Sys Rev Pharm 2020; 11(6): 58 – 68
A multifaceted review journal in the field of pharmacy
E-ISSN 0976-2779 P-ISSN 0975-8453

"Spectrophotometric Determination of Trifluoperazine Hydrochloride in Pharmaceutical Preparations by Oxidative Coupling Reaction"

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Article History: *Submitted: 09.03.2020* *Revised: 12.04.2020* *Accepted: 30.05.2020*

ABSTRACT

A fast and sensitive spectral analysis method has been developed to estimate microscopic amounts of Trifluoperazine Hydrochloride in an aqueous medium. The method is based on oxidative coupling reaction between Trifluoperazine Hydrochloride and 2-nitroso-1-naphthol-4-sulfonic acid as an Reagent with the presence of the oxidized agent potassium persulfate at pH= 4.2. The resulting product is red, which is absorbed at the wavelength of 500nm, in distilled water and is stable for 80 minutes. The Bear-Lambert Act follows the concentration range of 12–36 µg/mL. The value of the MLM 6726 $L.mole^{-1}.cm^{-1}$, Sandel significance value of 0.07143 $\mu g/cm^2$, the relative standard deviation does not exceed RS =0.9623, the relative error does not exceed RE = 0.8157, and the quantum limit $9.5x10^{-7}$ µg/mL, the detection limit 2.85×10^{-7} µg/mL, association coefficient R=0.9995, estimation coefficient R^2=0.9989. The developed method successfully applied to estimate Trifluoperazine Hydrochloride in the pharmaceutical drug Stellasil (5mg).

Keywords: Trifluoperazine Hydrochloride, Oxidative Coupling Reaction, 2-nitroso-1-naphthol-4-sulfonic acid.

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DOI: 10.31838/srp.2020.6.12

INTRODUCTION

Trifluoperazine Hydrochloride is a white colored powder with a melting point ranged (242-243 ºC) that is odorless and highly dissolved in water and alcohol, partially dissolved in diethyl ether and is kept isolated from the light in dark containers[(1)], its molecular weight 480.43 g/mole and its molecular formula is $C_{21}H_{24}F_3N_3S.2HCl$:

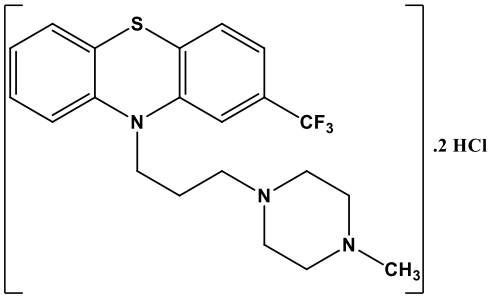


Figure 1: Chemical structure of Trifluoperazine Hydrochloride.

The scientific name of the drug is 10-(3-(4-Methyl-1-piperazinyl)propyl)-2-trifluoromethylphenorhiazine dihydrochloride. It can be found in pharmaceuticals in the form of tablets, its commercial names and its manufacturer are [(2)]: Salabid (SDI), Terfluzine (Theraplix), Eskazinyl (SK&F), Jatraneural (Procter&Gamble), Stelazine (SKB), Iralzin (SDI), Modalina (Maggioni-Winthrop). The drug is used in the treatment of depressive diseases [(3)], vomiting, nausea, schizophrenia [(4)] and hysteria, and affects pregnant women so it is not recommended to be used by pregnants[(5)], its side effects cause stomach pain, skin rash, inactivity, nausea, yellowish colored eye, heavy sweating, increased pulse rate, urination difficulty [(6)].

In this research, oxidative coupling reaction was applied to estimate the Trifluoperazine Hydrochloride drug in its pharmaceutical drug, as it involves a combination of two organic substances with an oxidizing agent under appropriate conditions towards reaction completion, to obtain a colored compound that can be spectrally measured. Trifluoperazine Hydrochloride was determined with different analytical techniques such as; Spectrophotometric methods [(7-16)], Chromatography methods [(17-26)], Atomic Absorption methods [(27-28)] and Electrochemistry methods [(29)].

EXPERIMENTAL SECTION

Equipment and chemicals used

Balance (Kern), (Shimadzu) Spectrophotometric Double Beam -Water bath (Memmert) – Heater and magnetic Stirrer (Heidolph) - (WTW) pH meter (1 cm) (glass cell). Chemicals used are also described in table (1) below:

Table 1: Chemicals used in this study.

NO.	Chemical Name	Molecular Weight g/mole	Chemical Formula	Company
1	Trifluoperazine Hydrochloride	480.43	$C_{21}H_{24}F_3N_3S.2HCl$	SDI/Iraq
2	Potassium persulfate	270.33	$K_2S_2O_8$	BDH
3	2-Nitroso-1-Naphthol-4-Sulfonic Acid	253.23	$C_{10}H_7NO_5S$	Fluka

Solution preparation of chemicals used

1. (1000 µg/mL) Trifluoperazine

(0.1g) of the material was weighed and dissolved with (50 mL) distilled water, and after it was dissolved, the volume was completed to the mark with distilled water in a (100 mL) volumetric flask.

2. Trifluoperazine Hydrochloride pharmaceutical solution (500 µg/mL)

is the pharmaceutical that contains Trifluoperazine Hydrochloride as tablets, produced by Cairo Pharmaceuticals Company (Cairo-Egypt), each tablet contains (5 mg) of Trifluoperazine Hydrochloride. The solution (1000 µg/mL) was prepared by weighing (20 tablets) that were grounded and dissolved with distilled water, filtered, and the volume was completed to the to the mark in a 100 mL volumetric flask, and to prepare a solution (500 µg/mL), (50 mL) of the (1000 µg/mL) solution were transferred and the volume was complete to the mark in a (100mL) volumetric flask.

3. (500 µg/mL) Trifluoperazine Hydrochloride Solution

(50 mL) of the (1000 µg/mL) drug solution has been transferred and diluted to the mark in a (100 mL) volumetric flask with distilled water, and the absorption spectrum of the solution has been measured against distilled water by taking (1 mL) of the drug solution and diluting it with distilled water to the mark in a (25 mL) volumetric flask to represent (20 µg/mL), The wavelength of the highest absorption was (309 nm). The absorption value of the solution is 0.154, as shown in Figure (2) below:

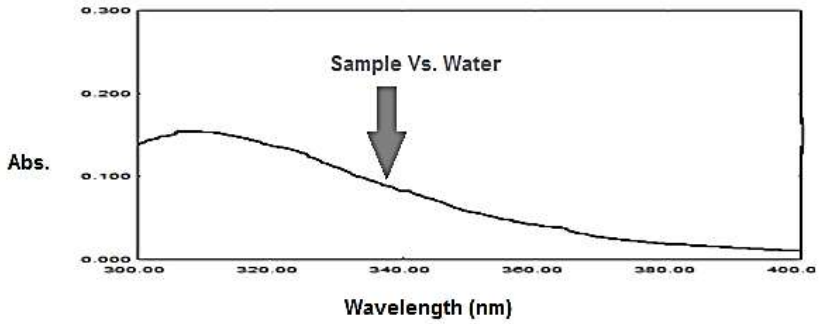


Figure 1: Absorption spectrum (20 µg/mL) before the reaction.

4. 2-Nitroso-1-Naphthol-4-Sulfonic Acid solution (5×10^{-3} M): (0.1266 g) of the material was weighed and dissolved in (30 mL) of distilled water and heated at a temperature of (40 ºC) for (5 min), after which, the volume was completed with the distilled water to the mark in a (100 mL) volumetric flask as the material is insoluble in cold water.

5. Potassium Persulfate solution (1×10^{-2} M): (0.2703 g) of the material was weighed and dissolved in a small amount of hot distilled water at (40 ºC), the volume was completed with the distilled water to the mark in a (100 mL) volumetric flask.

General Procedure

Yellow colored Reagent solution 2-Nitroso-1-Naphthol-4-Sulfonic Acid (5×10^{-3} M) was added to the colorless drug solution Trifluoperazine Hydrochloride (500 µg/mL), colorless oxidizing agent solution of potassium Persulfate (1×10^{-2} M) was also added to give a red color product.

Preliminary study

(1 mL) of the Reagent 2-Nitroso-1-Naphthol-4-Sulfonic (5×10^{-3} M) was transferred along with (1 mL) of the drug Trifluoperazine Hydrochloride (500 µg/mL), this was followed by the addition of (1mL) of the oxidizing agent Potassium Persulfate (1×10^{-2} M). The result was a red color compound as a product of an oxidative association, distilled water as a solvent was added to the mark in a (25 mL) volumetric flask. The absorption spectrum of the sample solution was taken against the blank solution, and the highest absorption of the sample solution was at wavelength (500 nm) due to its red color, and the highest absorption of the blank solution at wavelength (382 nm) due to its yellow color.

Studying and adjustment of the optimal conditions of the reaction

(1 mL) of (20 µg/mL) of Trifluoperazine Hydrochloride solution was transferred to a (25 mL) volumetric flask and is depended as the final concentration when studying the optimal conditions of the reaction at wavelength (500 nm) in a (1 cm) glass cell.

Studying the effect of the association Reagent quantity

different volumes (0.8-2.5 mL) of the Reagent 2-Nitroso-1-Naphthol-4-Sulfonic Acid (5×10^{-3} M) were taken with different concentrations (20-60 µg/mL) of Trifluoroperazine Hydrochloride with the use of (1mL) of the oxidizing agent Potassium Persulfate (1×10^{-2} M), the volume was completed with distilled water to the mark in a (25 mL) volumetric flask. The absorption of the solutions against the photoactive solution is measured at the wavelength of (500 nm), results are shown in Table (2).

Table 2: The effect of association Reagent quantity.

mL of Reagent	Conc. of Drug Abs.				
	20	**30**	**40**	**50**	**60**
0.8	0.093	0.121	0.143	0.165	0.181
1.0	0.113	0.133	0.158	0.179	0.192
1.3	0.153	0.166	0.187	0.213	0.230
1.5	0.207	0.320	0.351	0.330	0.310
1.7	0.263	0.299	0.323	0.311	0.303
2.0	0.251	0.277	0.309	0.299	0.284
2.3	0.241	0.253	0.288	0.277	0.261
2.5	**0.167**	**0.192**	**0.223**	**0.240**	0.253

The results showed that the volume (1.5 mL) of the Reagent solution gave the highest absorption value, and was depended in the subsequent steps.

Studying the effect of the oxidizing agent quantity
different volumes (1.0-2.6 mL) of potassium persulfate (1×10^{2} M) were taken with (2 mL) of Trifluoperazine Hydrochloride (500 µg/mL) and (1.5 mL) of the 2-nitroso-1-Naphtol-4-sulfonic acid Reagent solution (5×10^{-3} M), distilled water was added to the mark in a (25 mL) volumetric flask and the absorption of solutions is measured against the photoactive solution of each at wavelength (500 nm), the results are shown in table (3).

Table 3: The effect of the oxidizing agent quantity.

mL of Oxidant	Abs. Of Drug
1.0	0.350
1.4	0.361
1.6	0.369
1.8	0.374
2.0	0.388
2.2	0.377
2.4	0.361
2.6	0.354

The results showed that (2.0 mL) of oxidizing agent solution has given the highest absorption value, and this volume was depended in the following steps.

Studying the effect of the basic medium
different volumes of (0.5-3.0 mL) of NaOH (0.5 M) were added to (2 mL) of (500 µg/mL) Trifluoperazine Hydrochloride and (1.5 mL) of 2-Nitroso-1-Naphthol-4-Sulfonic Acid (5×10^{-3} M) and (2 mL) of the oxidizing agent Potassium Persulfate (1×10^{-2} M), added distilled water to the mark of (25 mL) volumetric flask resulted in a turbid solution, the latter step was avoided in the upcoming procedure.

Studying the effect of the acidic medium
different volumes of (1.0-4.0 mL) of acetic acid (1 M) were added to (2 mL) of (500 µg/mL) Trifluoperazine Hydrochloride and (1.5 mL) of 2-Nitroso-1-Naphthol-4-Sulfonic Acid (5×10^{-3} M) and (2 mL) of the oxidizing agent Potassium Persulfate (1×10^{-2} M), added distilled water to the mark of (25 mL) volumetric flask. The absorption of solutions against the photoactive solution was measured at wavelength (500 nm), the results are shown in the table (4) below.

Table 4: Studying the effect of the acid.

Conc. of Acid	of Drug Volume (mL) Acid / Abs.				
	without acid	**1**	**2**	**3**	**4**
0.1 M	0.385	0.351	0.349	0.331	0.309

0.5 M	0.387	0.315	0.288	0.254	0.221
1.0 M	0.388	**0.227**	**0.189**	**0.156**	0.122

The results showed that the absorption values were reduced by adding acid, so the acid addition was avoided to in the following steps.

Studying the impact of temperature over time

The effect of temperatures (15-50 ºC) over time (5-40 min) on the absorption value has been studied and is shown in Table (5).

Table 5: The impact of temperature over time.

Temp.	Abs. / min .							
	5	10	15	20	25	30	35	40
5	0.386	0.341	0.340	0.337	0.331	0.326	0.322	0.320
20	0.387	0.363	0.357	0.350	0.344	0.341	0.338	0.335
25	0.387	0.409	0.423	0.412	0.405	0.401	0.394	0.388
30	0.384	0.376	0.363	0.341	0.337	0.331	0.325	0.320
35	0.386	0.369	0.355	0.339	0.328	0.317	0.311	0.307
40	0.385	0.355	0.347	0.325	0.319	0.309	0.301	0.284
45	0.386	0.349	0.333	0.317	0.310	0.295	0.283	0.271
50	0.386	0.336	0.321	0.305	0.301	0.288	0.277	0.264

The results have shown that the ideal temperature over time is (25 ºC) in (15 min), and it was depended in the subsequent steps.

Studying the stability of the resulting product

The resulting product was prepared by using three different concentrations (14, 18, and 24 µg/mL) of the drug and adding it to the other components to study their stability over (5-80 min), the absorption values of the three solutions were measured at wavelength of (500 nm), the results are shown in table (6).

Table 6: Studying the stability of the product.

Conc. µg/mL	Abs. /min									
	5	10	15	20	30	40	50	60	70	80
14	0.103	0.102	0.1	0.102	0.103	0.101	0.101	0.102	0.103	0.102
18	0.192	1.193	0.191	0.194	0.194	0.192	0.193	0.194	0.194	0.194
24	0.251	0.252	0.253	0.252	0.25	0.253	0.253	0.251	0.253	0.25

Studying the impact of the components addition sequence

This study was conducted by changing the sequence of adding the chemical reactants, as it shown in table (7) below.

Table 7: The impact of the components addition sequence.

Order NO.	Abs.	Color	Order of addition
1	0.229	Red	D + O + R
2	0.361	Red	R + O + D
3	0.423	Red	D + R + O

The results showed that the best addition sequence is (3) (Drug + Reagent + Oxidant), this option was selected in the next steps.

Studying solvent effect

This study was done by completing the volume of the resulting compound to the mark in a (25 mL) volumetric flask using different solvents and the results are shown in Table (8).

Table 8: Studying the solvent effect.

No.	Abs.	Solvent
1	0.364	Methanol
2	0.387	Acetone
3	0.423	Water

The results showed that using water as a solvent has given the highest absorption value, due to its availability, non-toxicity, and its low-cost, and was chosen in subsequent steps.

Final absorption spectrum

The optimal conditions for the reaction have been applied as shown in Table (9) below.

Table 9: Optimal reaction conditions.

Experimental Conditions		
1	pH	4.2
2	Solvent	Water
3	Temperature	25 0C
4	λ max	500 nm
5	Oxidant / Potassium persulfate ($1x10^{-2}$ M)	2 mL
6	Drug / Trifluoperazine Hydrochloride (500 µg/mL)	2 mL
7	Reagent / 2-Nitroso-1-Naphthol-4-Sulfonic Acid ($5x10^{-3}$ M)	1.5 mL
8	Color	Red
9	Absorbance	0.423

The results were as shown in table (10) and figure (3).

Table 10: Final absorption spectrum.

Variable	Sample Solution – Blank Solution
Absorbance	0.423
Wavelength	500 nm

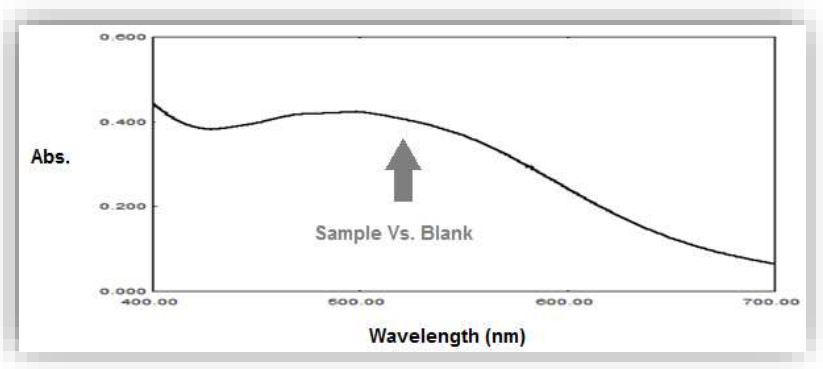


Figure 2: Absorbance at optimal conditions.

Calibration Curve

Different volumes (0.6 - 1.8 mL) of Trifluoperazine Hydrochloride solution (500 µg/mL) were taken and added to a series of 25 mL volumetric flasks, (1.5 mL) of the Reagent solution 2-nitroso-1-naphthol-4-sulfonic acid (5×10^{-3} M) was also added along with (2 mL) of the oxidizing agent potassium persulfate (1×10^{-2} M) to each volumetric flask, and the absorption was measured at wavelength (500 nm) under optimal conditions. Results showed that the calibration curve follows the Beer-Lambert's law at the concentration range (12-36 µg/mL). The estimation coefficient value is R^2=0.9989 and the correlation coefficient value is R=0.9995, The value of the slope = 0.0140, the value of Molar absorptivity = 6726 $L.mole^{-1}.cm^{-1}$, and the Sandel Index value = 0.07143 $\mu g/cm^2$, as shown in figures (4 and 5).

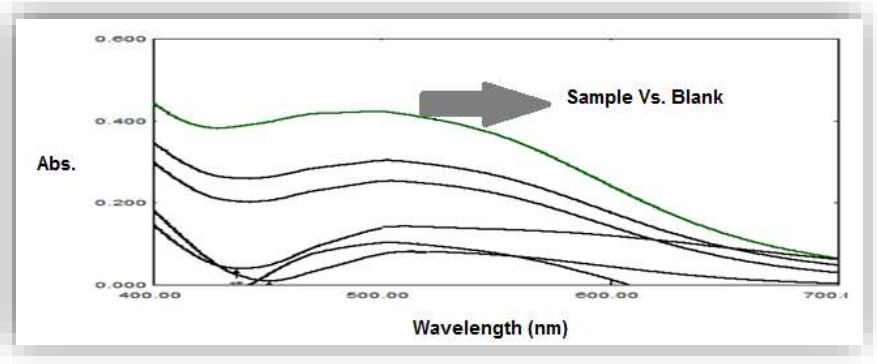


Figure 3: Calibration Curve.

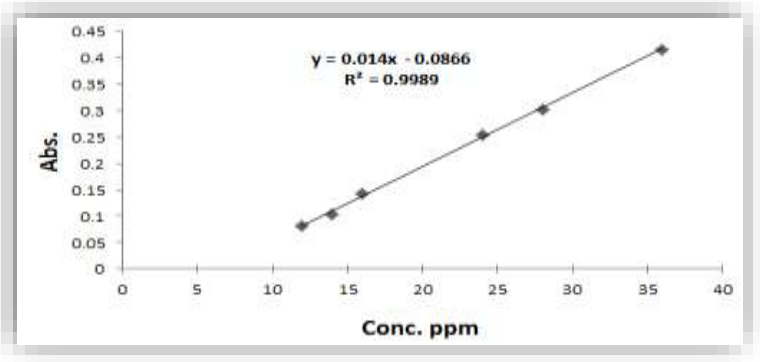


Figure 4: Calibration curve implementation.

Accuracy and precision

Concentrations of (14, 18, and 24 µg/mL) of the drug solution were taken and other components were added under optimal conditions according to table (11) below.

Table 11: Accuracy and precision.

Conc. Present µg/mL	Average Abs.	S %	RSD %	RE %	Recovery %
14	0.102	0.00098	0.9623	0.815661	100.8157
18	0.192	0.00127	0.6588	0.520833	100.5208
24	0.252	0.00082	0.3235	0.264201	100.2642

Detection limit and quantitative limit

The detection limit and quantitative limit values were determined from the measurement of the absorption values of six of solutions volume (0.6 mL) of (7.2×10^{-6}M) of the drug by using the previously fixed optimal conditions, it has been noticed that the detection limit value is (2.85×10^{-7} µg/mL), the quantitative limit value is (9.5×10^{-7} µg/mL), the results are shown in the table (12).

Table 12: Detection limit and quantitative limit.

Conc. Molarity	X-	S	L . O. D.	L . O. Q.
$7.2x10^{-6}$	0.0795	0.001049	$2.85x10^{-7}$ µg/mL	$9.5x10^{-7}$ µg/mL

The nature of the colored product

To study the association ratio between the drug and the detector, an equal concentration ($1x10^{-5}$ M) of Trifluoperazine Hydrochloride drug and Reagent 2-nitroso-1-naphthol-4-sulfonic acid were prepared in the Job method and the method of molar ratios, in Job method, 9 different volumes of the drug were transferred (1- 9 mL) To 25-mL volumetric flasks, the volume was completed to 10 mL with Reagent solution, the oxidizing agent was added according to the optimal conditions and the absorption values were measured at wavelength (500nm), it has been found that the ratio of the drug- Reagent link is 1:1, as in table (13) and figure (6).

Table 13: Job method.

NO.	V (mL) Drug (D)	V (mL) Reagent (R)	V (mL) D / V (mL) D + V (mL) R	Absorbance
1	1	9	0.1	0.198
2	2	8	0.2	0.182
3	3	7	0.3	0.240
4	4	6	0.4	0.323
5	5	5	0.5	0.438
6	6	4	0.6	0.378
7	7	3	0.7	0.288
8	8	2	0.8	0.168
9	9	1	0.9	0.112

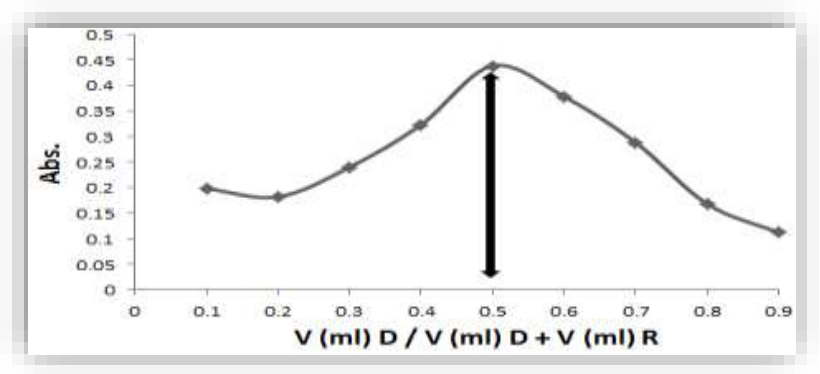


Figure 5: Job method.

In the molar ratio method, the solution volume of Trifluoperazine Hydrochloride was fixed at 2 mL and was added to a series of 9 volumetric flasks of 25 mL, and different volumes (0.5, 4.5mL) of 2-nitroso-1-napphol-4-sulfonic acid were added based on optimal conditions, the absorption values have been measured at wavelength (500nm), and the results showed that the linking ratio between the drug and the Reagent was also 1:1, which corresponds to the outcome of the Job method as it is shown in table (14) and figure (7).

Table 14: Molecular ratios method.

NO.	V (mL) Drug (D)	V (mL) Reagent (R)	V (mL) R / V (mL) D	Absorbance
1	2	0.5	0.25	0.109
2	2	1	0.5	0.163
3	2	1.5	0.75	0.271
4	2	2	1	0.401
5	2	2.5	1.25	0.408
6	2	3	1.5	0.434
7	2	3.5	1.75	0.431
8	2	4	2	0.438
9	2	4.5	2.25	0.456

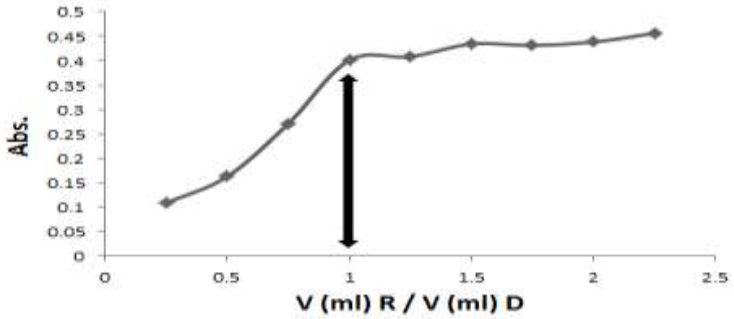
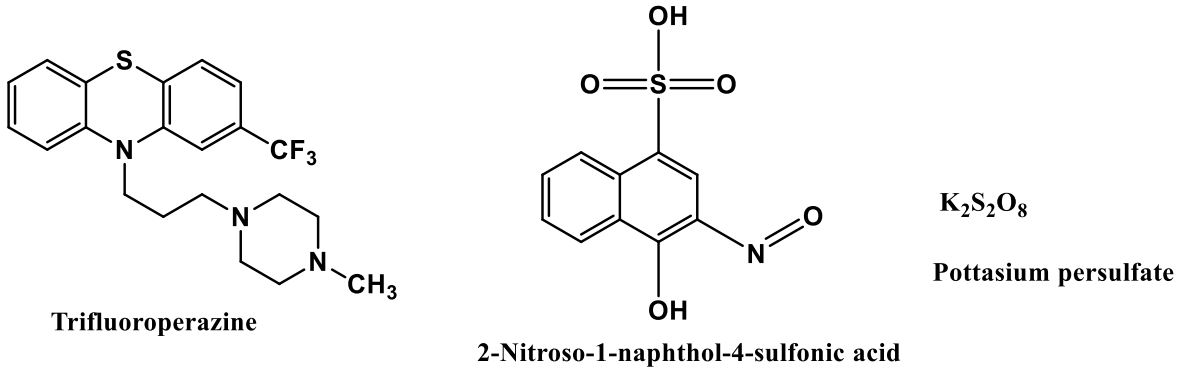


Figure 6: The nature of the resulted compound (Molar ratios method).

From the above, the reaction equation can be suggested as follows:



Equation 1: Suggested reaction with two possible compound.

Applications

The developed method has been applied to the Stellasil 5 mg medicinal tablets produced by Cairo Pharmaceutical Co.

(Cairo-Egypt), which contains Trifluoperazine Hydrochloride using:

1- The direct method: The direct method was applied by taking concentrations of (16, 20, and 32 µg/mL) of the pharmaceutical drug solution, the results are shown in Table (15).

Table 15: The direct method.

Conc. Present µg/mL	Average Abs.	S %	RSD %	RE %	Recovery %
16	0.142	0.000816	0.573651	0.468385	100.4684
20	0.230	0.000894	0.388881	0.289855	100.2899
32	0.336	0.000753	0.223928	0.165262	100.1653

The results showed that the success of the method developed in estimating Trifluoperazine Hydrochloride in the pharmaceutical product.

2- Standard addition method: The standard addition method was applied to know the efficiency of the proposed method for estimating the Trifluoperazine Hydrochloride drug in the Stellasil (5 mg) pharmaceutical product as tablets. Concentrations of (9-20 µg/mL) of the pharmaceutical drug were taken and transferred into 6 volumetric flasks of (25mL) , increased volumes (0.5-2.5 mL) of pure Trifluoperazine Hydrochloride were added, leaving one of the flasks without addition. The remaining components (Reagent and oxidizing agent) were added according to optimal conditions and the absorption values measured for 6 readings at wavelength 500nm, and the results as shown in Table (16) and Figure (8).

Table 16: Results of standard addition method.

Conc. Present µg/mL	Conc. Measured µg/mL	RE %	Recovery %
9	8.795	-2.278	97.72
20	19.85	-0.75	99.25

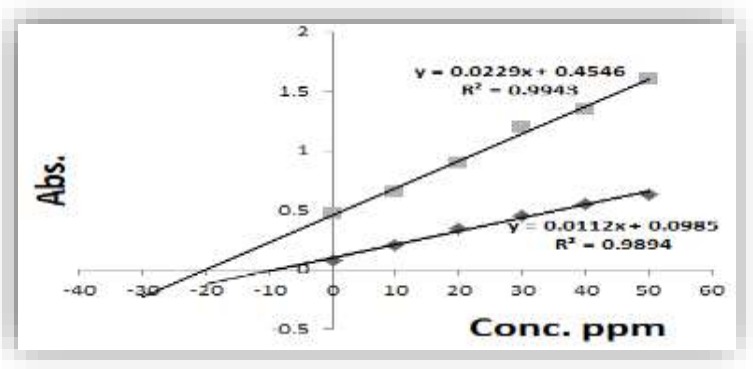


Figure 7: Standard addition method.

Results showed that ther was a good agreement with the direct method and in the extent of the allowed error.
Comparing the suggested method with other methods: the suggested method with other methods as in table (17).

Table 17: Comparing the suggested method with other methods>

No.	Analytical Parameter	Present Method	Literature (30) method	Literature (31) method
1	Reaction	Oxidative coupling	Oxidative coupling	Oxidative coupling
2	Reagent	2-Nitroso-1-Naphthol-4-Sulfonic Acid	p-Chloroanilne	Sulphanilic acid
3	Oxidant	Potassium Persulfate	Ammonium ceric sulfate	sodium hypochlorite
4	Color of the dye	Red	Violet	Red
5	Beer's Law Range µg/mL	12 – 36	4-50	0.2 – 7.0
6	Molar Absorptivity L.mol-1.cm-1	6726	3.74x103	5.15×103
7	Sandel Index	0.07143	0.108x10-3	0.3330

	µg/cm2			
8	pH	4.2	————	———
9	Temperature C0	25	————	25
10	RSD	0.9623	———	1.17
11	L.O.D µg/mL	10-7×2.85	2.21	———
12	Slope	0.0140	0.0092	———
13	Stability min.	80	45	———
14	R	0.9995	0.9987	0.9990
15	L.O.Q µg/mL	9.5x10-7	7.39	———

CONCLUSIONS

The developed method is an economical spectral analysis to estimate microscopic amounts of Trifluoperazine Hydrochloride in the pharmaceutical drug Stellasil (5 mg) as pharmaceutical tablets using oxidative coupling reaction with the Reagent 2-nitroso-1-naphol-4-sulfonic acid and the oxidizing agent potassium persulfate. The color of the resulting compound is red and is absorbed at wavelength (500 nm), and is soluble in water at pH= 4.2, stable at temperature (250 ºC) for (80 min), and follows Beer-Lambert's law in a concentration range of (12-36 µg/mL), and the value of the molar absorbance is (6726 $L.mol^{-1}.cm^{-1}$). Its Sandel's significance value is (0.07143 $\mu g/cm^2$) and does not exceed RSD = (0.9623), it is also does not exceed (RE = 0.8157 µg/mL), L.O.D.= (2.85×10^{-7} µg/mL) and L.O. Q.= (9.5×10^{-7} µg/mL), R= (0.999595), R^2 = (0.9989).

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