# A Simple Colorimetric Method for the Estimation of Metoclopramide Hydrochloride in Pharmaceuticals dosage

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***Abstract***

*A spectrophotometric method based on the use of diazotization and coupling reaction was developed for the determination of metoclopramide hydrochloride (METH) by reacting a nitrogenous drug complex (D-METH) with reagent 4-chlororesorcinol (4-CRS). The alkaline dye gives a stable azoic red dye in the aqueous media, which gave the highest absorption at the wavelength of 527 nm and the limits of Beer's law had a linear relationship located within concentrations of 1-15 µg/ml and with a molar absorption coefficient of 2.53 × 104 L/mol. cm.*

*Sandell's significance was 0.0140 µg/cm, while the LOD and LOQ values were 0.034 µg/ml and 0.114 µg/ml respectively. The proposed method has been successfully applied in the determination of metoclopramide hydrochloride in its pharmaceutical preparations in the form of tablets and injections.*

**Keywords**: Spectrophotometric, Diazotization, Coupling reaction, Metoclopramide hydrochloride, 4-chloroesorcinol, Color method.

## Introduction

Benzamide,4-amino-5-chloro-N-[2-(diethylamino)ethyl]-2-methoxy- monohydrochloride, monohydrate is a chemically name for metoclopramide hydrochloride (METH) with a chemical formula $C_{14}H_{22}ClN_3O_2.HCl.H_2O$ and has a molecular weight 354.3 g/mol, as seen in figure 1[26]. METH consists of odorless white crystals that are easily soluble in water and alcohol. They are stored at 25°C in firmly closed, light-protected containers[12].

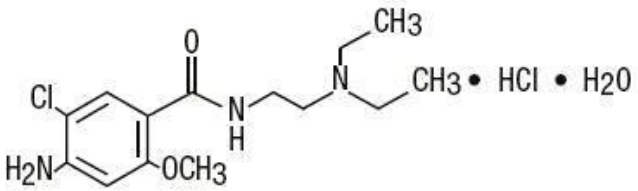



**Figure 1: Chemical structure of METH.**

Metoclopramide acts by blocking dopamine D2 and serotonin 5-HT3 receptors in the chemoreceptor trigger zone (CTZ) located in the area of the postrema of the brain[14]. Metoclopramide has been commonly used to treat gastrointestinal disorders as well as antiemetic nausea from chemotherapy, migraine and postoperative headaches[11] and has been considered a first-line option for nausea and vomiting during the first trimester of pregnancy[5] and has also been used to treat diabetic gastroparesis[25]. It is endorsed by the British Pharmacopei[7] which calls for potentiometric end-point detection in acid-base titration, while a chromatographic method is used for estimation of dosage forms for both tablet and injection.

The literature sources refer to the use of several reagents in the spectrophotometric determination of METH through different spectrophotometric reactions such as diazotization coupling and by using different reagents such as 1,7-dihydroxynaphthalene[3], phenylephrine hydrochloride[13], 4-nitrophenol,3,5-dimethylphenol[20], cloud point extraction with 1- naphthol[1]. Additionally, METH was identified spectrophotometrically using oxidative coupling[27], Schiff's base condensation[4], charge transfer[16], complexometric[23], redox[24], nucleophilic substitution[18], ion pair[21], UV spectrophotometry[2] and titrimetric method[6].

Several analytical techniques methods have been used in the quantification of METH as in chromatographic[17], electrochemical[19], flow injection analysis[15], spectrofluorometric[10] and atomic absorption[22]. The aim of the study in this research is to develop an easy and suitable method for the determination of METH by reaction of diazotized metoclopramide with 4-chlororesorcinol as coupling in the presence of NaOH as an alkaline medium to form a colored azo dye product which is soluble in an aqueous media and METH was determined in both its pure and dosage form.

## Material and Methods

**Chemicals and Materials:** A Jasco V-630 UV-Visible double beam (Japan) device spectrophotometer with spectra manager software using silica cell (1 cm) is used in spectrophotometric measurements along with professional benchtop BP3001 pH meter and balance of the type ABS 120-4.

**Chemicals:** All chemicals used were of analytical grade.

**The solutions utilized Diazotized Metoclopramide hydrochloride (D-METH) solution (100 µg/ml):** Metoclopramide hydrochloride (METH) in the concentration of 0.0100 g (2.8x10-4M) was dissolved in 30 ml of distilled water, then an equal molar of sodium nitrite (0.0019 g) was added. After that, 3 ml of diluted

hydrochloric acid at a concentration of 1 M was added and finally, the quantity was brought to 100 ml volumetric flask and stored in an opaque bottle.

**Reagent Solution 4-chlororesorcinol (0.1% 4 -CRS):** 0.1g of the reagent was dissolved in a few drops of ethanol to produce a solution of 4- chlororesorcinol at a concentration of 0.1%. The volume also was made to 100 ml with distilled water in the volumetric flask.

**Solution of hydrochloric acid (1 M approx.):** In a 100 ml volumetric flask, the solution was made by mixing 8.4 ml of concentrated acid with a small amount of distilled water. The volume was then filled with the remaining distilled water to the mark in the volumetric flask.

**Solution of sodium hydroxide (0.1 M):** This solution was made by filling a plastic volumetric container (10 M) with in one little container. Then take 0.1 ml of the concentrated solution, dilute it to 100 ml and transfer it to a plastic bottle to be stored in.

**Diazotized drug solutions**

**Tablets form (100 µg/ml):** The drug metoclopramide, Darnitsa, Ukrain, which contains 10 mg per tablet, was weighed as 10 tablets. The tablets then were crushed well, weigh the equivalent of 0.01 g and then dissolve in 50 ml of distilled water, shake well and then filter. The diazotized solution was prepared following the same procedures as with the standard solution.

**Approved working method and standard curve:** Increasing volumes of 0.1 to 1.5 ml of the D-METH solution (at a concentration of 100 µg/ml) were added to a series of 10 ml volumetric flasks containing 2 ml of 4-CRS (0.1%) solution and 0.5 ml of hydroxide solution. The absorbance of the colored solutions was measured against the blank solution at a wavelength of 527 nm. Figure 2 represents the standard calibration curve of the proposed method, which is compatible with Beer's law for the range 1-15 µg / ml and there is a negative deviation for concentrations higher than that. It was found that the molar absorbance value was 2.53 × 104 L / mol. cm and sandalwood significance was equal to 0.0140 µg/cm$^2$ while the detection limit and quantitative limit were 0.034 and 0.114 µg/cm respectively.

## Results and Discussion

**The optimal conditions for the reaction:** The factors affecting the interaction of the proposed method for the determination of metoclopramide hydrochloride (METH) were studied in order to obtain the highest absorption intensity and stability of the azo dye, as the azo dye consists of conjugation of metoclopramide hydrochloride (D-METH) with reagent 4 - chlororesorcinol (4-CRS) in the presence of a basic medium of sodium hydroxide and dilution with distilled water in a final volume of 10 ml and then reading the absorption of the azo dye formed against the blank solution at the wavelength of 527 nm.

**The effect of acid type:** Several types of acids used in the diazotization process were studied by preparing the diazotized medicinal compound prepared by adding 2 ml at a concentration (1M) of different types of acids with the rest of the components fixed and then reacting with 0.5 ml of the prepared nitrogenous solutions. 1.5 ml of the reagent 4-chlororesorsenol with a concentration (0.1%) and 0.5 ml of sodium hydroxide with a concentration (1M) are added. The HCl acid gave the highest absorption for the formation of the azo dye and it was relied upon in subsequent experiments.

**The effect of the amount of acid:** Different volumes of HCl acid used in the process of nitrogenizing the medicinal compound were taken to see the effect of the amount of HCl used in the diazotization process.

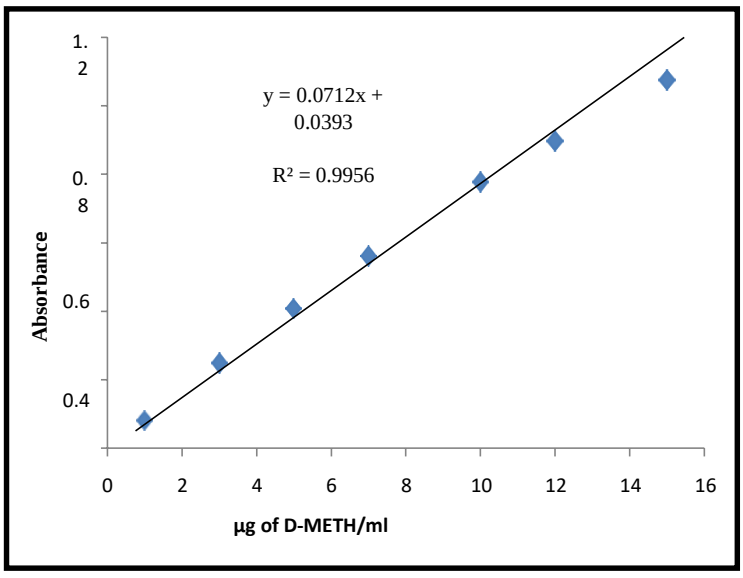



**Figure 2: The standard curve of the proposed method**

**The effect of the amount of reagent:** The effect of the presence of different quantities of the conjugation reagent 4-CRS on the azo dye formed was studied by adding volumes ranging from 1-2.5 ml of the reagent with a concentration of 0.1% and with increasing concentrations of D-METH and the results are shown in the table 3. A volume of 2 ml of the 4-CRS reagent gave the highest absorption of the formed azo dye and the highest estimation coefficient (R2 = 0.9968).

**The effect of the type of base:** The effects of several types of dilute solutions of strong and weak bases (at a concentration of 1 M) on the adsorption intensity of the azo dye formed by adding 0.5 ml to a solution containing 0.5 ml of D-METH and 2 ml of 4 were studied. The results of table 4 show that the highest absorption was by using a dilute solution of NaOH.

**The effect of the amount of base used:** Different volumes of 1 M of dilute sodium hydroxide solution were added to the same previously added volumes of D-METH and 4-CRS. It was observed from practical experiments that 0.5 ml of the diluted base gave the highest absorption intensity of the azo dye formed, so the same amount of base used in subsequent experiments was kept as shown in the results of table 5.

**The effect of surface active substances:** To demonstrate the extent of the effect of surface-active materials on the absorption and color variation of the azo dye formed, 2 ml of solutions of surface-active materials were added to the reaction solutions in different sequences. The results of table 6 indicate that these additives did not lead to a significant increase in the sensitivity of the method but led to a decrease in the absorption of azo dye and therefore it was excluded in the subsequent experiments.

**Table 1**
**The effect of the type of acid used in diazotization**

| Acid used (2ml,1M) | HCl | $HNO_3$ | $H_2SO_4$ | $H_3PO_4$ | $CH_3COOH$ |
|---|---|---|---|---|---|
| Absorbance | 0.296 | 0.287 | 0.270 | 0.245 | 0.242 |

**Table 2**
**The effect of the amount of acid used**

| ml added HCl (1M) | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| Absorbance | 0.278 | 0.293 | 0.342 | 0.315 | 0.248 |

**Table 3**
**The effect of the amount of coupling reagent 4-CRS on the absorption**

| ml of Coupling agent | Absorbance/µg D-METH/ml | | | | | | R2 |
|---|---|---|---|---|---|---|---|
| | 1 | 3 | 5 | 7 | 10 | 12 | |
| 1 | 0.044 | 0.155 | 0.288 | 0.387 | 0.472 | 0.589 | 0.9842 |
| 1.5 | 0.062 | 0.188 | 0.344 | 0.421 | 0.532 | 0.621 | 0.9775 |
| 2 | 0.087 | 0.232 | 0.405 | 0.529 | 0.722 | 0.931 | 0.9968 |
| 2.5 | 0.061 | 0.189 | 0.355 | 0.433 | 0.623 | 0.831 | 0.9891 |

**Table 4**
**Selecting the base type**

| Type of base(1M) | Absorbance |
|---|---|
| NaOH | 0.408 |
| KOH | 0.392 |
| $Na_2CO_3$ | 0.364 |
| $NaHCO_3$ | 0.341 |

**Table 5**
**Choosing the size of the base used**

| ml of base used (1M) | Absorbance |
|---|---|
| 0.3 | 0.371 |
| 0.5 | 0.410 |
| 1.5 | 0.398 |
| 2 | 0.356 |

**Effect of adding different solvents:** The effect of several organic solvents (in addition to water) on the absorption intensity of the azo dye formed was studied through the final dilution of the reaction solution with these solvents with a final volume of 10 ml and then measuring the absorption against the blank solution for each of them as shown in figure 3.

It is noted from the results of table 7 that the highest absorption was by using acetone as an organic solvent, but distilled water was retained as a solvent used in the final dilution due to its cheapness, safety and availability.

**Effect of time on the stability of the azo dye:** To find out the stability of the formed azo dye, two different concentrations of 5 µg / ml and 10 µg / ml were taken from the D-METH solution and the absorption of the reaction product was measured at different time periods. The results in table 8 show that the azo dye remains stable at room temperature for at least 60 minutes.

Table 9 summarizes the optimal experimental conditions which were established based on previous experiments.

**Final absorption spectrum:** The final absorption spectrum was measured after fixing the aforementioned optimal conditions by adding 2 ml of reagent 4-CRS at a concentration of 0.1% to 0.5 ml of the prepared D-METH solution followed by 0.5 ml of a NaOH solution of concentration 1 M. The absorption spectrum of the azo dye formed at the maximum wavelength of 527 nm was measured against the blank solution as shown in figure 4.

**Table 6**
**The effect of surface-active substances**

| Surfactant | Absorbance / ml of Surfactant added | | |
|---|---|---|---|
| | I | II | III |
| CPC | 0.339 | 0.327 | 0.357 |
| SDS | 0.331 | 0.347 | 0.308 |
| Triton –x-100 (1.0%) | 0.302 | 0.317 | 0.305 |
| Without | 0.406 | | |

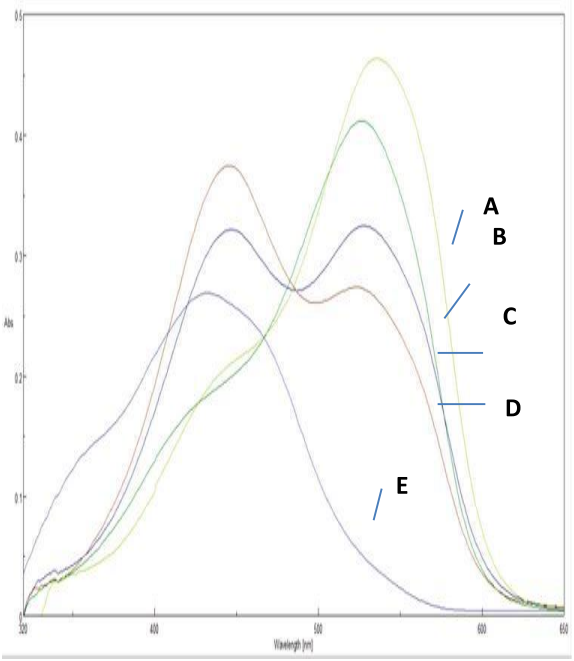



**Figure 3: The effect of solvents on the absorption of azo dye**

**Table 7**
**The effect of solvents on the absorption of azo dye.**

| Solvent | | λ max (nm) | Absorbance | ε(x105) l/mol.cm |
|---|---|---|---|---|
| A | Acetone | 536 | 0.463 | 3.30 |
| B | Water | 527 | 0.411 | 2.93 |
| C | Methanol | 446 | 0.374 | 2.67 |
| D | Ethanol | 447 | 0.322 | 2.30 |
| E | Acetic Acid | 432 | 0.268 | 1.91 |

**Table 8**
**Effect of time on the stability of azo dye.**

| Time, min. | Abs/µg of D-METH | |
|---|---|---|
| | **5** | **10** |
| Immediately | 0.398 | 0.747 |
| 5 | 0.410 | 0.747 |
| 10 | 0.411 | 0.748 |
| 55 | 0.411 | 0.746 |
| 20 | 0.413 | 0.748 |
| 55 | 0.415 | 0.749 |
| 30 | 0.414 | 0.750 |
| 55 | 0.414 | 0.751 |
| 40 | 0.416 | 0.754 |
| 55 | 0.415 | 0.755 |
| 50 | 0.414 | 0.758 |
| 55 | 0.414 | 0.759 |
| 60 | 0.413 | 0.762 |

**Table 9**
**Optimal conditions for the proposed method.**

| Variable | Optimality |
|---|---|
| Reagent used | 4-Chlororesorcinol |
| Percentage of reagent used | 0.1 |
| Amount of reagent used ( ml) | 2 |
| Based used NaOH(ml) | 0.5 |
| Concentration of base used | 1M |
| Amount of HCl(1M) used in diazotization,(ml) | 3 |
| λ max( nm) | 527 |

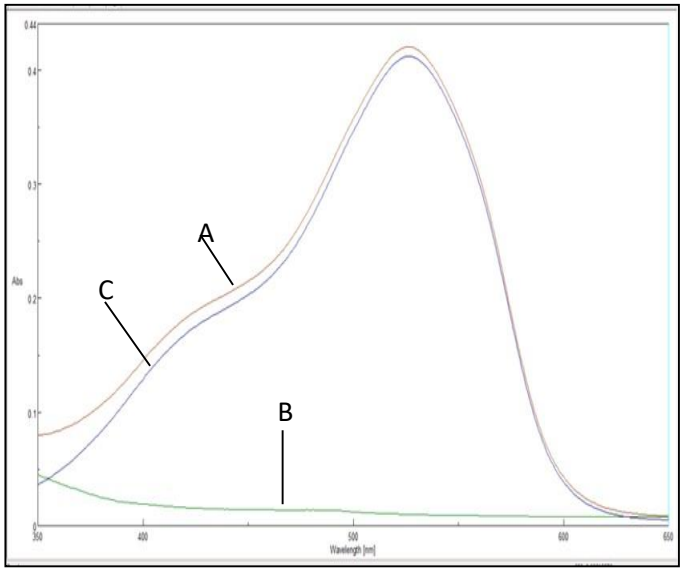



**Figure 4: The absorption spectrum of 5 µg / ml of D-METH according to the proposed method: A - vs. distilled water, B- vs. blank solution, C - blank solution vs. distilled water**

**Precision and compatibility of the method:** The accuracy and compatibility of the proposed method for estimating METH were calculated by calculating the relative error and the relative standard deviation, by applying the approved work method in measuring the absorbance values for three different concentrations as in table 10. The proposed method is characterized by accuracy and good compatibility.

**Studying the nature of the reaction product of METH with 4-CRS:** The continuous change method (Job's method)[8] was applied in order to find out the molar ratios of the interaction between the drug compound METH and the reagent 4-CRS, as equal concentrations of each of D -METH and 4-CRS at a concentration of 2.8 x 10-4 M and for different volumes of solutions. The total volume of the drug

compound METH and the reagent 4-CRS was 0.5 ml with a final volume of 10 ml as in figures 2 to 5a. Figure 5b shows the M ratio by adding increasing volumes of 4-CRS (0.25 - 3) ml at a concentration of 2.8 x $10^{-4}$ M to 1 ml of a D-METH solution with the same concentration of the used reagent, then 0.5 ml of the base was added, following optimal experimental conditions, with a total volume of 10 ml and then the absorption of the azo dye solution formed was measured. At the wavelength of 527 nm against the blank solution, figure 5 shows that the conjugation ratio was 1:1 (METH: 4-CRS).

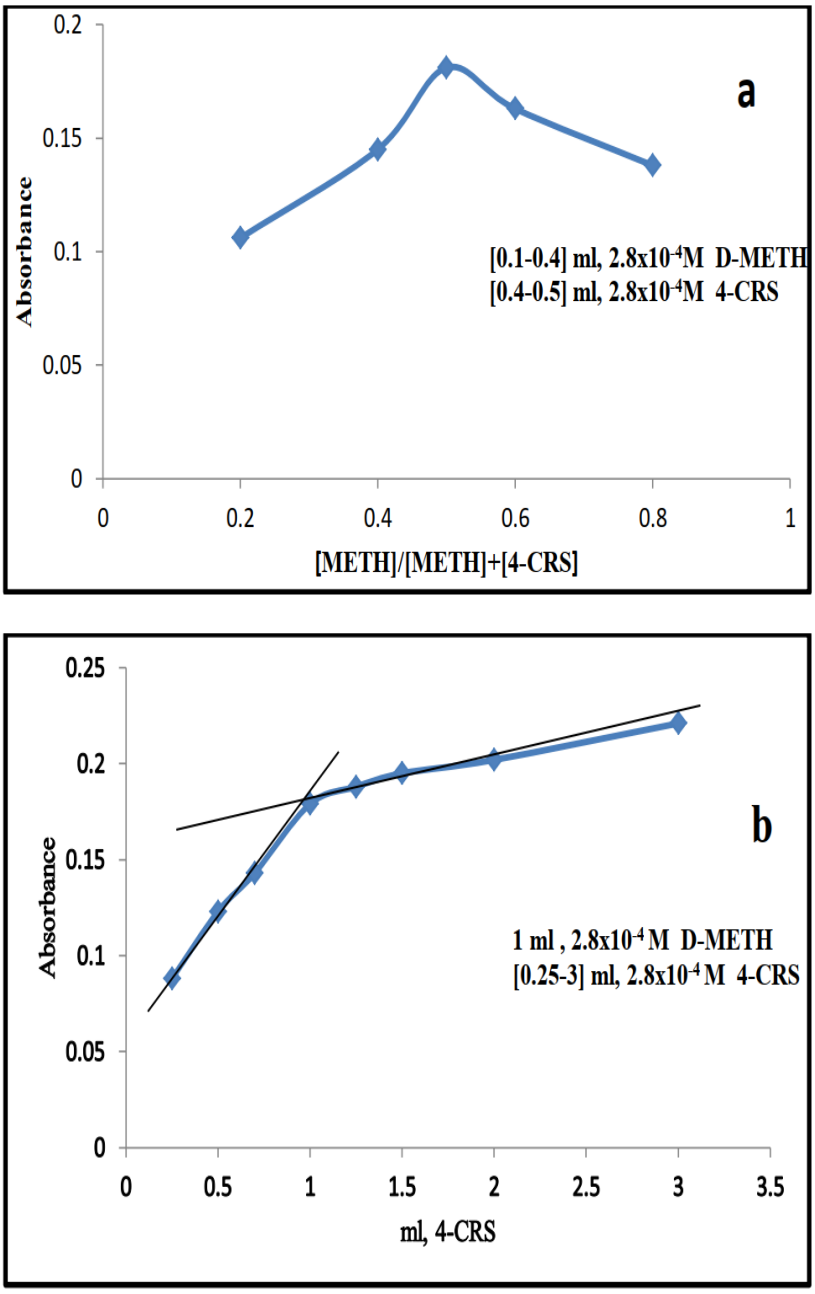



**Figure 5: (a) The continuous change curve, (b) The molar ratio curve of the azo dye formed from the conjugation of D-METH with 4-CRS.**

**Table 10**
**The accuracy and compatibility of the proposed method.**

| Amount of METH µg/ml | Recovery *% | RE% | RSD% |
|---|---|---|---|
| 3 | 98 | -2.0 | 1.33 |
| 7 | 96 | -4.0 | 2.12 |
| 12 | 100.1 | 0.10 | 1.93 |

* Average of five determinations.

**Table 11**
**Results of METH estimation in pharmaceutical preparations.**

| Drug content | METH taken µg/ml | METH found µg/ml | Recovery* % | RE % | RSD % | Drug content measured (mg) |
|---|---|---|---|---|---|---|
| Metocloramide 10 mg/tablet Darnitsa, Ukraine | 5 | 4.05 | 101.25 | 1.25 | 1.22 | 10.12 |
| | 7 | 6.82 | 97.42 | -2.57 | 1.15 | 9.74 |
| | 55 | .8855 | 99.00 | -1.00 | 1.01 | 9.90 |
| Meclobran/injection 10 mg/2ml Brawn, India | 5 | 4.11 | 102.75 | 2.75 | 1.05 | 10.27 |
| | 7 | 7.09 | 101.28 | 1.28 | 0.94 | 10.12 |
| | 55 | 11.91 | 99.25 | -0.75 | 1.09 | 9.92 |

* Average of five determinations

**Table 12**
**Standard addition method for estimating METH.**

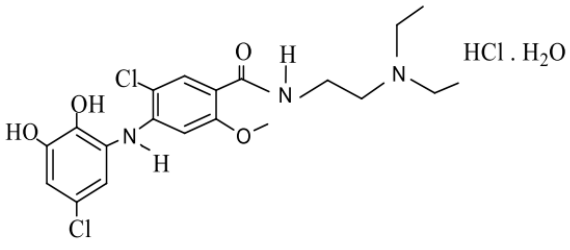
| Drug content | METH taken µg/ml | METH found µg/ml | Recovery* % | RE % | RSD % | Drug content measured (mg) |
|---|---|---|---|---|---|---|
| Metocloramide 10 mg/tablet Darnitsa, Ukraine | 4 | 4.07 | 101.75 | 1.75 | 1.23 | 10.17 |
| | 8 | 7.89 | 98.62 | -1.37 | 1.07 | 9.86 |
| Meclobran/injection 10 mg/2ml Brawn, India | 4 | 3.99 | 99.75 | -0.25 | 1.15 | 9.97 |
| | 8 | 8.02 | 100.25 | 0.25 | 0.97 | 10.02 |

* Average of three determinations.

**Table 13**
**Comparing some of the important analytical changes of the method with other methods**

| Variable | Present method | Ganduh et al[13] | Devi et al[9] |
|---|---|---|---|
| Type of reaction | Diazo-coupling | Diazo-coupling | Schiff's Base |
| Reagent Used | 4-chlororesorcinol | Phenylephrine Hydrochloride | Vanillin |
| λmax ( nm) | 527 | 452 | 410 |
| Linearity range(µg/ml) | 1-15 | 1-10 | 1.5-15 |
| E l/mol.cm | 2.53×104 | 1.91×104 | 1.89×104 |
| Sandell's Index (µg/cm2) | 0.0140 | -------- | 0.019 |
| LOD | 0.034 | 0.0121 | 0.51 |
| LOQ | 0.114 | 0.0406 | 1.55 |
| Color's product | Red | Orange | Yellow |

Depending on figure 5, the proposed formula for the formed azo dye can be written as:




**Red azo dye product.**

**Applied part:** The proposed method for the determination of METH was applied to some pharmaceutical preparations in the form of tablets and injections and from different origins, by taking three different concentrations of D-METH solution and applying the approved method of work according to optimal conditions. The results of table 11 show that the proposed method has proportions. Retrieval and relative errors are acceptable within the acceptable analytical errors, which do not exceed 5%.

**Evaluation of the proposed method using the standard addition method:** The standard addition method was applied to find out the selectivity of the proposed method for the determination of metoclopramide hydrochloride in its pharmaceutical preparations. Figure 6 and table 12 show that the standard addition method agrees well and is within the acceptable error range with the results of the proposed method.

**Comparison with other methods:** A comparison was made of the most important analytical variables of the proposed current method with similar ones in other spectrophotometric methods for the determination of metoclopramide hydrochloride. This proposed method is no less important than other methods and has sensitivity and results that can be accepted as shown in table 13.

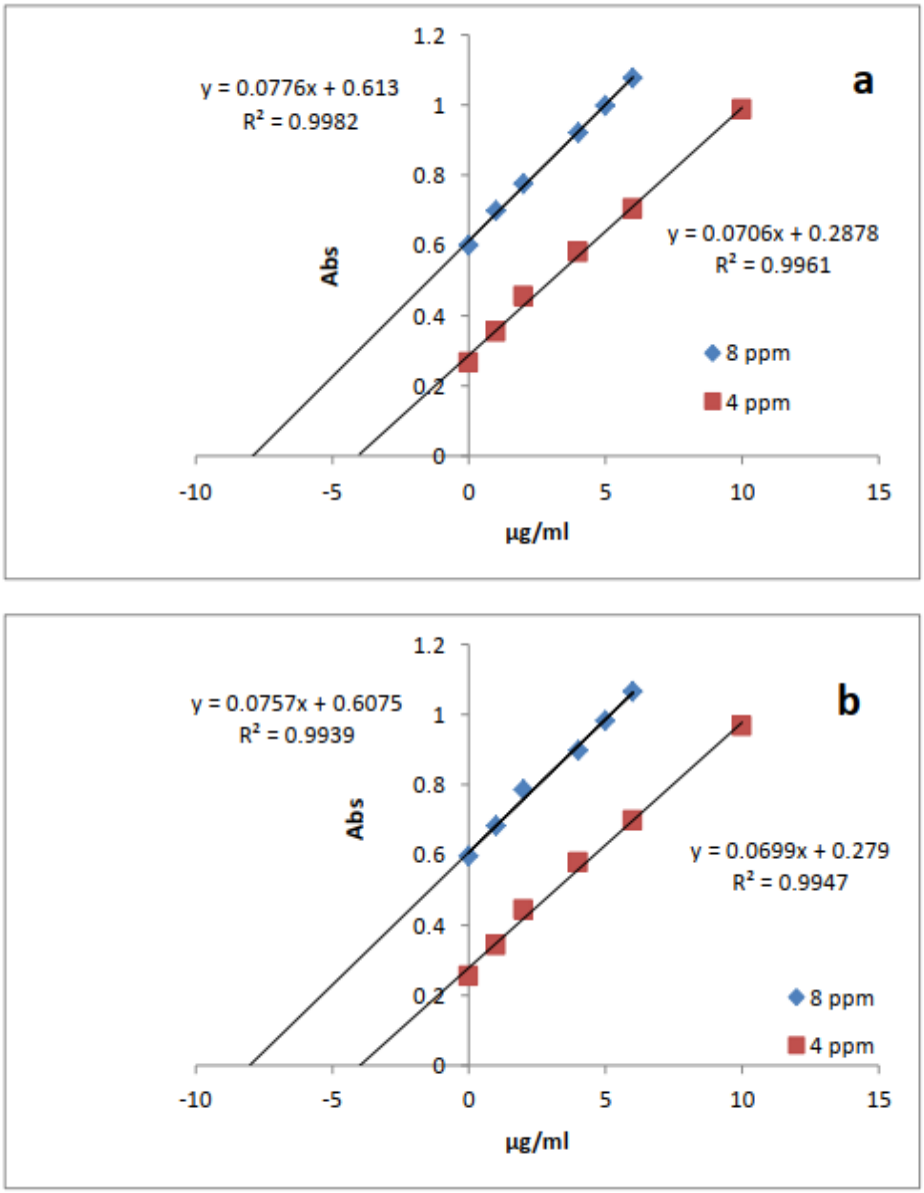



**Figure 6: Curve of standard addition method for estimating METH: a- tablets, b- syringe**

## Conclusion

The proposed spectrophotometric method for the determination of metoclopramide hydrochloride was characterized by its simplicity and sensitivity. It is not dependent on temperature and does not require any steps or prior preparations such as extraction. It is inexpensive and has been successfully applied through retrieval results for the determination of pharmaceutical preparations of metoclopramide hydrochloride in the form of tablets and injections.

## Acknowledgement

The researchers thank the Department of Chemistry, College of Science, University of Mosul for providing the facilities for the completion of this research.

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(Received 03rd March 2024, accepted 15th April 2024)