Cloud point Extraction Of Methimazole By Direct (UV- Vis Spectrophotometer) And Indirect (Flame Atomic Absorption) methods

Sawsan Askar Hasan[1], Shahla Jamal Shakkor[1]

[1]*Department of chemistry, College of science, University of Kirkuk*

KEYWORDS

Cloud point Extraction, Direct

ABSTRACT

Abstract A new technique based on the formation of a chelate Methimazole-Fe(III) at 400 nm was used for the determination of Methimazole 114 as a surfactant in some pharmaceuticals using indirect flame atomic absorption spectroscopy (FAAS) and UV-visible methods based on Triton turbidity extraction. The optimal turbidity extraction temperature was 75.0°C after 25 min of extraction of the complex [MET-Fe(III)] with ethanol. The structure of the Methimazole-Fe(III) chelate was determined by the molar ratio method. A 1:1 L:M (ligand:metal) ratio was produced. The Beer law was employed in the concentration range of 2.5-30 and 2.5-32.5 g/mL for the UV and FAAS, respectively.. The limits of detection (LOD) and quantification (LOQ) were (0.3784) g/ml and (1.2612) g/ml, respectively, for these techniques. The technique has been approved and successfully used in the production of pharmaceutical preparations such as: B. Methimazole capsules sold in Iraq. The analytical results were validated by statistical and recycling studies with satisfactory results.

1. Introduction

MET is used to treat hyperthyroidism, a condition in which the thyroid gland produces too much thyroid hormone [1]. It belongs to a family of thyroid drugs that work by preventing the enzyme thyroid peroxidase from producing thyroid hormone [2]. It is commonly used to treat conditions such as Graves' disease, in preparation for radioiodine therapy or thyroid surgery [3], and to treat extreme hyperthyroidism such as thyrotoxic crisis [4]. Methimazole is a thioamide derivative with a methyl group and a five-membered ring; more precisely, it is an imidazole derivative [5]. It is a white crystalline powder with the chemical formula C4H6N2S and the IUPAC name 1-methyl-2-thioimidazole. It is only somewhat soluble in water [6]. It is formed by the reaction of carbon disulfide and methylamine [7, 8], resulting in the formation of an imidazole ring and substitution of a methyl group at the 1-position. The thioamide structure and chemical properties of methimazole are crucial to its antithyroid activity [9]. Many autoimmune diseases, such as Graves' disease, which lead to hyperthyroidism, can be treated with methimazole [10]. Preparation for radioactive iodine therapy or thyroid surgery [11]: Before radioactive iodine therapy or surgery, balancing thyroid hormone levels may be helpful[12]. Thyrotoxic crisis: In cases of severe hyperthyroidism, such as thyrotoxic crisis, methimazole can be used to quickly adjust thyroid hormone levels. [13].

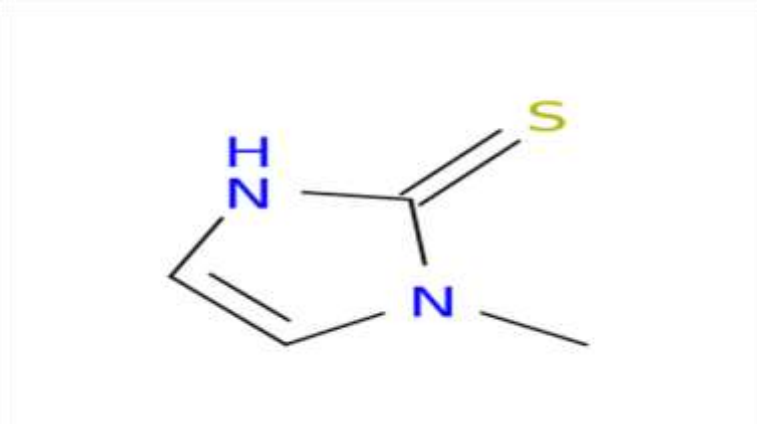

Figure 1: The composition of Methimazole [14]

The "turbidity point method" (CPE) is a method of calculating the cloud point. It's derived from the concept that, when water and a surfactant are incorporated in a ratio of 1:1, when the temperature or

pressure is altered, or when a component is added to the mixture, the mixture becomes cloudy and is split into two isotropic phases. [15]. This protocol describes a liquid chromatography technique for measuring bulk solids. Various techniques such as liquid chromatography-mass spectrometry have been used to ensure the volume of methimazole in dosage forms [16], high performance liquid chromatography [16-18], high performance thin layer chromatography [19], derivative spectrophotometry [17, 20], voltammetry [21], and capillary electrophoresis [22]. The studies [23-24-25] used the same method as this study to produce pure methimazole by processing the drug material using turbidity, providing highly accurate results...

2. Experimental Parts

2. Methodology

2.1.1.Apparatus

1. Two-beam ultraviolet-visible light spectroscopy for silica fibers. The ultraviolet-visible recording spectrophotometer T92-Spectrophotometer Model (China)
2. "GBC (933 plus), Flame Atomic Absorption Spectrometer
3. "Hotplate Stirrer (Hotplate Stirrer Model L-81 Laboratory Co. bv)"
4. Electricity Density (Sartorius, 4digitals, manufactured in Germany)
5. "Water Bath (A water-based temperature controller, model Unitemp)"
6. Centrifuge (Tripi International Corp,TRIU 800 Centrifuge, created in Korea).

2.2. Materials

"A pure grade of methimazole was obtained from sigma Aldrich company

"All the chemical stock solution were prepared from analytical grade BDH'

2.3. Preparation of Standard Solutions

All glassware was submerged in distilled water and allowed to soak for 30 minutes at 50 degrees Celsius before being used. Batch experiments were conducted to verify that the results and average value were repeatable. All metals employed were of the highest quality, and most solutions were made in distillate water..

A "stock solution of (0.008758 ppm) for methimazole .2.3.1

Was prepared by dissolving 0.1000 g in the smallest amount of water and diluted to mark with water in a 100 mL volumetric flask."

2.3.2. A "solution of (0.05758 M) for $FeCl_3$

Was made by dissolving 0.9 g of FeCl3 in a small amount of water and then completing the volume to 100 ml with a volumetric flask. ".

2.3.3. A "10% (v/v) of Triton X-114, Triton X-100, Tween 20

Were prepared by diluting 10 ml of each Triton X-114, Triton X-100, Tween 20 in distilled water in a 100 mL volumetric flask" Interference"

2.3.4. Preparation of 0.1 M NaOH

The solution was prepared by dissolving 0.4 g of NaOH in a known volume of distilled water in a 100 ml volumetric flask, then filling the volume with distilled water to the mark.

2.3.5. 10 mg tablet solution with a concentration of 100 mcg/ml.

Methimazole Pharmaceutical Formulation A is available in tablet form and is manufactured by one company (Akyurt – Ankara), each tablet containing 10 mg of methimazole. Prepare the solution and weigh 10 g; 1.132 g before crushing and 0.1 g after crushing. After dissolving the substance in distilled water, filter the precipitate and wash it several times, then place it in a 100 mL volumetric flask and fill it up with distilled water to obtain a 1000 µg/mL solution. Add 10 mL of the prepared solution to a 100 mL volumetric flask and make up to the mark to obtain the desired solution. This will create a 100% solution.

3. Result and Discussion

3.1. Results and discussion by UV-VIS Method

3.3.1. Absorption Spectra

The spectrum of absorption of the complex product MET - Fe (III) was recorded in comparison to a blank spectrum in the range (200-800) nm before obtaining the best conditions according to the CPE protocol. Figure 2 illustrates an absorption maximum at 400nm..

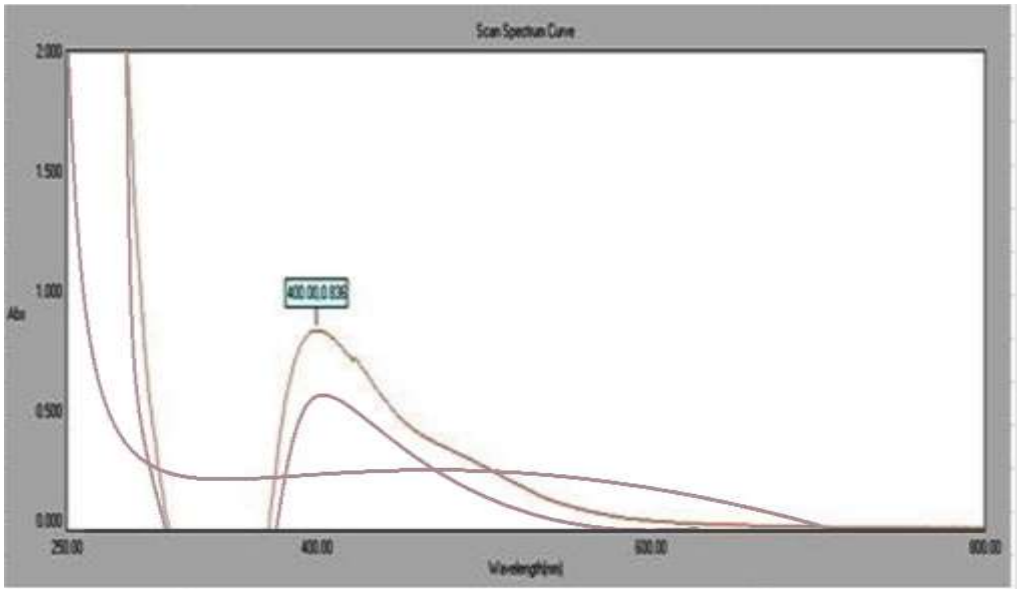

Figure 2. Absorption Spectra of (A) Complex of the MET – Fe (I1I) against metal blank, and (B) Metal versus distilled water (C) MET versus distilled water

3.3.2. Optimization of CPE Methodology"

A collection of experiments has been undertaken to explore the influence of numerous factors that affect the extraction efficiency the meth and optimize the sensitivity of the detection system for drug under study a conventional optimization. The factors such as the concentration of metal ion , Triton X -114's quantity, temperature and incubation time. ".

3.3.2.1. Effect of ferric ion ions volume

The effect of iron ion size was investigated by collecting different amounts of iron ions (0.5–3) mL in a series of volumetric flasks and measuring the absorbance at 400 nm. 10 ml was then added with 1 ml of methimazole (concentration: 1000 µg/ml), 1 ml of Triton X-114 surfactant solution, and distilled water until marked and measured. The absorbance The concentrations of gemcitabine at 400nm are listed in Table 1...

Table **1**. Effect of ferric ion ions size

V (ml)	Abs
0.5	0.630
1 0	0.677

1.5	0.710
2.0	0.863
2.5	0.743
3.0	0.611

The results showed that 2 ml of ferric ion Fe (III) gives the best absorption, so it was adopted in the experiments Suffix.

3.3.2.2. Effect of effective surface type with complex

The type of active surface was investigated using turbidity extraction, as each active surface (Tween 20, Triton X-100, and Triton X-114) has properties that are dependent on the solvent. Take a 10 mL full bottle and add 1 mL of each surface to each 10 mL full bottle with the other variables. After the experiment is complete, separate the surface-rich phase. Measure the effective absorbance of the methimazole drug at a wavelength of 400 nm..

Table **2**. Effect of effective surface type with complex

No	surface type	Abs
1	Tween 20	0.470
2	Triton X-100	0.523
3	Triton X-114	0.863

3.3.2.3. Effect of effective surface volume Triton X -114

1 ml of 1000 µg/ml methimazole concentration, 2ml of ferric ion, and escalating amounts of surface-active Triton X -114 were added to several 10-ml volumetric flasks. 0.2-2 (Triton X -114) ml, add distilled water to the appropriate amount, and then measured how well the solutions are absorbed at a 400 nm in wavelength. The results were shown in table 3.

Table 3. Effect of effective surface size

V (ml)	Abs
0.2	0.401
0.4	0.496
0.6	0.614
0.8	0.688
1.0	.8630
1.5	0.705
2 0	0.627

Table 3. shows that the best effective surface volume is 1 ml, so I relied on it in the experiments the suffix.

3.3.2.4. Temperature effect

The formation of the complex is mostly depend on temperature, which was altered from 25 to 90 ˚C. The findings below indicate that the optimal temperature is reached at this point. In the studies that followed, this temperature was adopted for absorption at 75 ˚C.

Table 4. Effect of temperature

Time (min)	Abs
25	0.543
35	0.634
45	0.688
55	0.765
65	0.812

75	0.863
85	0.835
90	0.830

3.3.2.5. The effect of the sequence of additions:

The results in the table above suggest that the sequence of different chemicals has the same effect on the absorption spectrum as the coloring material. The sequence A and B that was employed in the procedure of the MET as it produced the greatest amount of absorption power for the color-coded product formed.

Table 5. The effect of the sequence of additions

no	order of addition	AbS.
1	(D + M + B +T)	0.863
2	(M + D + B +T)	0.643
3	(M + B + D +T)	0.452
4	(D + B + T +M)	0.211

3.3.2.6. Stabilization effect study

For this study, 1 ml of 1000 µg/ml methimazole and 2 ml of 1000 µg/ml ferric acid were added, followed by 1 ml of Triton X-114 and 0.5 ml of NaOH (10 ml volume), the remaining space was filled with distilled water and then placed in a water bath. After 25 minutes at 75°C, the contents of the volumetric flask were added to the centrifuge and allowed to run for 20 minutes. The complex was then separated and dissolved in 4 ml of distilled water and 1 ml of ethanol. When examined at 400 nm, the absorption changes between 2 and 60 minutes, but only 20 minutes were sufficient for complete formation of the complex. The results are listed in Table 6 below...

Table 6. Stability

Time (min)	Abs
2	0.837
4	0.836
6	0.839
8	0.842
10	0.844
15	0.862
20	0.863
25	0.863
30	0.860
40	0.860
50	0.861
60	0.860

3.3.2.7. Optimal working method and calibration curve

Gradual volumes (0.1–1.0) of the drug were added to a series of 10 mL measuring vials. Methimazole was prepared to a concentration of 1000 µg/ml, with a final concentration in the range of (10-100) µg/ml. Then 2 ml of Fe(III) ion solution and 1 ml of 10% surfactant Triton X-114 were added. The mixture was then heated in a water bath at 75°C for 25 min, followed by a 20 min separation process in a centrifuge to separate the complex. The complex was dissolved in 1 mL of ethanol and 4 mL of distilled water. Finally, the absorbance The concentration of the solution was determined at a wavelength of 400nm. and compared with a reference solution. Beer's law follows the concentration range of (10-100) µg/ml. The estimated coefficient was 0.9993, the Sandel significance was 0.1134 µg*cm-2, the molar absorbance was 1007.23 l/mol*cm, the limit of detection LOD was 0.3784 µg/ml,

and the limit of quantification LOQ was 1.2612 µg/ml.

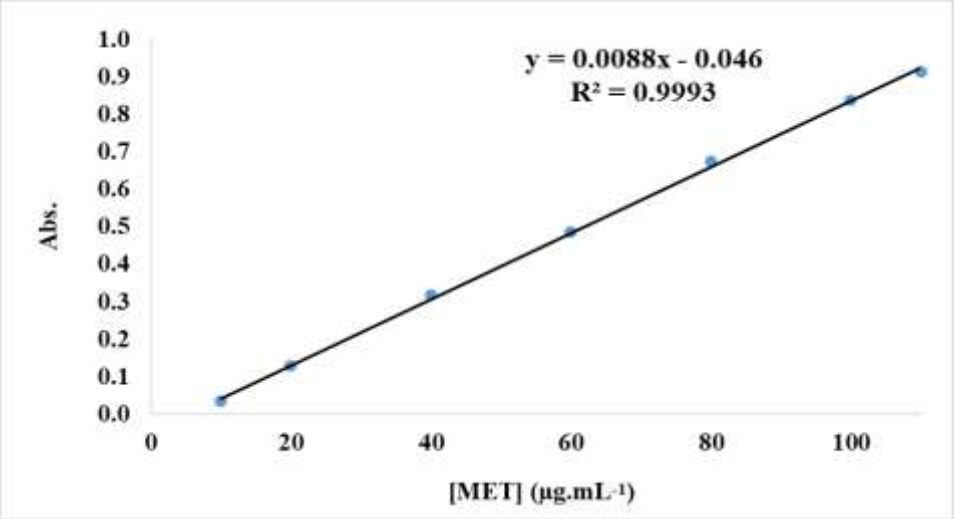

Figure 3: (MET – Fe (III)) Calibration Curve

The molar absorptivity value is 1000 Lmol-1 cm -1. The value of the molar absorption coefficient enables the quantitative analysis of methimazole in pharmaceuticals directly. " .

3.3.2.8. Accuracy and compatibility

The most effective conditions were employed in the program to assess the accuracy of the calibration graph and the fidelity of its measurement of methimazole. Five different concentrations of methimazole were tested in order to follow Bell's law. The results demonstrated that the method had high accuracy and good consistency. The outcomes are listed in the table.. 7.

Table 7. Accuracy and compatibility

Present µg/ml	Found µg/ml	Erorr	Recover %	Average %	RSD %
20	19.73	- 0.271	98.64	99.57	0.781
60	60.10	0.103	100.17		0.173
100	99.91	- 0.087	99.91		0.066

3.3.2.9. Limit of detection and limit of quantification.

The detection limit and quantitation limit for methimazole determination were determined through the measurement of absorbance of the lowest concentration in the 10 µg/ml calibration curve, by averaging five readings obtained under ideal experimental conditions. and the results shown in table 8.

Table 8. Detection limit and quantitative limit

Conc. of meth.µg m/ml	∂	SD	LOD	LOQ
10	0.0088	0.0011	0.3784	1.2612

3.3.2.10. The nature of the product formed

The continuous variation method, also known as the Job method, uses a series of measuring bottles to analyze methimazole. Different amounts of methimazole (0.1 to 0.9 ml) were added to 10 ml volumetric bottles. Additional amounts of ferric ion solution and active surfactant-114 were added. The absorbance of the solution at a wavelength of 400 nm was compared with the control solution, as shown in Figure 4, indicating that the binding ratio between methimazole and ferric ion was 1:1. To confirm that the reaction ratio between the drug tepronin and the reagent was 1:1, the molar ratio method was used. To ensure the binding ratio between iron (III) and methimazole, the molar ratio method was also used. 1 1 ml of methimazole at a concentration of 1000 µg/ml was added to several 10 ml volumetric bottles. Different amounts of ferric ion (0.1 to 3 ml) were added, and then 1 ml of

active surfactant-114 as measured against the standard solution with those obtained using the continuous

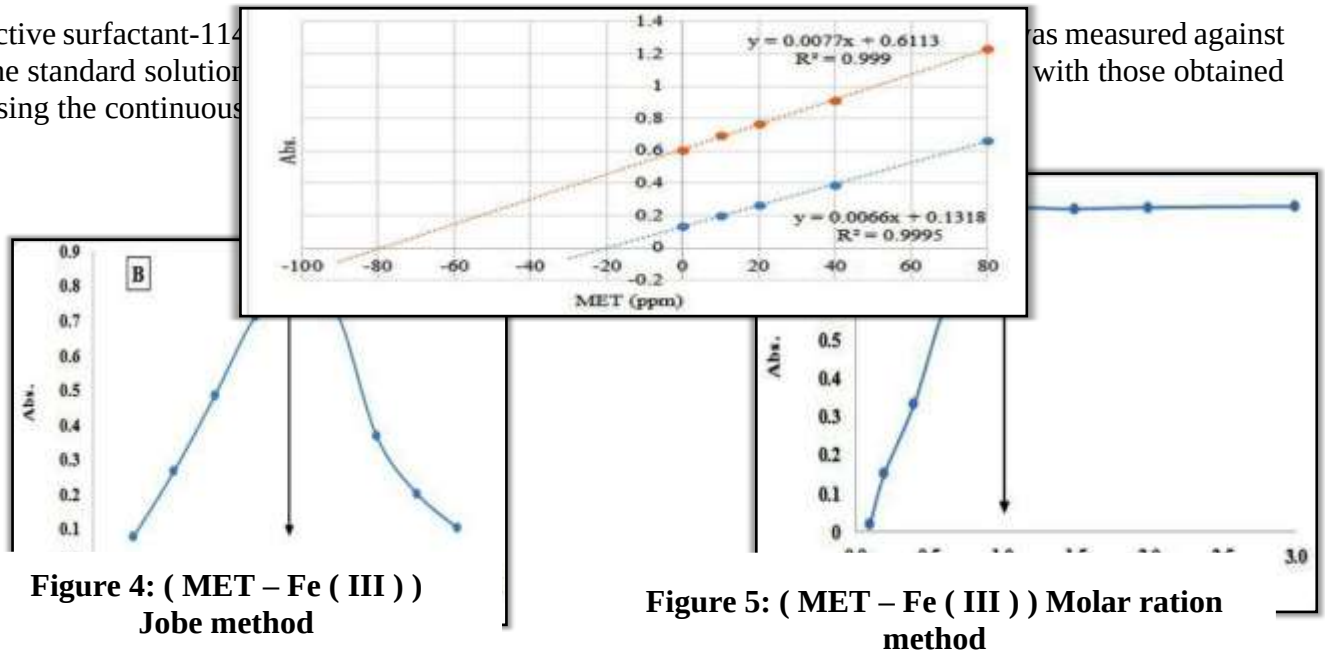

Figure 4: (MET – Fe (III)) Jobe method

Figure 5: (MET – Fe (III)) Molar ration method

3.3.3 Applications

The proposed method was applied to the pharmaceutical preparation that contains taiopronin in the form of pills in the following way:

3.3.3.1 The direct method

The drug manufacturing application involves the manufacture of drug solutions as described in the "Manufacturing Solutions" section. Three different concentrations of the prepared solutions were used (10, 60, 80 mcg/ml). Cloud point extraction (CPE) was then performed following a series of specific steps. The The results are listed in the table.. 9.

Table 9. The direct method

present µg/ml	foundµg/ml	Recovery %	Average%
10	9.64	96.40	99.2
60	59.85	99.76	
80	81.16	101.46	

3.3.3.2. Standard addition method

In order to validate the proposed method and ensure that it is free from interferences, a standard addition method for the determination of methimazole in a pharmaceutical preparation was used. The method involves the addition of a fixed amount (0.2 and 0.8 ml) equivalent to (20 – 80) µg/ml from a solution of the pharmaceutical preparation at a concentration of 1000 µg/ml. The addition was performed in two sets of 10 ml volumetric flasks. Subsequently, incremental volumes of the drug (0.1, 0.2, 0.4, 0.8 ml) were introduced at a concentration of 1000 µg/ml. The solutions were treated identically to the preparation of the calibration curve and the absorbance values The concentrations of the solutions were measured at a wavelength of 400nm in comparison to the control solution. The conclusions are shown in the table. 10.

Figure 6: Standard addition curve for the determination of taiopronin in pharmaceutical tablets

Table 10. Standard additions

amount takenµg/ml	amount measured µg/ml	recovery%	average recovery%
20	19.97	99.85	99.54
80	79.39	99.24	

3.3.4. Results and discussion by (FAAS)Method

3.3.4.1. Indirect determination of MET by Flame atomic absorption spectrophotometry (FAAS)

An alternative technique to UV-VIS was used for the determination of MET-Fe(III) drug complexes using flame atomic absorption spectrophotometry (FAAS). The MET concentration was determined by indirectly measuring the absorption of Fe(III) in the complex, as shown in Figure 6. The MET-Fe(III) complex was carefully prepared at optimized pH, temperature, appropriate solvents, and other parameters identical to those previously described in the UV spectrophotometer analysis. Notably, only the concentration of Fe(III) ions was varied. It was found that the optimal concentration of Fe(III) resulted in a maximum absorption of 25 µg/mL within the organic layer, leading to an increase in the absorption of the complex. Furthermore, the MET concentration in these drug formulations was quantified using the calibration curve of the indirect FAAS method. The results obtained were in good agreement with those obtained using the UV method.

3.3.4.2. Effect of iron (III) ion concentration

Figure 7 illustrates the effect of different Fe(III) ion volumes on the absorbance values of the complex extracted with 1000 µg/mL drug solution. After analysis, it was found that the optimal metal ion volume for the complex to achieve maximum absorption was 1 mL Fe(III). The absorption level was then measured and the corresponding results are shown in Figure 7. 7.

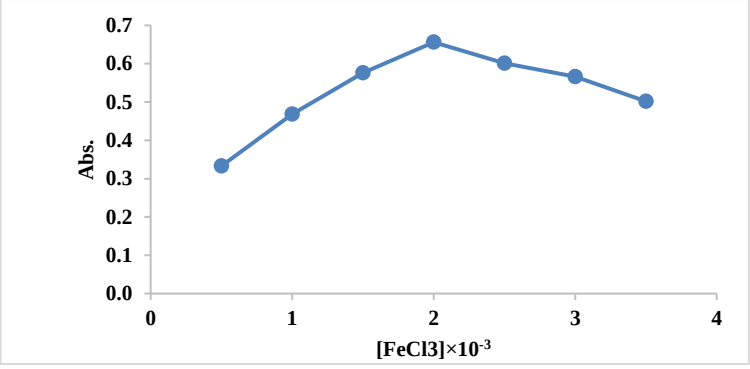

Figure 7: Effect of Fe (III) concentration of (MET – Fe (III)) by AAS method

3.3.4.3 Preparation of Calibration Curve for methimazole

To evaluate the linearity of the method under the optimized conditions determined for the methimazole method, a calibration curve was constructed by correlating the absorbance with the methimazole concentration. The calibration curve represents the relationship between the average absorbance value of the turbidity point and the concentration of the methimazole iron complex (in g/mL), as shown in Figure 1. 8.

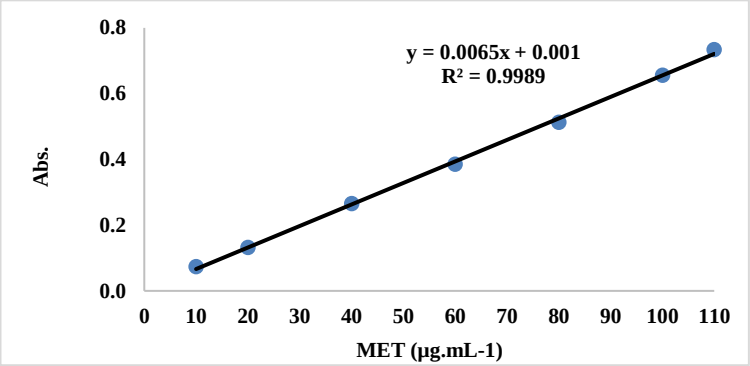

Figure 8: (MET – Fe (III)) Calibration Curve.

3.3.4.4. Comparison between the two methods of the proposed method

For the determination of methimazole, a comparative analysis of UV-Vis and FAAS methods was performed and the statistical parameters are explained in Table 11. Both methods are simple, cost-effective, accurate, follow the principles of green chemistry, have high selectivity, avoid the use of hazardous chemicals, etc. From the perspective of scientific analysts, the first method is preferred because it does not have interferences that often occur in the UV-Vis region and has better statistical calculation parameters..

Table 11. Comparison between the Two methods of the Proposed method to determination of methimazole

Parameter	Complex (meth-fe) by UV-VIS Method	Complex (meth-fe) by FAAS Method
Concentration rang (µ g mL^{-1})	10-100	10-100
Regression equation	y=0.0088-0.046	y=0.0065-0.001
Linearity coefficient R^2	0.9999	0.9989
Slope (m)	0.0088	0.0065

The newly proposed method was effectively benchmarked against existing literature methodologies, showcasing significant advancements in spectrophotometric analysis for methimazole drug determination. It emerged as a rapid, precise, highly selective, and sensitive technique.

4. Conclusion and future scope

The method is simple, sensitive, and avoids stringent experimental conditions such as heating. It has accuracy and precision that make it a useful alternative to current spectrophotometric techniques for the evaluation of methimazole in metals using CPE and for the determination of Fe(III) in certain pharmaceutical preparations. In particular, this method provides very low limits of detection and is in line with the principles of green chemistry.

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