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Spectrophotometric determination of Trifluoperazine Hydrochloride by oxidative coupling reaction with 4- amino benzoic acid using potassium iodate

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Abstract :

A new sensitive spectrophotometric method for the determination of trifluoperazine hydrochloride (TFPH) is developed. The method is based on an oxidative coupling reaction with 4- amino benzoic acid using potassium iodate as oxidizing agent in acidic midium to produce a violet color, soluble in water, stable product absorbs at 550 nm. Beer's law is in the linear range 10 - 80 µg/ml of TFPH. The molar absorptivity, Sandell's and detection limit (LOD) are 0.8032×10^4 liter. $mol^{-1}.cm^{-1}$, 0.0598 $\mu g/cm^2$, 0.3882 µg/ml respectively. The RSD value is 0.177 – 0.295 %. This method is applied successfully for the determination of trifluoperazine hydrochloride in pharmaceutical formulations (tablets of salabid) and injection

المستخلص

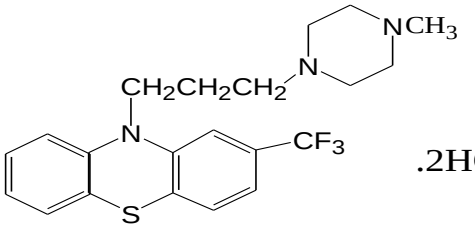
. يتضمن البحث تطوير طريقة طيفية حساسة لتقدير عقار هيدروكلوريد ثلاثي فلوبيرازين، الطريقة تستند على تفاعل الا زدواج التأكسدي مع الكاشف 4- امينو حامض البنزويك باستخدام العامل المؤكسد يودات البوتاسيوم في وسط حامضي لتكوين ناتج بنفسجي اللون ذائب في الماء ويعطي أعلى امتصاص عند الطول الموجي550 نانوميتر. كانت حدود قانون بير في مدى التراكيز 10-80 مايكروغرام/مل من هيدروكلوريد ثلاثي فلوبيرازين والامتصاصية المولارية 0.8032 × 10^4 لتر/مول. سم ودلالة ساندل 0.0598 مايكروغرام/سم^2. وتراوحت قيمة الانحراف القياسي النسبي 0.177-0.295 % ، وحد الكشف 0.3882 مايكروغرام/ مل .تمّ تطبيق هذه الطريقة بنجاح لتقدير هيدروكلوريد ثلاثي فلوبيرازين في المستحضرات الصيدلانية (حبوب السيلابيد) وكذلك الحقن.

Introduction

Trifluoperazine Hydrochloride

Trifluperazine hydrochloride is very important phenotiazine derivative which is 10 - [3] 4 - Paraxin - 1 - Propyl - 2 - Tri - Flammethyl Phenothiazine Dihydrochloride and TFPH (10] -3-4-methylepiprazin-1-yl] propyl] -2-trifluoromethyl- phenothiazine dihydrochloride[(1)]:

The structural formula is as follow:



.2HCl

The molecular formula is $C_{21}H_{24}F_3N_3S.2HCl$, the molecular weight is 480.4 gm mol^{-1}.[(2)]

Trifluperazine hydrochloride is a white powder with a bitter taste, a melting point of 240 ° C which is colorless and pale yellowish, dissolves in water at 20 ° C and is sensitive to light[(3)]. This drug is determined using spectral methods[(4-7)], high performance liquid chromatography[(8-9)] and thin layer chromatography[(10)]. In this study a sensitive and simple spectrophotometric method for determinatin of trifluoperazen hydrochloride **(**TFPH) in pure form as well as in pharmaceutical formulations based on the oxidative coupling using 4- amino benzoic acid in presence of potassium iodate.

Experimental

Preparation of solutions

Standard TFPH solution (500 µg/ml)

This solution is prepared by dissolving 0.05 g of TFPH in amount of distilled water and the volume is diluted to 100 ml with distilled water in a volumetric flask. This solution is kept in a brown bottle, where it is stable for one week, at least.

4- amino benzoic acid reagent solution (1 ×10^{-2}M)

This solution is prepared by dissolving 0.1371mg of 4- amino benzoic acid in 5 ml of ethanol

and the volume is completed to 100 ml in a volumetric flask with distilled water.

potassium iodate solution (1×10^{-2}M)

A 0.2140 g of potassium iodate is dissolved in amount of distilled water and the volume is completed to 100 ml in a volumetric flask with distilled water.

Hydrochloric acid solution(approximate,1M)

This solution is prepared by dilution of 4.2 ml of the concentrated hydrochloric acid (11.8 M) solution to 50 ml with distilled water in a volumetric flask and completed to 100 ml in a volumetric flask with distilled water.

Solution of TFPH tablets formulation (500 µg/ml)

Salabid (1mg), production of the General Company for the manufacture of pharmaceuticals and medical supplies SDI Samarra - Iraq , every tablet contains 1mg of TFPH and the solution is prepared as follows: 12.5 tablets are weighed and gives (2.7962g) which contains 12.5 mg of TFPH,and then powdered well. A weight of (0.2237g) of this powder is dissolved in an amount of distilled water, and then the solution is filtered by paper filtration (604, RUNFILTER, Q240 mm), the volume is completed with distilled water in a volumetric flask of 25 ml , which gives the concentration of 500 µg/ml.

.Preliminary Investigations

A 1.0 ml of 4- amino benzoic acid reagent(1×10^{-2}M) is added to 3.0 ml of standard TFPH solution(500 µg/ml) and 1.0 ml of potassium iodate solution(1×10^{-2}M) and diluted with distilled water in a 25 ml volumetric flask, a violet color product is obtaind with λ max 550 nm against blank.

Results and Discussion

Optimization of the experimental conditions

To establish the optimum conditions, the effect of various variables on the intensity of the absorption was studied by adding 3 ml of standard TFPH solution (500µg/ml), and

measuring the absorption at 550 nm versus the blank .

Effect of the amount of oxidizing agent

This study is to select the best amount of oxidizing agent KIO_3 (1×10^{-2} M) by adding different volumes (0.5-3.5 ml) of oxidizing agent to volumetric flasks containing 3.0 ml of TFPH (500 µg/ml) and 1.0 ml of the reagent solution (1×10^{-2}M), then addition 1.0 ml of 1.0 M hydrochloric acid and the volume was completed to 25ml with distilled water, the results are shown in (Table 1).

Table 1: Effect of the amount of oxidizing agent

ml of 10^{-2} M KIO_3	0.5	1	1.5	2	2.5	3	3.5
Absorbance	**0.806**	0.632	0.648	0.591	0.534	0.509	0.464

The results shown in the (Table 1) indicate that the volume of 0.5 ml of KIO_3 (1×10^{-2}M) is the optimum amount because of highest absorbance, so it was used in subsequent experiments.

Effect of the amount 4- amino benzoic acid

The effect of the amount 4- amino benzoic acid is studied by adding different volumes (0.5-3.5ml) of (1×10^{-2} M) to the volumetric flasks containing 3.0 ml of TFPH (500µg/ml) and 0.5 ml of the KIO_3 (1×10^{-2}M), then the addition of 1.0 ml of 1.0 M hydrochloric acid and the volume is completed to 25ml with distilled water, the results are shown in (Table 2).

Table 2: Effect of the amount of coupling reagent

ml of 10^{-2} M 4-aminobenzoic acid	0.5	1	1.5	2	2.5	3	3.5
Absorbance	0.593	0.805	**0.930**	0.877	0.793	0.707	0.607

It is clear that the volume of 1.5 ml of coupling reagent (1×10^{-2}M) is the optimum amount because it gave the highest absorption. So it is adopted in subsequent experiments

Effect of acidic solution

This study is carried out using different sizes ranging from 0.5 - 3.5 mL of 1 M hydrochloric acid, (Table 3) to investigate the acid effect.

Table 3: Effect of acid

HCL 1M	0.5	1	1.5	2	2.5	3	3.5
Abs.	0.589	0.932	**0.985**	0.872	0.746	0.632	0.555

Note from the above table when acid is used to increase absorption at volume 1.5 but starts to decrease as acidic solution increases.

Effect of oxidation time

To a series of volumetric flasks, each containing 3.0 ml of TFPH (500 µg/ml), 0.5 ml of KIO_3 (1×10^{-2}M) and the solutions are left for different periods of time, then 1.5 ml of 4- amino benzoic acid reagent (1×10^{-2}M) and 1.5 ml of 1.0 M hydrochloric acid solution are added. The volume is completed to 25ml with distilled water, and the absorption of solutions is measured at a wavelength of 550 nm versus blank, the results are shown in (Table 4).

Table 4: Effect of oxidation time.

Time minutes	5	10	15	20	25	30	35	40	45	50	55	60
Absorbance	0.679	0.875	0.950	**0.995**	0.996	0.995	0.994	0.997	0.996	0.994	0.993	0.992

(Table 4) shows that 20 min is sufficient for the oxidation to be completed , so it is 20 min adopted in the subsequent experiments**.**

Effect of temperature

The effect of temperature(5-60°C) on the absorption of the formed colored product are studied by using 1.5 ml of 4- amino benzoic acid reagent (1×10^{-2}M) and 3.0 ml of TFPH solution (500µg/ml) and 0.5 ml of KIO_3 (1×10^{-2}M), and 1.5 ml of 1.0 M hydrochloric acid solution are added, then the volume is completed to 25 ml with distilled water in a volumetric flasks, and the absorption is measured at a wavelength of 550 nm versus blank reagent, the results are shown in (Table 5). The optimum temperature is 18°C , so it is adopted in the subsequent experiments

Table 5: Effect of temperature

Temp C°	5	10	18	20	25
Absorbanc	0.003	0.996	**0.996**	0.989	0.984
30	**35**	**40**	**45**	**50**	**60**
0.980	0.971	0.952	0.926	0.889	0.822

Effect of time on stability of the colored product

The stability time of the formed colored product is studied by taking 3.0 ml of TFPH (500 µg/ ml) with addition 0.5 ml of KIO_3 (1×10^{-2}M) and the solution is left for 20 min for oxidation, then 1.5 of 4- amino benzoic acid (1×10^{-2}M) and 1.5 ml of 1.0 M hydrochloric acid solution are added, the volume is completed to 25 ml in a volumetric flasks with distilled water. It is observed that the absorption becomes constant directly after dilution and remains constant for 60 min. The results are shown on (Table 6).

Table 6: Effect of time on stability of the colored product

ml of TFPH	Absorbance / min. standing time									
	5	10	15	20	25	30	35	40	50	60
3	0.995	0.995	0.995	0.995	0.995	0.994	0.995	0.995	0.995	0.993

Final absorption spectrum

The spectrum of the formed colored product by coupling of TFPH with 4- amino benzoic acid (1×10^{-2}M) in the presence of KIO_3 (1×10^{-2}M) in acidic medium and temperature 18°C against blank shows a maximum absorption at 550 nm in contrast to the blank of zero absorbance at λ_{max}. The spectra are shown on (Figure 1).

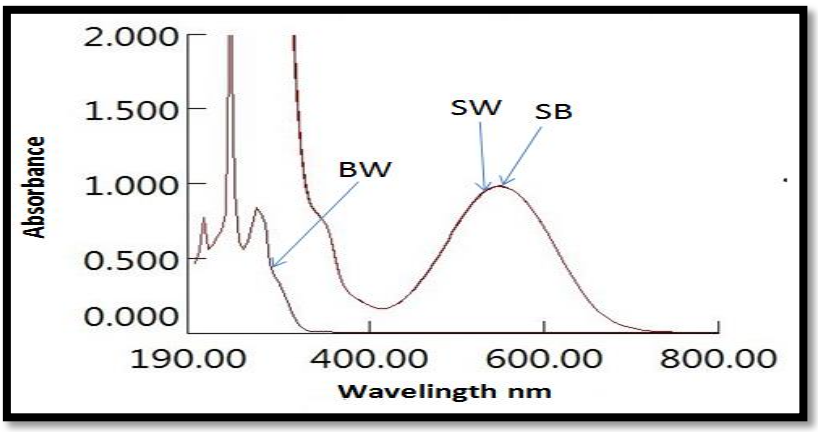


Fig. (1): Final absorption spectrum of the determination of TFPH

SB : Absorption spectrum of TFPH solution versus blank.
SW: Absorption spectrum of TFPH solution versus distilled water.
BW: Absorption of blank versus distilled water.

Procedure for construction of calibration curve

To a series of volumetric flasks (25ml), 0.5-4.0ml of (500 µg/ml) of TFPH are transferred, 0.5 ml of KIO_3 (1×10^{-2}M) is added and the solutions are left for 20 min for oxidation, then 1.5 ml of 4- amino benzoic acid reagent (1×10^{-2}M) and 1.5 ml of 1.0M hydrochloric acid solution are added at 18°C and the volumes are completed to the mark with distilled water. The absorbance is measured after 5min dilution at 550 nm against the blank reagent. (Figure 2) illustrates that the calibration curve is linear over the concentration range of 10 - 80 µg/ml while higher concentrations show a negative deviation from Beer's law. The molar absorptivity value is 0.8032×10^4 liter. $mol^{-1}.cm^{-1}$and the Sandell's sensitivity index 0.0598 $\mu g/cm^2$.

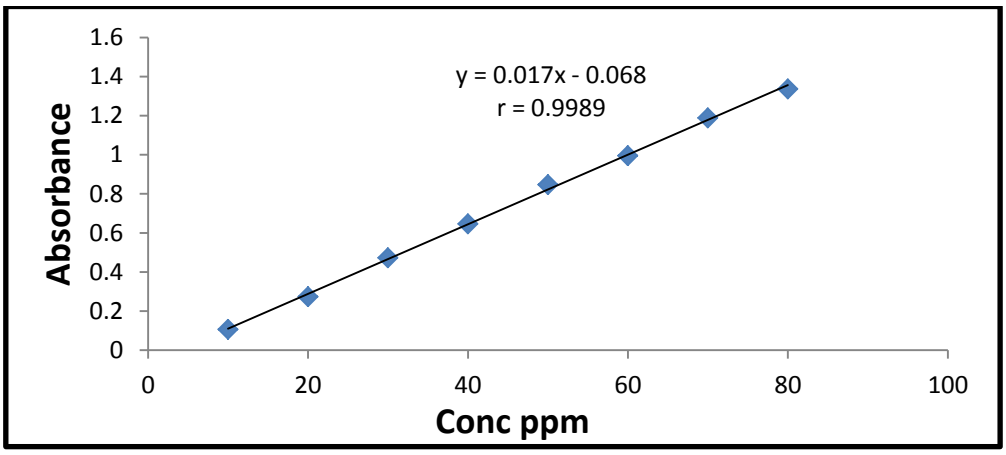


Fig. (2): Calibration curve for determination TFPH by oxidative coupling with 4- amino benzoic acid reagent.

Accuracy and precision

Accuracy and precision are studied by measuring absorption (n=7) at 550 nm for three different concentrations of the drug within the limits of Beer's law, the average recovery (102.57 %) and the Average relative standard deviation (0.229%) indicate that the method is of high accuracy and precision . The results are shown in (Table 7).

Table (7): Results of accuracy and precision

Conc.of TFPH µg /ml	Conc.of TFPH Observed*	RE%	Recovery,*%	RSD*,%
20	20.085	0.29	100.29	0.295
60	62.529	4.21	104.21	0.216
80	82.588	3.23	103.23	0.177

*** n=7**

Detection limit

Detection limit is calculated by measuring the absorption for the lower concentration 10 µg/ml at optimal conditions (eleven times) at 550 nm. The results are shown in (Table 8).

Table (8): Detection limit

Concentration µg /ml	P*	S**	LOD µg/ml
10	0.017	0.002	0.3882

***n=11**

P= Slope

****S= Standard deviation**

The nature of the formed product

To know the nature of the formed violet color product (stoichiometry of drug with the reagent), Job's method and molar ratio method are applied. In both methods, the concentration of each of the standard TFPH solution and 4- amino benzoic acid reagent solution is equal to 5 $\times 10^{-4}$ M. In Job's method, in a series of volumetric flasks (25 ml), different volumes of the drug solution ranging from1-9 ml and different volumes (9-1 ml) of reagent solution are mixed. A 0.5 ml of KIO_3 (1×10^{-2} M) and 1.5 ml 1.0 M of hydrochloric acid solution are added and volumes are completed to the mark with distilled water. The absorbance is measured at 550 nm against the blank reagent. The results (Figure 3) show that the ratio is 1:1.

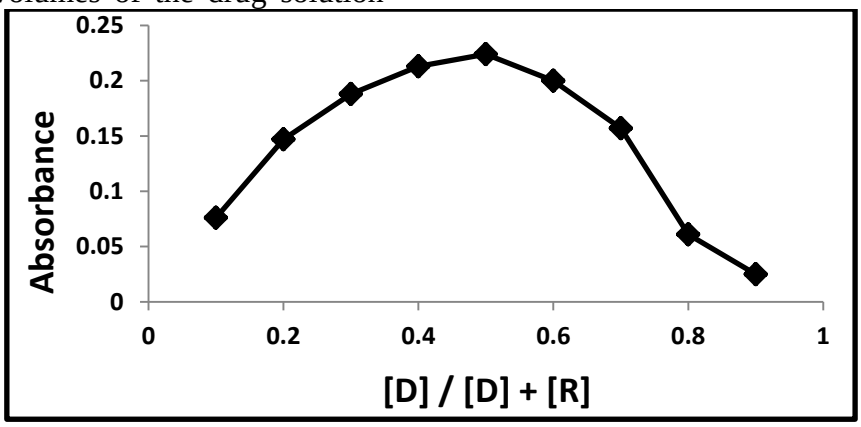


Fig. (3): Job's method of formed product by oxidative coupling of TFPH with 4-amino benzoic acid reagent.

In molar ratio method, 3 ml of the standard drug solution in a series of volumetric flasks (25 ml) are transferred and different volumes 0.5-5 ml of 4- amino benzoic acid reagent solution, 0.5 ml of KIO_3 (1×10^{-2}M) and 1.5 ml 1.0 M of hydrochloric acid solution are added. The volumes are completed to the mark with distilled water and the absorbance is measured at 550 nm against the blank . Molar ratio is found to be 1:1. The results are shown in (Figure 4) which is in agreement with the Job's method results.

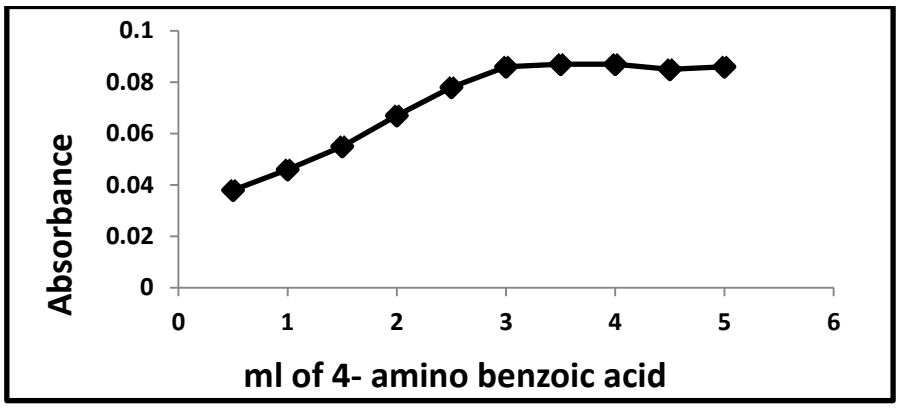


Fig. (4): Molar ratio method for the product formed by oxidative coupling of TFPH with 4- amino benzoic acid reagent.

Applications

Direct method

In this method, different volumes (0.5,3,4 ml) of a pharmaceutical formulation solution (500 µg/ml) are transferred to 25 ml volumetric flasks and the resulting concentrations (10.60.80 µg/ml) and are treated as in construction of calibration curve. The absorbance is measured at 550 nm for five times. RE is calculated and the results are shown in (Table 9).

Table 9: Determination of TFPH in pharmaceutical formulation

Conc of TFPH µg/ml	Conc of TFPH Observed	RE	%Recovery
20	20.235	1.17	101.17
60	61.588	2.64	102.64
80	82.176	2.72	102.72

standard additions method

To prove that the developed method is free from interferences , method of standard additions is applied for determining the stoichiometry of TFPH reagent product. (1 ml) of a pharmaceutical formulation solutions (500 µg/ml) is transferred to each eight volumetric flasks (25 ml), then increasing volumes (0.2-3.5 ml) of 500µg/ml of TFPH standard solution are added with leaving the eightth flask without addition.The solution is treated as in the construction of calibration curve. The absorbance is measured at 550 nm (Figure 5). The measured concentration is calculated from the equation of the straight line and the results of Recovery and RE are shown in the Table (11).

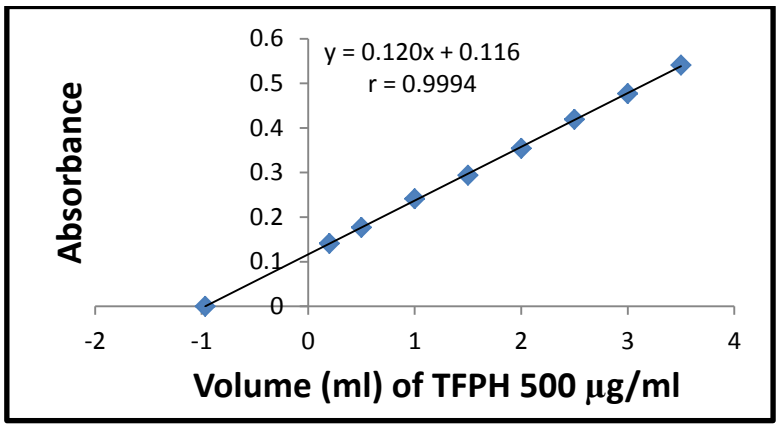


Fig. (5): Standard additions curve for the determination of TFPH in injection

Table 10: Results of standard additions method

Type of Drug	Traifluoperazine present µg/ml	Traifluoperazine measured µg/ml	Recovery, (%)
Tablets salabid Trifluoperazine 1mg S.D.I Iraq	20	19.4	97

The results shown in (Table 10) indicate that method of standard additions is in agreement with the direct method within the acceptable range of error, indicating that the method is satisfactory and free from interferences.

Conclusions

The results obtained confirm that the proposed method is simple and of good sensitivity for the determination of trifluoperazine hydrochloride TFPH. The method is based on oxidative coupling between TFPH and 4- amino benzoic acid reagent in presence of potassium iodate in acidic medium to form a violet colored which is water soluble, stable and shows a maximum absorption at 550 nm. This method does not require temperature control, not use of organic solvents, or solvent extraction and it can be applied directy and successfully for determination of TFPH in pharmaceuticals formulation.

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