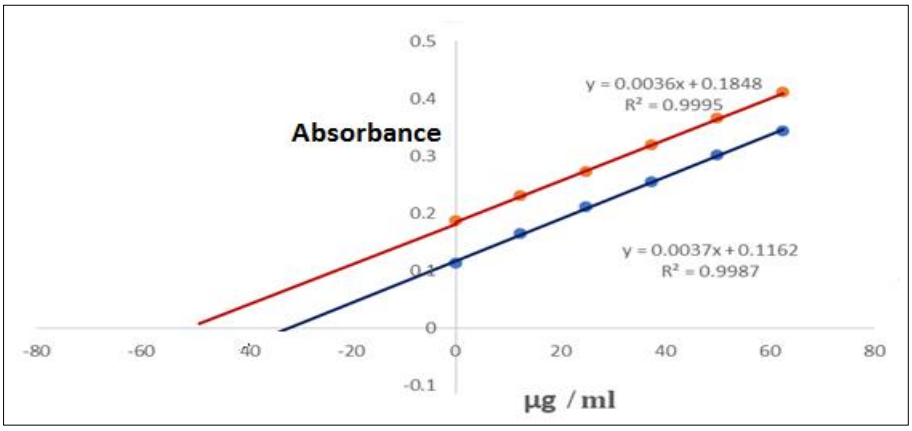

Figure 6 : standard addition Trifluoperazine-HCl/tablet (1mg, S.D.I. Iraq)

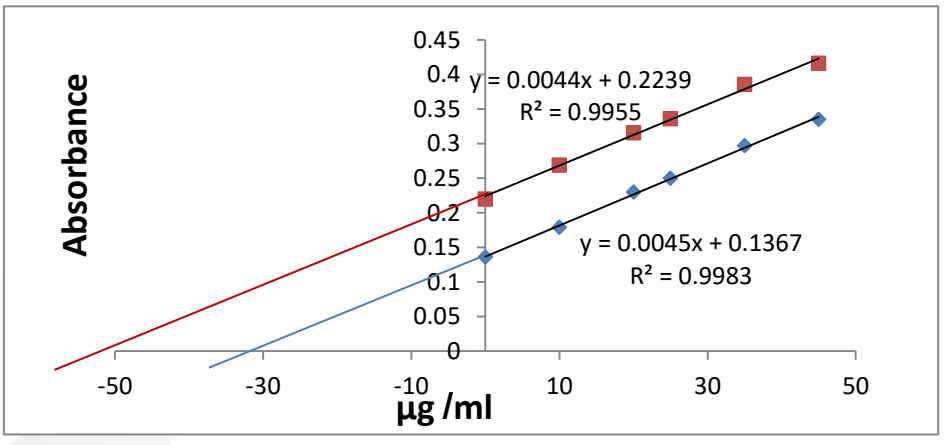

Figure 7: standard addition Trifluoperazine-HCl/tablet (5mg, S.D.I. Iraq)

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Table 9: The results of standard addition method.

Pharmaceutical preparation	µg TFPH present	µg TFPH measured	Recovery (%)	Drug contain mg
Trifluoperazine-HCl/tablet (1mg, S.D.I. Iraq)	30	31.40	104.66	1.04
	50	51.33	102.66	1.02
Trifluoperazine-HCl/tablet (5mg, S.D.I. Iraq)	30	30.37	101.23	5.06
	50	50.88	101.76	5.08

From the results shown in Table 9, it is clear that the standard addition method is in great agreement with the proposed method for the determination of trifluoperazine hydrochloride in its pharmaceutical preparations.

Analytical Applications:

The developed method was successfully applied in the determination of TFPH in tablet dosage forms available in Iraqi markets (Table 10).

Table10: The results of analytical applications.

Pharmaceutical preparation	µg TFPH present	µg TFPH measured	Recovery, %	T exp
Trifluoperazine-HCl/ tablet (1mg ,S.D.I. Iraq)	30	30.010	100.03	0.487
	50	50.015	100.03	0.879
Trifluoperazine-HCl/tablet (5mg , S.D.I. Iraq)	15	15.010	100.06	0.511
	35	15.005	100.03	0.238

* Average of four determinations.

The results in Table 10 indicated that the recoveries% were good, which indicates that the proposed method has good accuracy and efficiency. The calculated t-value of the extracted concentrations is less than the tabular value with degrees of freedom 3 and at a confidence level of 95% according to these results The method is credible and reliable in the estimation of TFPH in dosage forms.

Conclusions

For the determination of trace quantities of TFPH, a simple, fast, exact, and sensible spectrophotometric method has been established based on an oxidation-reduction reaction with Fe(III) ions in presence of 4,7 diphenyl-1,10 phenanthroline in aqueous solution. The proposed method has been effectively applied to pharmaceutical tablets.

Acknowledgments

We would like to extend our sincere thanks to the Department of Chemistry at the College of Science, University of Mosul for the facilities they gave us to carry out the research.

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