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Development of a New Indirect Method for the Determination of Trifluoperazine-HCL in Pharmaceutical Formulations

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Abstract: The estimation of trifluoperazine hydrochloride in pure and dosage forms has been developed using a simple spectrophotometric approach. The method employs an oxidation-reduction reaction with ceric sulfate in acidic medium the unreacted oxidant bleaches the color of complex prepared previously outside the reaction medium from reaction of 4,7-diphenyl 1,10phenanthroline with ferrous ammonium sulfate to produce a red-violet colored product with a maximum absorbance of 533nm. The molar absorptivity of $0.700x10^4$ L. mole $^{-1}$.cm^{-1}, Beer's law is followed over a concentration range of 1.25-62.5 µg ml-1. The proposed approach was successfully used to determine trifluoperazine hydrochloride in tablets. For the determination of trace quantities of TFPH, a simple, fast, exact, and sensible spectrophotometric approach has been suggested.

Keywords: *Trifluoperazine hydrochloride, 4,7diphenyl 1,10phenanthroline, Spectrophotometry, ceric sulfate*.

Introduction

Living creatures have a variety of defense mechanisms that lower the number of reactive oxygen species (ROS) by scavenging free radicals, chelating catalytic metals, and serving as electron donors [1][2]. Many earlier studies have suggested the biological effect of natural antioxidants, including the suppression of reactive oxygen species (ROS). Antioxidants, thereby, shield living organisms from the generation of ROS that leads to lipid peroxidation, and protein and DNA damage [3][4][5].

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[1]. The scientific name of trifluoperazine hydrochloride is 10-[3-(4-methyl-1-piperazinyl) propyl] trifluoperazine hydrochloride-2-trifluoro-methylphenothizine di-hydrochloride), it has the following chemical structure as shown Figure1.

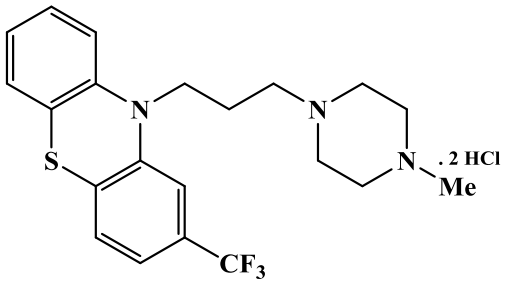

Fig. 1: Chemical structure of Trifluoperazine- HCl

It has been known to induce QT prolongation and ventricular tachycardia, which can lead to sudden death[2] and is therefore used in the treatment of various mental diseases like schizophrenia. The drug is used in the treatment of depressive diseases[3]. It was estimated by via various methods including electrochemical using electrodes made of carbon[4]. Various spectrophotometric methods used these methods included oxidative coupling reaction.[5-10] Ultraviolet spectrophotometric[11]. Also, other types of techniques have been used: indirect atomic absorption method[12]. Voltammetry method[13], Potentiometric sensors[14]. Electrochemical Sensing[15]. Flow injection analysis[16,17], RP-HPLC[18,19], HPLC[20] and derivative spectrophotometric, HPLC, and thin layer chromatographic densitometry [21]

This paper proposes a spectrophotometric method for determining trifluoperazine hydrochloride, which depends on an oxidation-reduction reaction of the compound under study using the oxidizing agent ceric sulfate and the remainder of the oxidizing agent working to bleaching the color of the reagent (Ferron). The proposed approach was used to determine trifluoperazine hydrochloride in its formulations such as tablets.

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 company, BDH) and the Trifluoperazine-HCl in its pure

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form will be brought from the State Company for Pharmaceutical Industry Samarra - Iraq

Trifluoperazine hydrochloride (500 µg/ml) Weigh 0.0500 g of the pure trifluoperazine-HCl and dissolve it in distilled water and complete the volume to the mark of 100 ml and keep in an opaque container.

Ferrous ammonium sulfate solution (2×10^{-3} M):

This solution was prepared by dissolving 0.0568 g of ferrous ammonium sulfate (equipped by Fluka Company) in a quantity of distilled water, then completing the volume to 100 ml with distilled water using a volumetric vial. This solution is prepared daily and kept in an opaque.

Ceric Sulfate solution .(2×10^{-3}) M

This solution was prepared by dissolving 0.0664 g of reagent (prepared by BDH) in 0.5 M sulfuric acid and completed to the mark in a volumetric flask of 100 ml.

4,7-diphenyl-1,10-phenanthroline (2×10^{-3}) M: Dissolve 0.0664 g of the pure reagent) BDH) in 100 ml of ethanol and this solution is kept in an opaque container and this solution is stable for one day.

Preparation of pharmaceutical preparation

Five tablets (5mg /tablet, S.D.I), were carefully weighed and after crushed and mixing well, an amount of the powder equivalent to 0.0100 g of pure TFPH was weighed and dissolved in distilled water then filtered into a volumetric flask of ٢٠ml and supplemented with distilled water up to the mark.

Fifteen tablets for (١mg / tablet, S.D.I), were carefully weighed and after crushed and mixing well, an amount of the powder equivalent to 0.0100 g of pure TFPH was weighed and dissolved in distilled water then filtered into a volumetric flask of ٢٠ml and supplemented with distilled water up to the mark.

Recommended Procedure.

The method is based on an oxidation-reduction reaction of the compound under study using the oxidizing agent Ceric sulfate and the remainder of the oxidizing agent working to bleaching the color of the reagent (derivative of Ferroin). The formation of a colored product gives the highest absorption at the wavelength of 533nm.

Results and Discussion

Absorption Spectrum

The absorption spectrum was taken for the colored product formed from the reaction of 500 µg of trifluoperazine hydrochloride with Iron (II) ammonium sulfate solution 2 x 10^{-3} molar and 4,7-diphenyl-1,10-phenanthroline in 10 ml final volume. The formation of a colored product (Ferroin complex) gives the highest absorption at the wavelength of 533 nm.

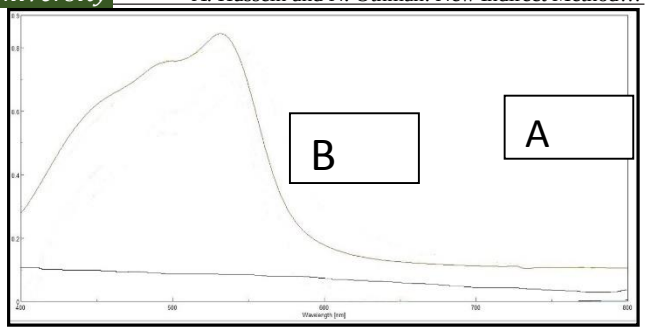

Fig. 2: Absorption spectra in (A) 50µg/ ml trifluoperazine hydrochloride treated according to the procedure of forming Ferroin. (B) blank solution versus distilled water.

The optimum conditions were studied in this research that affect absorption.

Effect of Acid

Different types of acids studied on the oxidation of the drug trifluoperazine hydrochloride, as 1 ml (500 µg/ml) of trifluoperazine hydrochloride was taken and 1.25 ml of the oxidizing agent was added, then 0.5 ml of the different acids were added and waiting for 15 minutes, then 0.5 ml of the reagent was added for each type. The absorbance was measured after bleaching color of derivative Ferroin after dilution to 10 mL at the wavelength of 533 nm and the results are shown in Table (1).

Table 1: The effect of various acids on absorbance.

1Moler Type of Acid (ml)	Without	HCl	HNO_3	H_2SO_4	CH_3COOH
Absorbance	0832	0.7211	0.1230	0.5998	0.3814

From the results shown in Table (1), it was noted that hydrochloric acid gave the best value for the absorbance of the residual dye, which indicates that a larger amount of trifluoperazine hydrochloride had oxidation, and therefore it was used in subsequent experiments.

Effect of the amount of hydrochloric acid

The amount of hydrochloric acid needed to complete the oxidation process of trifluoperazine hydrochloride was studied, as shown in Table (2).

Table 2: Effect of the amount of hydrochloric acid on the process of oxidation and shortening.

١M HCl (1ml)	Absorbance
٠,٢٥	٠,٤٣٢٥
٠,٥	٠,٧٢٢٥
٠,٧	٠,٨٣٣٢
١	٠,٤٧١٥

Effect of oxidation time:

The effect of the time required for the oxidation of trifluoperazine hydrochloride was studied by the calculated amount of oxidizing agent Ceric sulfite in an acidic medium and then left for different periods of time 2-15 minutes, and

the absorbance was measured at the wavelength of 533 nm and the results are shown in Table (3).

Table 3: Effect of time on oxidation of the drug compound.

Time	Absorbance
2	.٠8٦٥١
٥	٠,٨٣٤٢
١٠	٠,٨٠٠٤
١٥	٠,٧٨١١

The results in Table (3) show that the best time for oxidation of trifluoperazine hydrochloride is 2 minutes, so it was adopted in subsequent experiments.

Temperature effect:

He studied the effect of temperature in taking different temperatures, from room temperature to 60 ^{0}C for a period of 5 minutes, and it was noted that at high temperatures it leads to a decrease in absorbance while room temperature gives the highest absorption. The results are shown in Table (4).

Table 4: The effect of temperature.

Temperature, ^{0}C	Absorbance
Room temperature	٠,٨٣١٤
40	0.6008
50	0.4761
60	0.3493

From the results shown in Table (4) the room temperature gave the highest absorption, so the room temperature was adopted in the subsequent steps.

The sequence of adding reaction components:

Several experiments were conducted with different sequences to add the oxidizing agent in order to obtain the best absorption of the remaining dye. Results Table (5).

Table 5: the effect Sequence of adding reaction components.

Reaction component	Order number	**Absorbance**
S+OX+H$^+$+R	I*	0.8383
OX+S+H$^+$+R	II	0.7163
H$^+$+S+OX+R	III	0.6234

S (Triflouperazine HCl) + H (Hydrochloric acid) + OX (Ceric sulfate), R (4,7-diphenyl-1,10phenanthroline + iron(II) ammonium sulfate)

From the results of Table (5), the sequence I used in previous experiments was adopted in the next experiments in order to give it the highest absorbance of the remaining color of derivative Ferroin, which indicates the largest amount of the drug compound oxidized.

Interaction stability:

The stability of the resulting complex was studied by measuring the absorbance of the colored solution at different time intervals and the absorbance of the model was measured against its mock solution at a wavelength of 533 nm, and the results are shown in Table (6).

Table 6: The effect of time on the residual Ferroin.

TFPH µg / Time	Absorbance							
	5	10	15	20	30	40	50	60
15	0.2784	0.2789	0.2785	0.2782	0.2780	0.2778	0.2772	0.2768
50	0.8385	0.8387	0.8389	0.8384	0.8379	0.8370	0.8366	0.8364

From the results shown in Table (6), it is noted that the residual Ferroin is stable for a period of 60 minutes, and this period is sufficient to perform many of the measurements necessary to complete the experiment.

Calibration Graph

A linear calibration graph for TFPH (Figure 3) is obtained using the optimum conditions described in the recommended procedure, demonstrating that Beer's law is obeyed over the concentration range of 1.25–62.5µg/ml with a determination coefficient of 0.9996 and. The colored product generated had a conditional molar absorptivity of 0.82×10^4 L.mol^{-1}.cm^{-1}.

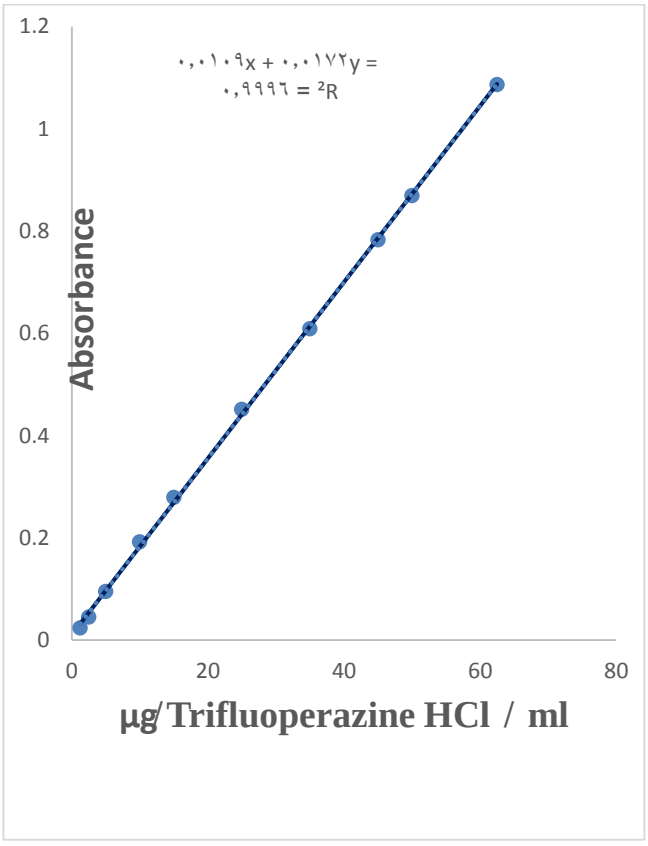

Fig. 3: Calibration graph for determination of TFPH.

Precision and Accuracy*:*

TFPH was determined at three different concentrations. The Outcome appears in Table 7, good accuracy and precision (Table 7) were gated it with the suggested method.

Table 7: Accuracy and precision of the suggested method.

Concentration of Trifluoperazine HCl(µg/ml)		Recovery* (%)	Relative error, %*	RSD* (%)
Present	Found			
10	9.892	98.92	0.28	0.33
25	24.753	99.01	0.02	0.14
50	50.14	100.28	-0.22	0.13

*Average of five determinations.

The Stoichiometry of Colored Product

The colored complex formed from the reaction (Ferroin complex), the complexity ratio is known and proven in the literature[22] with 1 [Fe (II)] to 3 [4,7- diphenyl-1,10phenanthroline]. Figure 4 shows the chemical structure of the formed colored complex.

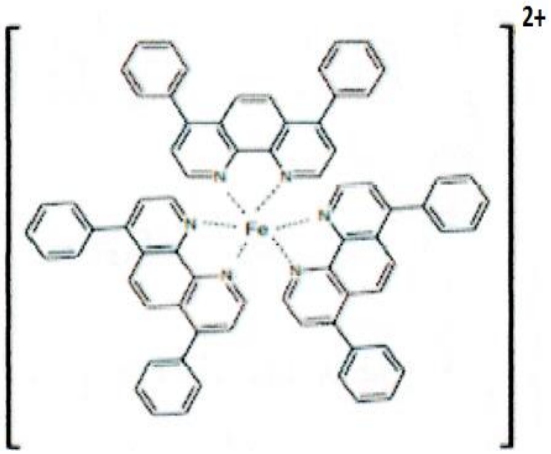

Fig. 4: The structure of TFPH- Fe^{+2} complex (Ferroin).

The standard addition method was used to show the efficiency and accuracy of the proposed method in estimating trifluoperazine hydrochloride in its pharmaceutical preparations. The results are shown in Table (٨) and Figures (5 and 6).

Table ٨: The results of applying the standard addition method.

Pharmaceutical preparation	µg Trifluoperazine HCl present	µg Trifluoperazine HCl measured	Recovery, %
Trifluoperazine-HCl /tablet 1mg (S.D.I. Iraq)	25	24.40	97.60
	37.5	36.18	96.48
Trifluoperazine-HCl/tablet 5mg (S.D.I. Iraq)	25	25.58	102.32
	37.5	37.13	99.01

From the results shown in Table (٨), 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.

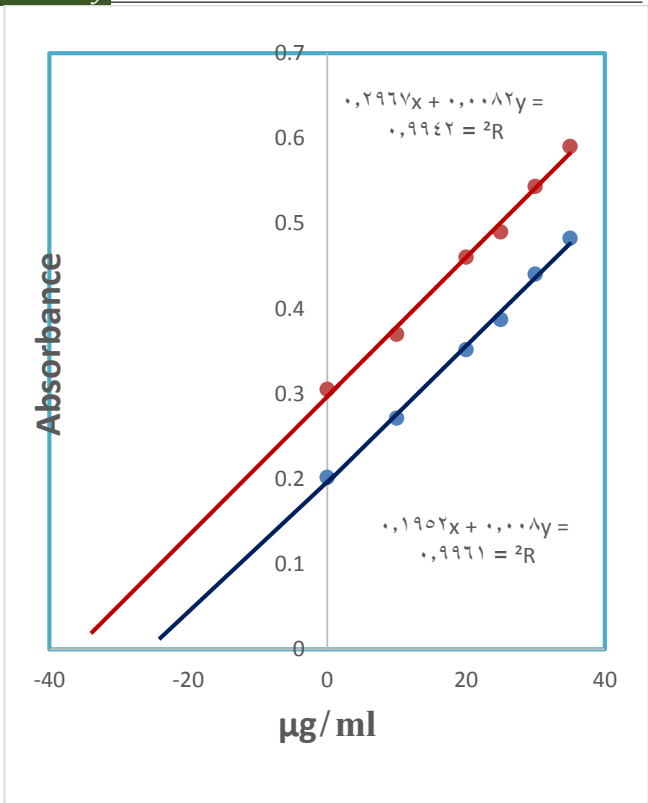

Fig. 5: Plot of Trifluoperazine-HCl/tablet 1mg (S.D.I. Iraq).

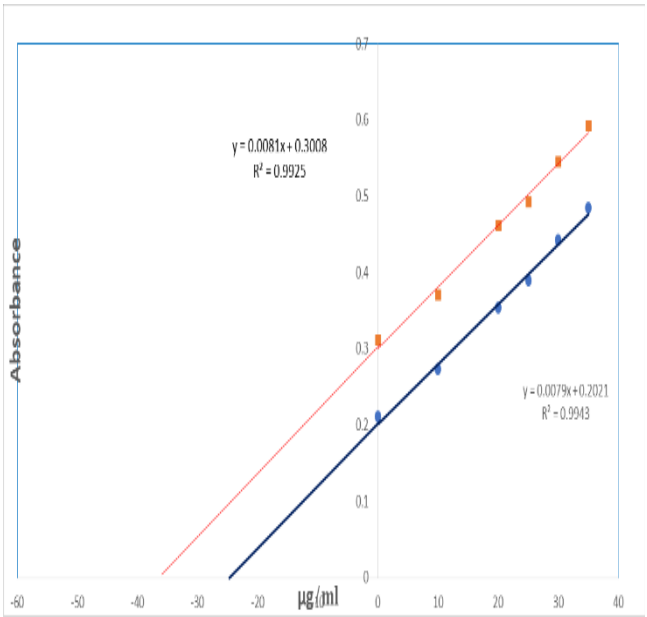

Fig. 6: Plot of Trifluoperazine-HCl/tablet 5mg (S.D.I. Iraq)

Analytical Applications:

The proposed method for the determination of trifluoperazine hydrochloride has been applied to various models of pharmaceutical preparations of trifluoperazine-hydrochloride (tablets). Different quantities of trifluoperazine hydrochloride were taken from the samples of pharmaceutical and the proposed method was applied, and the results are shown in the table(9).

Table 9: The results of analytical Applications.

Pharmaceutical preparation	µg Trifluoperazine-HCl present	µg Trifluoperazine-HCl measured	Recovery, %	RSD%	Texp
Trifluoperazine-HCl 1mg /tablet (S.D.I. Iraq)	١٠	10.003	100.030	0.1701	0.352
	30	30.004	100.013	0.0739	0.333
Trifluoperazine-HCl 5mg /tablet (S.D.I. Iraq)	١٠	10.01	100.100	0.262	0.763
	٥٠	50.004	100.008	0.034	0.467

* Average of four determinations.

It can be inferred from the result in Table (9) that the recovery rate is very good, which indicates that the method has good accuracy and efficiency in estimation. The value of t that was calculated for concentrations 10 and 30 for the drug 1mg and for concentrations 10 and 50 for the drug 5mg for Samarra Pharmaceutical Company available in the local market is less than the tabular value and with degrees of freedom 4 and at a confidence level of 95%, which indicates the success of the proposed method under study**.**

Conclusion

For the determination of trace quantities of TFPH, a simple, fast, exact, and sensible spectrophotometric approach has been established. Based on its, an oxidation-reduction reaction with excess amount of ceric sulfate then the unreacted ceric sulfate bleaches the color of derivative Feroin indicator that prepared from the reaction of 4-7 diphenyl 1,10 phenanthroline with iron (II) ammonium sulfate. The proposed method has been effectively applied to pharmaceutical tablets.

References

[1] British Pharmacopoeia Incorporating the 3th Ed.of the European pharmacopeia,2001,CD-Rom.

[2] Se-Young C., Young-Sang K., and Su-Hyun J., Inhibition of human ether-a-go-go-related gene K+ channel and IKr of guinea pig cardiomyocytes by antipsychotic drug trifluoperazine, J. Pharmacol. Exp. Ther. 313 (2005):888-95.

[3] Walash ,M.I.,Rizk,M., andAbou O. Titrimetric determination of some N-substituted phenothiazine derivatives. Analyst, 108;(1983):626-32.

[4] Aveen K. Mohammed, Ali I.Khaleel. Determination of triflouperazine hydrochloride by new constructed coated carbon selective electrodes. J. University of Garmian., (2019):398-410.

[5] Mohammad J Hamzah, Rawa M M Taqi, Muna M Hasan, Raid J M Al-Timimi, Spectrophotometeric determination of trifluoperazine-HCl in pure forms and pharmaceutical preperations. IJPCR,9(5); (2017): 337-342.

[6] Al-Rufaie MM, Kathem KH. New spectrophotometric method for determination of trifluoperazine hcl in pharmaceutical preparations by using oxidative coupling reaction. World J. Pharm. Res. 3(6);(2014): 1202-1214.

[7] MarwanT.J. Spectrophtomertic determination of triflouperazine hydrochloride in pharmaceutical preparations by oxidative coupling reaction, Sys Rev Pharm. 11 (6); (2020): 58-68.

[8] Maadh T., Kamal M M. Spectrophotomertic determination of triflouperazine hydrochloride using oxidative coupling reaction, Inter. J. Innovative Res. in Tech. (2016): 23-27.

[9] Mohammad, S.Abdulaziz .spectrophotometric determination of trifluoperazine hydrochloride in pure Forms and pharmaceutical preparations by oxidative coupling reaction as a reagent in the presence of N-Bromosuccinimide, International Journal of Drug Delivery Technology. (٢٠٢١).,**11**(1):153-158.

[10] Jalal MT. Spectrophotometric determination of trifluoperazine HCl in pharmaceutical preparations by oxidative coupling reaction. Sys Rev Pharm. 2020;11(6):58-68.

[11] Nief R. A. Ultraviolet spectrophotometric determination of trifluoperazine. HCl in pharmaceutical preparations and environmental wastewater samples: Application to content uniformity testing, Res.& Rev. J. Pharma. Analysis. (2014): 2347-2340.

[12] Ameen W. Qassim,Zuhair A. K., Ashraf S.R. An indirect atomic absorption spectrophotometric determination of triflouperazine hydrochloride in pharmaceuticals, Arabian J. Sci. and Eng. 36; (2011): 553–563.

[13] Stankovi´c D., T. Dimitrijevi´c D., Kuzmanovi´c M. P., Krsti´c B. B. Voltammetric determination of an antipsychotic agent trifluoperazine at a borondoped diamond electrode in human urine, RSC Adv., 5;(2015): 107058-107063.

[14] Ahmed K. H., Suhaam T. Ameen., Bahruddin Saad., Suad M AI-Aragi.. Potentiometric sensors for the determination of trifluoperazine hydrochloride in pharmaceutical preparations Analytical Sciences 25(11):1295-9 .

[15] Sura M., Eman A.Electrochemical sensing for trifluoperazine determination at a pth/mwnts film-

modified graphite electrode, Egyptian Journal of Chemistry 65 (4): 13-17, 2022.

[16] Moath T.A. Flow injection spectrophotomertic determination of triflouperazine hydrochloride using oxidative coupling reaction, International J. Current Research.9(4); (2017): 49218-49222.

[17] Kamal M. and Maadh T.A. Flow injection spectrophotometric determination of triflouperazine hydrochloride using oxidative coupling reaction, Inter. J. Current Res.9(4); (2017): 49218-49222.

[18] Bhadani S., Ekta P. R. Development and validation of RP-HPLC method for simultaneous estimation of chlordiazepoxide, trifluoperazine hydrochloride and trihexyphenidyl hydrochloride in tablet dosage from, Inter. J. Current Res. in Pharma.1(1); (2015): 50-59.

[19] Suman P. A. Novel RP-HPLC method development and validation for simultaneous estimation of trifluoperazine and isopropamide in tablet dosage form. Inter. J. Pharma. Sci. and Drug Res., 7(1); (2015): 105-109.

[20] Jameel M., Dhabab A. and Taufeeq H. Separation and determination of trifluoperazine and prochlorperazine in pharmaceutical preparations by HPLC, J. Assoc. of Arab Univ. for Basic and Appl. Sci., 13(1); (2013): 14-18.

[21] El-Gindy, A., El-Zeany, B., Awad, T., & Shabana, M. M. Derivative spectrophotometric, thin layer chromatographic densitometric and high-performance liquid chromatographic determination of trifluoperazine hydrochloride in presence of its hydrogen peroxide induced-degradation product. Journal of Pharmaceutical and Biomedical Analysis, 27(1-2); (2002): 9-18.

[22] Othman N. S., Mohanad M. S. and Shielan A. O. Indirect spectrophotometric methods in determination of cefadroxil in pharmaceatical preparations. Raf.J.Sci., 26(1); (2017):56-65.