وزارة التعليم العالي و البحث العلمي
جامعة بابل ـ كلية العلوم – قسم الكيمياء

بحث مقدم الى مجلس قسم الكيمياء كلية العلوم جامعه بابل بعنوان

دراسة نظرية لطرق تقدير بعض مركبات الصيدلانية
(PROPANOLOL HCl , TRIFLUOPERAZINE , AMITRIPTYLINE HCl)

وهو جزء من متطلبات نيل درجة البكالوريوس علوم الكيمياء

من قبل الطالب
((سيف الدين مفيد))

بإشراف الدكتور :
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2022 م – 1443 هـ

بسم الله الرحمن الرحيم

ٱللَّهُ لَآ إِلَٰهَ إِلَّا هُوَ ٱلْحَىُّ ٱلْقَيُّومُ ۚ
لَا تَأْخُذُهُۥ سِنَةٌ وَلَا نَوْمٌ ۚ لَّهُۥ مَا فِى ٱلسَّمَٰوَٰتِ وَمَا فِى ٱلْأَرْضِ ۗ
مَن ذَا ٱلَّذِى يَشْفَعُ عِندَهُۥٓ إِلَّا بِإِذْنِهِۦ ۚ يَعْلَمُ مَا بَيْنَ أَيْدِيهِمْ
وَمَا خَلْفَهُمْ ۖ وَلَا يُحِيطُونَ بِشَىْءٍ مِّنْ عِلْمِهِۦٓ إِلَّا بِمَا شَآءَ ۚ
وَسِعَ كُرْسِيُّهُ ٱلسَّمَٰوَٰتِ وَٱلْأَرْضَ ۖ وَلَا يَـُٔودُهُۥ حِفْظُهُمَا ۚ
وَهُوَ ٱلْعَلِىُّ ٱلْعَظِيمُ ﴿٢٥٥﴾

صدق الله العلي العظيم

ـ الإهداء ــ

بسم الله الرحمن الرحيم

صدق الله العلي العظيم

الشُكرُ لله و الحمدُ لهُ جل جلالُه , فإليهِ يُنسبُ الفضلُ كلُ الفضلِ في إكمالِ هذا البحث الذي يعتبرُ آخرَ متطلباتِ نيلِ درجة البكالوريوس في علومِ الكيمياء , و الذي يعتبرُ نهايةَ 16 عاماً منَ الجهدِ و التعبِ و المثابرةِ في سبيلِ كسبِ العلمِ و طلبهِ و الوصولِ الى أسماهُ و أفضلهِ , و الصلاةُ و السلامُ على سيدنا و نبينا محمد مُرشدنَا و نورِ ديننا و على آلهِ المنتجبين و صحبهِ المخلصينَ و سلمَ تسليمًا كثيرا .

بعدَ حمد الله و شكرهِ و الثناء عليهِ , أتقدمُ بالشكرِ الجزيلِ لأمي و أبي اللذانِ لم يوفرا جُهدًا إلا بَذلاهُ في سبيلِ دعمِي و تشجيعِي و تسهيلِ كلِ أمورِ حياتي و تيسيرها فلهُما مني كَلَ الشكرِ و العرفانِ و التقديرِ و الوفاء و الدعاء و أسمى مشاعرِ الحبِ , حيثُ أهدي لهُمَا ثمرةَ جُهدِي و عنائِي و اسألُ اللهَ أن يديمَ لهُما عافيتَهما و يجعَل لهُما عوضًا عن ما بذَلاهُ جنانَ الخلدِ و النعيمِ الدائمِ المقيم .

و آخراً أتقدم بالشكر الجزيل لأساتذتي و زملائي حيث شاركوني مسيرتي هذه و كانوا خيرَ الناسِ فلهم مني كل الحب و التقدير .

- الفهرس -

- Abstract-

In this research , I took briefly , 3 medical drugs and explained them descriptive , industrially , formally and classified them each one by it self , these drugs are :

1- propranolol hydrochloride .

2 – TRIFLUOPERAZINE

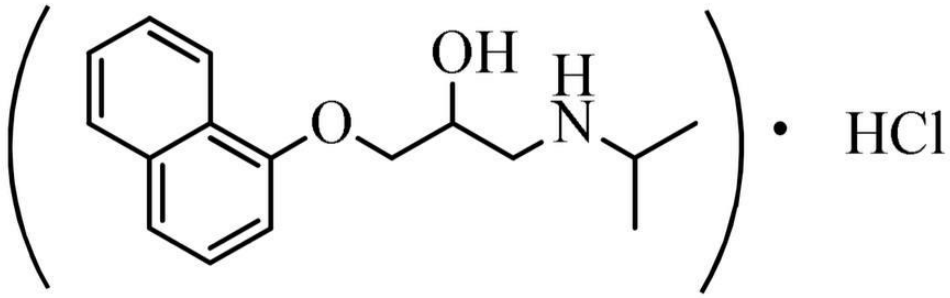
3 – AMITRIPTYLINE HCl

I took several spectrophotometric studies for each one of these drugs and merged them into one and cleared the preparatory methods and MSDS for them and a summary for qualities for each one and the building structure , As following : -

1- Propanolo Hydrochliride :-

Chemical Name:

2-Propanol,1-(isopropylamino)-3-(1-naphthyloxy)-, hydrochloride



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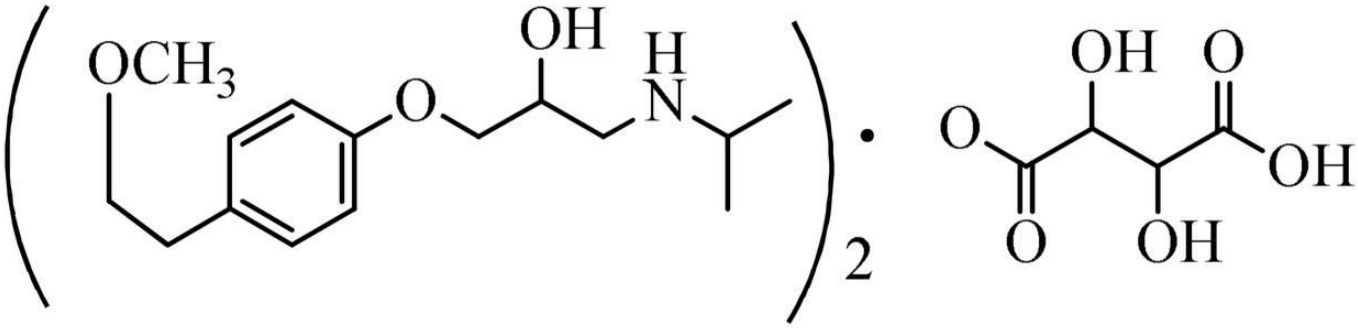

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- Propanolo Hydrochliride – [1]

Physical and Chemical Properties :

Physical state and appearance: Solid. (Solid powder.)

Odor: Odorless.

Taste: Bitter.

Molecular Weight: 295.81 g/mole

Color: White.

Boiling Point: Not available.

Melting Point: 162°C (323.6°F) - 165 C

Water/Oil Dist. Coeff.: The product is more soluble in water;

log(oil/water) = -0.4

Dispersion Properties: See solubility in water.

Solubility: Soluble in cold water.

Insoluble in diethyl ether.

Practically insoluble in benzene, and in ethyl acetate [1]

Uses and Side Effects :-

- Uses :

This medication is a beta blocker used to treat high blood pressure, irregular heartbeats, shaking (tremors), and other conditions. It is used after a heart attack to improve the chance of survival. It is also used to prevent migraine headaches and chest pain (angina). Lowering high blood pressure helps prevent strokes, heart attacks, and kidneyproblems. Preventing chest pain can help improve your ability to exercise.This drug works by blocking the action of certain natural chemicals in your body (such as epinephrine) that affect the heart and blood vessels. This effect reduces heart rate, blood pressure, and strain on the heart. [8]

Side Effects :

This medication is a beta blocker used to treat high blood pressure, irregular heartbeats, shaking (tremors), and other conditions. It is used after a heart attack to improve the chance of survival. It is also used to prevent migraine headaches and chest pain (angina). Lowering high blood pressure helps prevent strokes, heart attacks, and kidneyproblems. Preventing chest pain can help improve your ability to exercise.This drug works by blocking the action of certain natural chemicals in your body (such as epinephrine) that affect the heart and blood vessels. This effect reduces heart rate, blood pressure, and strain on the heart. To reduce the risk of dizziness and lightheadedness, get up slowly when rising from a sitting or lying position. This drug may reduce blood flow to your hands and feet, causing them to feel cold. Smoking may worsen this effect. Dress warmly and avoid tobaccouse.[8]

Several spectroscopic studies :

- First method : The method is based on the derivatization of the amino function present in these drugs to the corresponding yellow copper (I) drug dithiocarbamate derivative through reaction with carbon disulphide, pyridine and copper (I) perchlorate in aqueous acetonitrile and measuring absorbance at 406 nm for propranolol and 400 nm for metoprolol. The different experimental parameters affecting the development and stability of the colour were carefully studied and optimized. As A result The Beer's law is obeyed in the range of 1.0-40.0 μg/ml of each drug solution with a correlation coefficient 0.999. The maximum relative standard deviations (RSDs) in the analysis of pure PRO and MTP were 1.01 and 1.52 % respectively. The recoveries of the drugs from pharmaceutical formulations, spiked water samples and biological fluids were in the range 98.0-100.5 % with RSDs in the range 0.23-1.94% indicating good accuracy and precision of the method. So we can conclude that The instantaneous development of colour and its stability, well-established stoichiometry of the reaction and above simplicity and rapidity of procedures are some special attributes of the proposed method. [2]

- Second Method :

This study included the development of a simple, sensitive, accurate, fast and economical spectrophotometric method to quantitative determination of propranolol in its pure, pharmaceutical form and human urine, the method is based on the reaction of propranolol PRO with Ninhydrin NIN to form a complex of high absorption at 292 nm. The method was liner over the concentration (20 - 80µg/mL), the value of (r2) was 0.999. The value of relative standard deviation (RSD %) ranged between (1.869-0.209%), the value of recovery percentage (Rec %) between (103.131-96.366%), the detection limit and quantification limit (LOD) and LOQ were (1.0615 µg / mL) and (3.5384 µg / mL) respectively. The absorptivity was (5.232x103 L / mol.cm), Sandell's index (0.0495 µg / cm2) this method successfully applied to the determination of propranolol in pharmaceuticals forms and human urine. As a result A survey of the wavelengths between 400-190 nm for complex concentrations of PRO- NIN ranged between 10-130 ppm showed the highest absorbability at wavelength 292.0 nm . [3]

- Third Method :

Precise, rapid and simple spectrophotometric method for the estimation of Propranolol hydrochloride (PRO) drugs has been developed. This method is based on an oxidative coupling reaction between above drugswith 1,4-diamiobenzene reagent solution in a basic medium (pH 11.17) in the presence of N-Bromosuccinimideto production anorange colour, stable,soluble in water and gave absorption at 463 nm.With correlation coefficient 0.998 Beer's law isobeyed in the linear range (2.5-0.75)µg/ml of (PRO),thedetection limit, Sandell's sensitivity andthe molar absorptivity were 4.229 µg/ml, 0. 09µg.cm-2 and3.283x10 3liter. mol-1.cm-1 respectively while RSD value andrecovery were2.02%,100.007.% The proposed method was plate good success to the estimation of (PRO)drug in tablets. As a result The final spectrum of the orange product by oxidative coupling reaction of PROwith1,4-diamiobenzenereagent (1x10-2M) in the presence of N-Bromosuccinimide (1x10-2 M) in temperature 25°C andbasic medium verses reagent blank show a maximum absorption at 463 nm while the blank reagent gave zero absorbance at λmax. So we conclude that The developed method isaccurate, preciseand selectivefor the estimation of PRO. It's based on oxidative coupling reaction between PRO and 1,4-diamiobenzenereagent in presence of N-Bromosuccinimidein basic mediumto form orange colored productwhich isstable, water soluble shows a maximum absorption at 463 nm. The proposed method can be carried out with no need for furthersteps such as solvent extraction step, pH or Temperature control and it can be applied successfully for in estimation of (PRO) drug in tabletsandpharmaceutical formulation. [4]

- Fourth Method :

A spectroscopic method has been used in this study for determining the drug compound (Propranolol Hydrochloride) as a pure substance and in pharmaceutical preparations using UV-Vis. spectroscopy. The procedure included reduction of Fe (III) ions to Fe (II) ions which reacted with potassium, hexa ferriccyanide, to form a bluish-green precipitate soluble in acidic solution. The maximum absorption has been measured at wavelength (726)nm. The reaction conditions have been studied including sequence additions, concentration and volume of reactants, acidity, temperature and time of reaction. The optimum conditions of reaction have been fixed and two methods have been used for determining Propranolol hydrochloride (PPH), the first, is the direct standard calibration curve, and the second is standard additions curve. Both methods showed linearity range between (0.25-7.0)µg.ml-1, detection limit (0.084)µg.ml-1, correlation coefficient (r) = 0.9998 and the absorption coefficient molarities for the complex formed (Ɛ) = 2.9 ×104 L.mol-1.cm-1, and sandel sensitivity = (0.0007)µg.cm2, recovery percentage value (%Rec.) = 99.932, the relative standard deviation (%RSD) = 0.5, which means that there are matching between both two methods in determination clearly. [5]

Mechanism of the reaction

The procedure depends on oxidative reaction for Propranolol hydrochloride with Fe (III) followed by coordination with ferric (III) cyanide potassium to form the colored product, The steps of reaction can be illustrated by the following equations:

PPH (reductant) + Fe^{+3} ⟶ Fe^{+2} + PPH (oxidant)

Fe^{+2} + $K_3[Fe^{III}(CN)_6]$ ⟶ $KFe^{II}[Fe^{III}(CN)_6].XH_2O$

Potassiumferro ferriccyanide

So we conclude that The present method showed the possibility of determination of (PPH) drug (one of the amines) in the measurement when the availability of appropriate technical. The results obtained showed the success of this method in according to the analytical results and statistical data obtained. It also showed that the method is of high precision its pharmaceutical preparations (Inderal and Becardin).

- Fifth Method :

A method for determination of propranolol hydrochloride in pharmaceutical preparation using near infrared spectrometry with fiber optic probe (FTNIR/PROBE) and combined with chemometric methods was developed. Calibration models were developed using two variable selection models: interval partial least squares (iPLS) and synergy interval partial least squares (siPLS). The treatments based on the mean centered data and multiplicative scatter correction (MSC) were selected for models construction. A root mean square error of prediction (RMSEP) of 8.2 mg g^{-1} was achieved using siPLS (s2i20PLS) algorithm with spectra divided into 20 intervals and combination of 2 intervals (8501 to 8801 and 5201 to 5501 cm^{-1}). Results obtained by the proposed method were compared with those using the pharmacopoeia reference method and significant difference was not observed. Therefore, proposed method allowed a fast, precise, and accurate determination of propranolol hydrochloride in pharmaceutical preparations. Furthermore, it is possible to carry out on-line analysis of this active principle in pharmaceutical formulations with use of fiber optic probe. Then we Figures of Merit of UV Spectrometry Reference Method by Coefficient of

determination better than 0.99 was obtained and relative standard deviation (RSD) lower than 5% was obtained for determination of propranolol hydrochloride in pharmaceutical preparations. About 300 mL of methanol was required for each sample and sample throughput of 5 samples (in triplicate) per hour was achieved.

When that been acheaved we Calibrate and Predict Sets , Thirty-three samples were prepared by mixtures of propranolol hydrochloride and excipients. These samples were randomly divided into calibration set (24 samples) and prediction set (9 samples). The concentration of calibration and prediction set ranged from 57.6 to 222.5 mg g^{-1} and from 64.2 to 211.7 mg g^{-1} of propranolol hydrochloride, respectively. Calibration set was used to build the models and prediction set was used to evaluate the predictive ability of the each model. So we can conclude that Results obtained demonstrated that FTNIR/PROBE associated with multivariate analysis is a convenient method for propranolol hydrochloride determination in pharmaceutical preparations. Results obtained using siPLS models for determination of propranolol hydrochloride in powder pharmaceutical preparations showed suitable prediction capacity (lower RMSEP). Variable selection methods were able to produce better models in comparison to the PLS full-spectrum model. Results obtained for propranolol hydrochloride using the better siPLS (s2i20PLS) model were in agreement with results obtained by reference method. The proposed procedure using FTNIR/PROBE and PLS algorithms is faster, less expensive, accurate, and precise and minimizes solvent use when compared to pharmacopoeia UV method. [12]

2 – TRIFLUOPERAZINE :

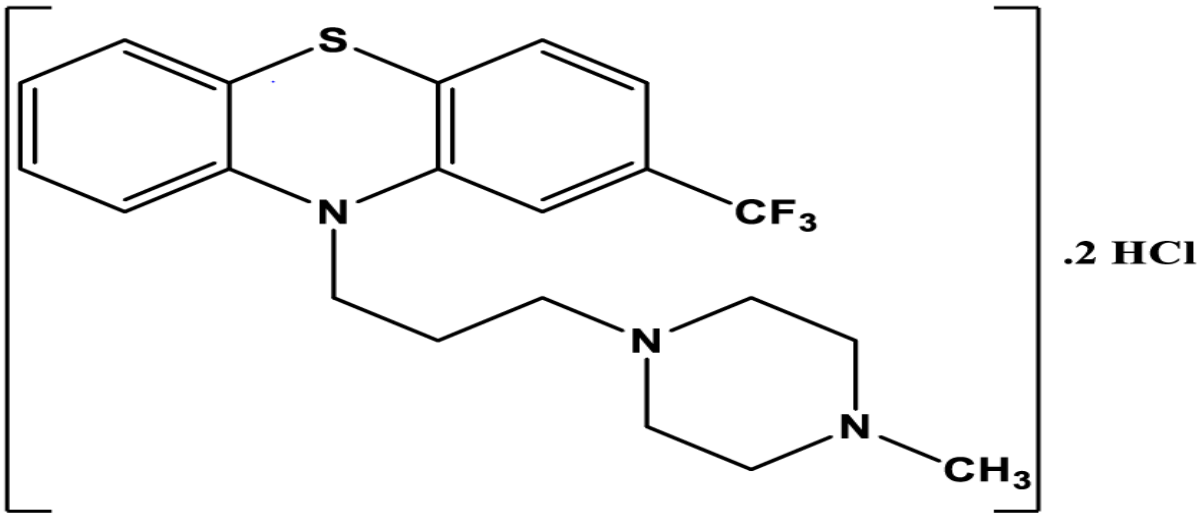


Figure 1: Chemical structure of Trifluoperazine Hydrochloride.

PHYSICAL AND CHEMICAL PROPERTIES :

Appearance Form: powder Colour: white, off-white

Melting point/freezing point Melting point/range: 243 °C (469 °F) - dec.

Water solubility 50 g/l – clear

Chemical stability Stable under recommended storage conditions.

Hazardous decomposition products Other decomposition products - no data available In the event of fire [1]

Uses And Side Effects : -

Uses :

This medication is used to treat certain mental/mood disorders (such as schizophrenia, psychotic disorders). Trifluoperazine helps you to think more clearly, feel less nervous, and take part in everyday life. It can reduce aggressive behavior and the desire to hurt yourself/others. It may also help to decrease hallucinations (hearing/seeing things that are not there). Trifluoperazine is a psychiatric medication that belongs to the class of drugs called phenothiazine antipsychotics. It works by helping to restore the balance of certain natural substances in the brain.This medication has also been used for the short-term treatment of anxiety. However, there are safer drugs to treat anxiety that should be used first before trifluoperazine. [1]

Side Effects :

Drowsiness, dizziness, lightheadedness, drymouth, blurred vision, tiredness, constipation, weight gain, and trouble sleeping may occur. If any of these effects persist or worsen, tell your doctor or pharmacist promptly. Dizziness and lightheadedness can increase the risk of falling. Get up slowly when rising from a sitting or lying position. This drug may cause muscle/nervous systemproblems (extrapyramidal symptoms-EPS). Your doctor may prescribe another medication to decrease these side effects. Tell your doctor right away if you notice any of the following side effects: feelings of anxiety/agitation/jitteriness, drooling/trouble swallowing, restlessness/constant need to move, shaking (tremor), shuffling walk, stiff muscles, severe muscle spasms/cramping (such as twisting neck, arching back, eyes rolling up), mask-like expression of the face. [1]

Several Spectroscopic Studies :

- First Method : 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 µg/cm2, 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 R2=0.9989. The developed method successfully applied to estimate Trifluoperazine Hydrochloride in the pharmaceutical drug Stellasil (5mg). The results showed that the success of the method developed in estimating Trifluoperazine Hydrochloride in the pharmaceutical product. So we conclude that 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 Beercentration 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 µg/cm2) 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.= (9.5×10-7µg/mL), R= (0.999595), R2 = (0.9989). [8]

- Second Method : A simple spectrophotometric method has been developed for the determination of trifluoperazine hydrochloride in pure and in dosage forms. The method is based on the oxidative coupling reaction with sulfanilic acid in the presence of sodium hypochlorite in acetic acid medium to give an red coloured product with absorption maximum at 510 nm. The product is stable for more than 6 h. Beer's law is obeyed over the concentration range of 0.2–7.0 μg ml-1 with molar absorptivity of 5.15×103 l.mol-1cm-1. Different experimental parameters affecting the development and stability of the formed coloured product were carefully studied and optimized and a proposal of the reaction pathway was presented. The proposed method was applied successfully to the determination of trifluoperazine hydrochloride in tablets and compared favorably with the official method. Common excipients used as additives in pharmaceutical preparations do not interfere in the proposed method. As a result An orange-coloured oxidizing coupling product with an absorption maximum at 510 nm is formed when trifluoperazine hydrochloride was allowed to react with sulfanilic acid in the presence of sodium hypochlorite in acetic acid medium. the spectra of orange product formed and of the reagent blank, so; the maximum absorption at 510 nm is used in all subsequent experiments. So we conclude that A simple, rapid, precise and sensitive spectrophotometric method has been developed for the determination of trace amounts of trifluoperazine.hydrochloride in aqueous solution based on its oxidative coupling reaction with sulfanilic acid and sodium hypochlorite in the presence of acetic acid. The proposed method does not require temperature control or the solvent extraction step; the method was applied successfully on pharmaceutical tablets. [9]

- Third Method : The aim of this study is to develop simple, sensitive, rapid, accurate, precise and economical spectrophotometric method based on simultaneous equation method for the simultaneous estimation of isopropamide and trifluoperazine in combined tablet dosage form. Materials and Methods: The method is based on the simultaneous equation and first-order derivative method for analysis of both the drugs using methanol:water in the ratio of 7:3 (v/v) as solvent. Isopropamide has absorbance maxima at 248.5 nm and trifluoperazine has absorbance maxima at 227.0 nm in methanol. Results and Discussion: The linearity was obtained in the concentration range of 5-30 µg/mL for isopropamide and 2-12 µg/mL for trifluoperazine in both the methods. The concentration of drugs was determined by using simultaneous equation method. The result of analysis has been validated statistically and by recovery studies. The results of mean recovery and other validation parameters were found within the acceptable limits. Both methods were applied to estimate the marketed formulation and found good recovery of the drug. The methods were found to be simple, sensitive, accurate and precise and were applicable for simultaneous determination of isopropamide and trifluoperazine in pharmaceutical dosage form. As a result In this method, methanol:water in the ratio of 7:3 (v/v) was used as a solvent and drug's showed absorbance at 248.5 nm for isopropamide and 227 nm for trifluoperazine .

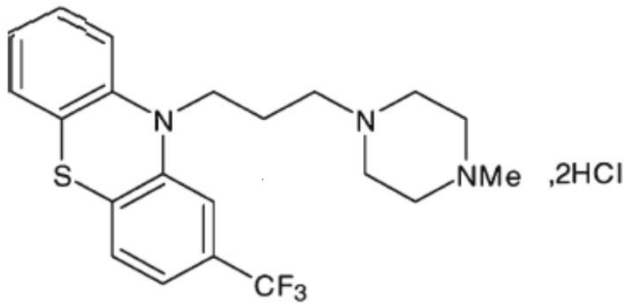
. The linearity of analytical method at five concentration levels ranging from 2 - 12 µg/mL for trifluoperazine and 5-30 µg/mL for isopropamide, respectively, was determined and are presented in Table 1. The regression equation of calibration curves were y = 0.023× + 0.123 and y = 0.040× + 0.018 for isopropamide and trifluoperazine, respectively and are shown in Figure 3. The results show that an excellent correlation exists between response factor and concentration of drugs within the concentration range. The correlation coefficient (r2) was found to be 0.999 and 0.999 for both the drugs. Thus, the above data represents that simultaneous equation method obeyed Beer-Lambert's Law. The LOD was found to be 0.05 µg/mL for trifluoperazine and 0.10 µg/mL for isopropamide. LOQ was found to be 0.20 µg/ mL for trifluoperazine and 0.4 µg/mL for isopropamide. The developed method was found to be accurate from percentage recovery studies and the results are shown in Table 2. The mean percentage assay shown in Table 3 was found to be 98.36% and 99.24% for trifluoperazine and isopropamide, respectively. They are obtained by comparing the results with the stated label claim. Validation results of the proposed method are presented . The results obtained had satisfactorily fulfilled the criteria. [11]

- Fourth Method : A simple, accurate, precise, rapid, economical and sensitive UV spectrophotometric method has been developed for the determination of trifluoperazine Hydrochloride in pharmaceutical preparations and environmental wastewater samples, which shows maximum absorbance at 257 nm in distilled water. Beer's law was obeyed in the range of 10 -100 µg/ ml ,with molar absorptive of 5.284×103 L.mol-1.cm-1 , relative standard deviation of the method was less than 1.6%, and accuracy (average recovery %) was 100 ± 1.2 . No interference was observed from common excipients and additives often accompany with trifluoperazine Hydrochloride in pharmaceutical preparations .The method was successfully applied to the determination of trifluoperazine Hydrochloride in some pharmaceutical formulations (tablets) and industrial wastewater samples. The proposed method was validated by sensitivity and precision which proves suitability for the routine analysis of trifluoperazine Hydrochloride in true samples. As a result UV- Visible spectrophotometry is still considered to be a convenient and low cost method for the determination of pharmaceuticals. The method used for the determination of trifluoperazine Hydrochloride in

pharmaceutical preparations and environmental wastewater samples was found to be sensitive ,simple ,accurate ,and reproducible .Beer s law was obeyed in the concentration range of 10-100 μg/ml Fig 3 with correlation coefficient of 0.998 ,intercept of 0.003 and slope of 0.011 .The conditional molar absorptive was found to be 5.284 x103 l/mol.cm. So we coclude that In this work, a simple, rapid, precise and accurate UV-Spectrophotometric method was developed and validated for the determination of trifluoperazine Hydrochloride in pharmaceutical preparations and industrial waste water samples. The method free from such experimental variables as heating or solvent extraction steps. The method rely on the use of simple and cheap chemicals and techniques and can be used for rapid routine determination and quality control of trifluoperazine Hydrochloride in pure form, pharmaceutical preparations and real industrial waste water sample. [19]

- Fifth Method:

a simple, speedy, and sensitive spectrophotometric method to determine the trace amounts of trifluoperazine dihydrochloride (TFPH) in an aqueous solution. The method involves the oxidative coupling reaction of TFPH with N, N-dimethyl-p-phenylenediamine dihydrochloride (DMPPDA.2HCl) reagent in an acidic medium during availability of N-bromosuccinimide to develop an intense violet color. This water-soluble product exhibits maximum absorbance at 552 nm. Beers law follows a concentration range of (1–20) µg/mL, with a molar absorptivity of 1.4×104 L/mol.cm, Coefficient determination (R2 = 0.9989). Sandel's index of 0.030 µg /cm2 . The average recovery is 100.8045 % and D.L of 0.1435 µg/mL, Q.L. of 0.4349, and relative standard deviation of 0.11–0.59%. The proposed method gets compared with the other standard method using t-test and F-test. The results reflect no significant variation between both the methods. The proposed method was applied conveniently, to determine Trifluoperazine.2HCl in its pure state and pharmaceutical formulations.



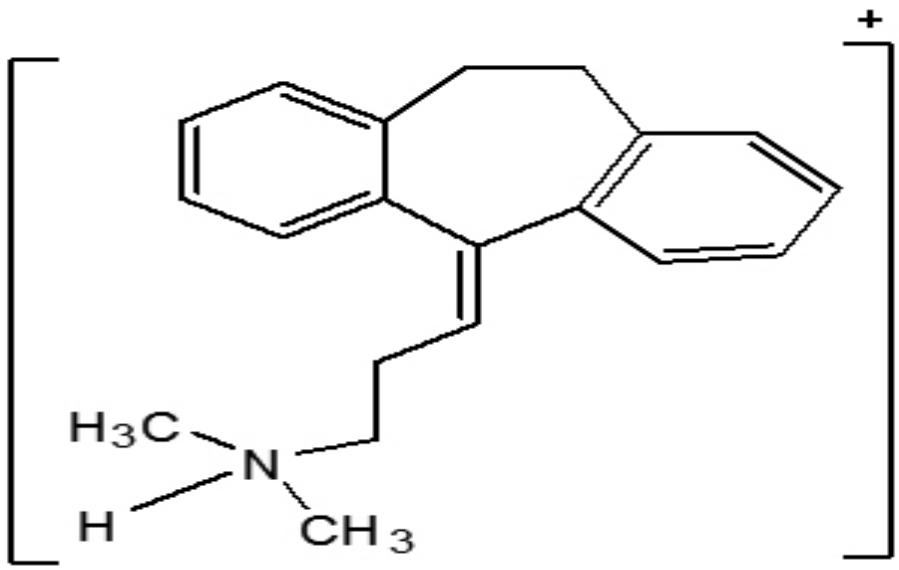
Scheme 1

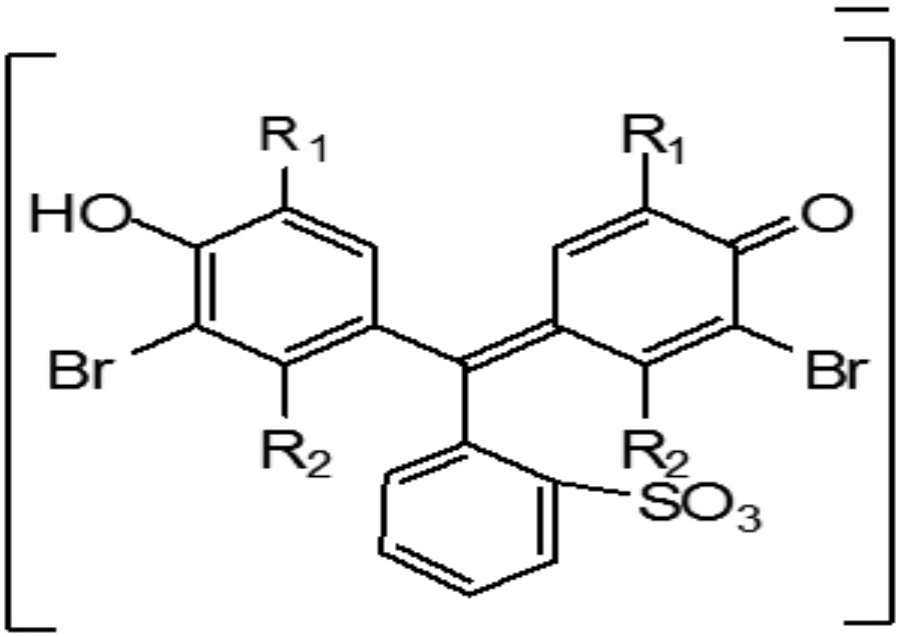
This study helps in identifying the most promising oxidizing agent and its amount, NBS (5×10-3 M), by adding different volumes (0.5–3.0 mL) of oxidizing agent to volumetric flasks containing 2.0 mL of TFPH (250µg/mL) and 2.0.0 mL of the reagent solution (1×10-2M), then adding 1.0 mL of 1.0 M acetic acid and the volume filled with 25ml with distilled water. The results indicate that the volume of 2.0 mL of NBS (5×10-3M) is the optimum amount because of the highest absorbance, so it was used in subsequent experiments. After selecting DMPPDA.2HCl, adding DMPPDA.2HCl (5×10- 3 M) of (0.3–3.0 mL) to the volumetric flasks containing 2.0 mL of TFPH 250µg/mL) and 1 mL of the NBS (5×10-3M), then the addition of 0.5 mL of 1.0 M acetic acid and remaining volume upto 25ml with distilled water, from the results obtained it is clear that the volume of 1.0 mL of DMPPDA.2HCl coupling reagent (5×10-3M) is the optimum amount because it gave the highest slope (0.149) and the correlation coefficient (0.9976). So it is adopted in subsequent experiments. Some of the weak and strong acids (H2SO4, HCl, CH3COOH, 1M) have been used and found 1 mL of acetic acid give the maximum absorption intensity, and this volume was elected in all following measurements. The results indicate that the volume of 1.0 mL of acetic acid (1M) is the optimum amount because of the highest absorbance, so it was used in subsequent experiments. After 1M acetic acid fixed the best acid, then the pH of solution studied by adding deferent volumes of (0.3-1.5 mL) acetic acid shows the best pH solution (pH3.4). That means 0.5ml acid addition is the best, gives the highest absorbance. Therefore, it is adopted in subsequent experiments. The proposed method was successfully applied to the determination of TFPH in it's pharmaceutical preparation (Salabid, tablets 5 mg). The results, which are shown in Table 3 indicate that good recoveries were obtained. [20]

3 - AMITRIPTYLINE HCl :-

CHEMICAL NAME :

1-Propanamine, 3-(10, 11-dihydro-5H-dibenzo [a, d] cyclohepten-5-ylidene)-N,N-dimethyl-, hydrochloride.





- PHYSICAL AND CHEMICAL PROPERTIES :

DESCRIPTION : White or practically white, odorless or practically odorless, crystalline powder or small crystals

FLAMMABILITY : May be combustible at high temperature

ODOR : Practically odorless or odorless

pH : 5 - 6 (1%)

MELTING POINT : (196 - 197)°C, (384.8-386.6)°F

FREEZING POINT : (196 - 197)°C

SPECIFIC GRAVITY : 0.1 - 0.2

LOWER FLAMMABLE/ EXPLOSIVE LIMIT(S) : 85 mg/L

VAPOR PRESSURE : < 1 mm Hg (20° C)

AUTO-IGNITION VISCOSITY TEMPERATURE : 372 °C, 701.6 °F

SOLUBILITY : Freely soluble in water, in alcohol, in chloroform, and in methanol; insoluble in ether . [1]

- Uses And Side Effects :

- Uses : This medication is used to treat mental/mood problems such as depression. It may help improve mood and feelings of well-being, relieve anxietyand tension, help you sleep better, and increase your energy level. This medication belongs to a class of medications called tricyclic antidepressants. It works by affecting the balance of certain natural chemicals (neurotransmitters such as serotonin) in the brain. [1]

- Side Effects :

dizziness, dry mouth, blurred vision, constipation, weight gain, or trouble urinating may occur. If any of these effects persist or worsen, notify your doctor or pharmacist promptly . To reduce the risk of dizziness and lightheadedness, get up slowly when rising from a sitting or lying position. To relieve dry mouth, suck on (sugarless) hard candy or ice chips, chew (sugarless) gum, drink water, or use a saliva substitute. To prevent constipation, eat , drink enough water, and exercise. You may also need to take a laxative. Ask your pharmacist which type of laxative is right for you Remember that this medication has been prescribed because your doctor has judged that the benefit to you is greater than the risk of side effects. Many people using this medication do not have serious side effects. [1]

Several Spectroscopic Studies :

- Methods A , B and C :

The methods A, B and C are based on the interaction of the drug with Bromothymol blue (BTB), Bromophenol blue (BPB) and Bromocresol purple (BCP) respectively, to form chloroform extractable ion pair complexes which absorb around 415 nm. The absorbance of this band increases with increasing the concentration of the drug and formed a basis for the quantification of the drug. The dyestuffs were used as 0.025% solutions in doubly distilled water. Sodium acetate-hydrochloric acid buffers of *p*H 2.8, 2.5 and 2.5 were prepared by mixing 50ml of 1.0*M* sodium acetate solution with 49.50 mL, 50.50mL and 50.50 mL of 1.0 M HCl solution respectively and diluted to 250 mL with doubly distilled water. The *p*H of each solution was adjusted to an appropriate value with the aid of a *p*H meter. As a result AMT forms ion-pair complexes in acidic buffer with dyestuffs *viz.*, BTB, BPB and BCP which are quantitatively extracted into chloroform. Ion-pair complexes of drug with dyes absorbed maximally at 415 nm . AMT contains a tertiary nitrogen atom and in strongly acidic medium it exists as a cation and sulphonic acid group present in the dyes that is the only group undergoing dissociation in the *p*H range 1-5. Finally the protonated AMT forms ion-pairs with the dyestuff which is quantitatively extracted into chloroform. [14]

- Method D Kinetic method : The method depends on the oxidation of the drug with alkaline KMnO4 (1x10-2 *M*) to produce Manganate ion which absorbs at 610 nm and formed a basis for quantification of drug. A solution of 0.45*M* NaOH is used to produce required alkalinity. Mixing the solutions of permanganate and the drug slowly developed green color and hence kinetics of the reaction was followed spectrophotometrically. The initial rate and fixed time methods are followed for the determination of AMT. The literature survey reveals that Amitriptyline undergoes oxidation at exocyclic double bond and gives rise to dibenzosuberone 22. [14]

- Method E : The method depends upon the interaction of neutralized drug with Iodine that generates iodide ion having an absorption band at 366 nm. The absorbance of this band increases with increasing the concentration of the drug and formed a basis for the quantification of the drug. Mixing the solution of iodine prepared in DCE with AMT resulted in a change of violet color of iodine into light brown to pale yellow and as a consequence, absorption spectra exhibited a new band of 366nm. This is attributed due to I3 - ion formed by the interaction of iodine with drug. So we conclude that The proposed spectrophotometric methods present selective and simple, specific and inexpensive analytical procedures for determination of AMT, in pure or in tablet dosage forms without interference from common excipients. Moreover, the developed methods are time saving and do not require elaborate treatments associated with chromatographic methods. These attributes, make them suitable for routine analysis in quality control laboratories. [15]

- Calibration curves for method A, B and C :

Different aliquots of drug solution were transferred into 125 mL separating funnel. To this 5 mL of buffer, 5 mL of dye were added and total volume was made up to 20 mL with water. 10 mL of chloroform was added and the contents were shaken for 5 min. The two layers were allowed to separate for 5 min and the organic layer was separated and absorbance of yellow colored solution which is stable at least for 3 hr is measured at 415 nm against blank similarly prepared. The same procedure of analysis is followed either for assay of pure drug or for dosage form. The calibration graphs are linear over a range of drug 1.25 - 25µgmL-1 (BTB), 1.5 – 25µgmL-1 (BPB), 2.0 – 25µgmL-1 (BCP). [16]

- Another Method is newly found : simple approach for spectrophotometric determination of tricyclic antidepressant drug amitriptyline. Enhancement of the colour intensity of the Fe(III)-SCN− complex on addition of the drug amitriptyline forms the basis of the proposed method.The value of molar absorptivity of the Fe(III)-SCN− amitriptyline ion pair complex in terms of the drug lies in the range of (2.82–3.36) × 103 L·mol−1 ·cm−1 at the absorptionmaximum 460 nm. The detection limit of the method was 0.3 μg·mL−1. The slope, intercept, and correlation coefficients for the present method were found to be 0.008, 0.002,

and +0.998, respectively.The effect of analytical variables on the determination of the drug and the composition of the complex are discussed in the paper.The method is applicable in the determination of amitriptyline in pharmaceutical preparations. As a result *ReactionMechanismand Composition of Complex.* Ferric ions react with SCN− ions to give a variety of red-orange complexes, but the presence of amitriptyline activates the formation of a higher thiocyanato species, which enhances the colour intensity of the complex. The proposed reaction for the formation of higher thiocyanato complex in presence of the drug cation, that is, [AMIYTP]+ can be expressed as

$$\mathrm{Fe}^{3+} + n\mathrm{SCN}^{-} + m[\mathrm{AMIYTP}]^{+} \rightleftharpoons [\mathrm{Fe(SCN)}_n]^{3-n} \cdot m[\mathrm{AMIYTP}]^{+},$$

where the value of n may vary from 2 to 6. This reaction has been used for the determination of cationic antidepressant drug in the present work. The mole ratios of Fe(III) to SCN− and [AMIYTP]+ ions involved in formation of the ion-associated complex were determined on the basis of the spectrophotometric analysis of these constituents at their different concentrations. The values of Aeq (the absorbance of the complex when the reagent was in equilibrium) and Amax (the absorbance when the

reagent was in constant excess) were determined spectrophotometrically, and the values of (Aeq/Amax − Aeq) were calculated for different concentrations of Fe(III), SCN− and [AMIYTP]+. Their molar ratio was determined using curve-fittingmethod by plotting log (Aeq/Amax−Aeq) versus log$M$(where$M$=molar concentration) values of SCN−, and [AMIYTP]+. The values of slope for SCN− and [AMIYTP]+ were found to be 4.2 and 0.7 close to integers 4 and 1, respectively. For each mole of Fe(III), the involvement of SCN− and [AMIYTP]+ was assumed to be 4: 1. Hence, the curve-fitting method suggested the molar ratio of Fe(III), SCN−, and drug cation in the complex to be in 1 : 4 : 1 ratio, Respectively . So we conclude that Themethod was successfully applied for the determination of amitriptyline in the pharmaceutical preparation.Themethod is very simple as there is no requirement of prior separation or extraction of the complex, and the reagents are low cost and commonly available in routine laboratories. The results obtained from the proposed method were comparable with the established methods. The method has good potential in simplicity, sensitivity, and reproducibility, and the reaction used in the proposed work is expected to give better results with flow injection analysis.[29]

- References : -

1. MSDS WEB Site .

2. Kirk- othmer, Encyclopedia of Chemical Technology, John Wiley & sons, 27th volume, 2004.

3. W.C.Bowman and M.L.Rand, Textbook of Pharmacology, Blackwell Science publication, 1992.

4. Pankaj Soni, Santosh K.Sar, Rajmani Patel, *JASMI*, **2**,103, (2012)

5. A.A Omran, A.Y.El-Sayed, A.M.Shehata, M.Ahmed, M.A.El-Erian, *J. Applied. Sci. Res*. **3**, 1730, (2007).

6. M.G. Gehad, A.F. Nour El-Dien, Faten, M.A.Nehad, *Spectrochimica Acta.* **68**, 1244, (2007).

7. Seja Patel, N.J. Patel, *Indian J.PharmSci*.**71**, 472, (2009)

8. M.G. Gehad, A.F. Nour El-Dien, S.M. Khalil, M.A.Nehad, *Spectrochimica Acta*. **65**, 1221,(2006).

9. J. O. Onah, Global. *J. Pure. App. Sci*. **11**, 237, (2005).

10. J.Karpinska, J. Szostak, *Spectrochimica Acta*.**61**, 975, (2005)

11. A. Tehssen, A. A Kazi, I. H. Mohamed, A. Tal, *Anal. Letters*. **33**, 2477, (2000).

12. F. A. Mohamed, H. A. Mohamed, S. A. Hussein, S. A. Ahmed, *J. Pharm. Biomed. Anal*. **39**,139, (2005),

13. R.M. El-Nashar, N.T. Ghani Abdel, A.A. Bioumy, *Microchemical J.* **78**, 107, (2004).

14. E.M. Elnemma, F.M. ElZawwy, S. M. Hassan, Saad, *Microchimica Acta.* **110**, 79, (1993).

15. T.Ghani Nour, A. El. Nashar, R. M. Bioumy, A. Abeer, *FABAD. J. Pharm. Sci*. , **29**, 195, (2004).

16. C. Jessica, R. Alberto, A. Emillio , J. Elena, *J. Incl. phenom Macrocycl che*. (2007).

17 W. Lu, S. A. Shamsi, T.D. McCarley, I.M. Warner, *Electrophoresis*, **19**, 2193, (1998).

18. K.L.Johnson-Davis, J.M.Juenke, R.Davis, G.A. McMillin, *Methods.Mol. Biol.* **902**, 175, (2012)

19. Susheela Rani, Ashwini Kumar, Ashok Kumar Malik, Baldev Singh, MS, *Chromatographia*.**74**, 235, (2011)

20. G.M. Greenway, Sarah J.L.Dolman, *Analyst*, **124**,759, (1999)

21. J.Trocewicz, *J. Chromatogr. B*, **801**, 213, (2004)

22.S.D Lamani ,S.T. Nandibewoor , *J. Thermodyn Catal*. **2**,110, (2011)

23. J.C.Miller, J.N.Miller, Statistics and chemometrics for Analytical Chemistry, Harlow, England, 2005.

24. P. Job, *Anal. Chim Acta.* **9**, 113, (1928).

25. J. Rose Advanced Physicochemical Experiments, Pitman, London, UK, 1964.

26. W. Likussar D.F. Boltz, *Anal. Chem*. **43**, 1265, (1971).

27. K. Momoki, J. Sekino, H. Sato, N. Yamaguchi, *Anal. Chem*. **41**, 1286, (1969).

28. H. A. Benesi, J. R Hildebrand, J. *Am. Chem. Soc.* **71**, 2703, (1949).

29. International Conference on Harmonization (ICH) of Technical Requirement for the Registration of Pharmaceuticals for Human use, Validation of analytical procedures: definitions and Terminology Genera (1996).