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Spectrophotometric Determination of Metoclopramide Hydrochloride in Pharmaceutical Preparations Using Diazotization Reaction

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ABSTRACT

A simple, rapid and sensitive spectrophotometric method has been developed for the quantitative determination of metoclopramide hydrochloride in both pure form and in its pharmaceutical formulations. The method is based on diazotization of primary amine group of metoclopramide hydrochloride with sodium nitrite and nitric acid followed by coupling with 8-hydroxyquinoline in alkaline medium to form a pinkish – red coloured species, which showed a maximum absorption at 528 nm against reagent blank. Beer's law was obeyed over the concentration range of 5-300 µg / 25 ml. with a molar absorptivity 3.1×10^4 $l.mol^{-1}.cm^{-1}$. The method is suitable for the determination of metoclopramide hydrochloride in the presence of other ingredients that are usually present in dosage forms and the recoveries were obtained in the range of 98.9-100.0%. The method does not resort to temperature control or to solvent extraction. The effect of organic solvent on the spectrophotometric properties of the azo dye, the composition and stability constant have been worked out. The method has been successfully applied to the determination of metoclopramide in its pharmaceutical preparations (tablet, syrup and drop) .

Keywords: metoclopramide- HCl , determination , 8-hydroxyquinoline, spectrophotometry

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التقدير الطيفي للهيدروكلوريد ميتوكلوبراميد في بعض المستحضرات الصيدلانية باستخدام تفاعل الاقتران الازوتي

الملخص

تم اقتراح طريقة طيفية بسيطة وسريعة وحساسة لتقدير هيدروكلوريد الميتوكلوبراميد في بعض المستحضرات الصيدلانية تعتمد الطريقة على ازوتة مركب الميتوكلوبراميد بواسطة نتريت الصوديوم وحامض النتريك ثم اقتران الميتوكلوبراميد المؤزوت مع الكاشف 8-هيدروكسي كوينولين في وسط قاعدي لتكوين صبغة آزوية ملونة، كانت الصبغة المستقرة والذائبة في الماء قد أعطت أعلى امتصاص عند الطول ألموجي 528 نانوميتر. وان حدود قانون بير ضمن مدى التركيز5- 300 مايكروغرام من الميتوكلوبراميد في

حجم نهائي 25 مل وكانت قيمة معامل الامتصاص المولاري 3.1×10^4 لتر.مول$^{-1}$.سم$^{-1}$. الطريقة المقترحة لا تحتاج إلى السيطرة على درجات الحرارة أو الاستخلاص بالمذيب. لقد تمت دراسة تأثير عدد من المذيبات العضوية وتركيب الصبغة وثابت الاستقرارية والمتداخلات، وطبقت الطريقة بنجاح لتقدير الميتوكلوبراميد في نماذج مختلفة من المستحضرات الدوائية الحبوب والشراب والقطرات.

INTRODUCTION

Metoclopramide hydrochloride (MCP), 4-amino-5-chloro-2-methoxy-N-(2-diethylamino-ethyl) benzamide, is used as an anti-emetic in the treatment of some forms of nausea and vomiting and also to increase gastrointestinal motility. It is of little benefit in the prevention for treatment of motion sickness or in the treatment of nausea and vertigo due to Meniere disease or other labyrinth disturbance (Tas *et al*., 2006). Many analytical methods have been developed for the determination of MCP, the most of them are spectrophotometric methods based on diazotization and coupling with dibenzoylmethane (Revanasiddappa and Manju, 2001), benzoylacetone (Omran, 2005), aniline (Shah *et al.,* 2005), β-naphthol (Patel *et al*., 2006), impramine hydrochloride (Revanasiddappa and Veena, 2006) and 2,4-dihydroxyacetophenone (Khalil, 2010). other spectrophotometric methods involve iona ssociation complex formation (Abdel-Gawad and El-Guindi, 1995), an oxidative coupling reaction (Al-Talib and Mohammed, 1996; Ahmed and Ali, 2006), charge-transfer complex formation (Al-Gabsha *et al*., 2004), Redox reaction (Amin and Ragab, 2003), or through formation of the Schiff's base with p-(dimethylamino) cinamaldehyde (Moussa, 2000). Other methods based on fluorimetric (Attia and Aboaly, 2010), Flow injection (Al-Arfaj, 2004), chromatographic techniques (Radwan, 1998, Cossa *et al.,* 2008; Shaabani and Adergani, 2009), voltammetry (Farghaly *et al.,* 2005) and H^1 NMR spectroscopy (Hanna and Lau-Cam, 1991). Some of these methods suffer from several disadvantage, such as, use of heating step, low range of determination and critical working conditions and poor selectivity. Other methods are typically less sensitive, relatively complicated, or require expensive instrumentation. The British pharmacopoeia reported a potentiometric method using perchloric acid solution for the determination of MCP powder and a UV method for tablets and ampoules (British Pharmacopoeia, 1998). The potentiometric method requires about 250 mg of drug, whereas the UV method is liable to interferences from tablets excipients, and requires pre-extraction with chloroform. These deficiencies have encouraged the authors to develop a simple, selective, sensitive and inexpensive method for the analysis of the studied drug. The present work describes the application of 8-hydroxyquinoline as a coupling agent for the determination of MCP in both pure form and pharmaceutical preparations.

EXPERAMENTAL

Apparatus

The absorption spectra were recorded on a double-beam Shimadzu UV-Visible recording spectrophotometer UV-160 with 1.0 cm matched silica cells. The absorbance measurements were obtained using single–beam Unico 1100 spectrophotometer with 1-cm plastic cells. pH measurements were preformed using Philips PW 9420 pH meter.

Reagents

All chemical used were of analytical grade reagent.

- **MCP (100 µg / ml)solution**. It was prepared by dissolving 0.01 g of MCP in distilled water and the volume was completed to 100 ml with distilled water in a volumetric flask. The solution was then transferred to a dark bottle and is stable for at least one month. Working solution of MCP was prepared by appropriate dilution of the stock solution with distilled water.
- **8-Hydroxyquinoline (0.2 %) solution**. It was prepared by dissolving 0.20 g of 8-hydroxyquinoline reagent (Hopkin and Williams) in 2 ml acetic acid and the volume was completed to 100 ml with distilled water in a volumetric flask.
- **Sodium nitrite (1%) solution**. This solution has been prepared by dissolving 1.0g of sodium nitrite (BDH) in 100 ml distilled water.
- **Sulphamic acid solution, 3% (w/v)**.This solution was prepared by dissolving 3.0 g of sulphamic acid (Fluka) in 100 ml distilled water.
- **Solutions of 1M KOH and 1M HNO_3** were also prepared.

Recommended Procedure and calibration curve

An aliquot of standard solution (5-500) µg of MCP was transferred into a series of 25-ml volumetric flask. To each flask, 1 ml of nitric acid solution and 0.5 ml 1% sodium nitrite solution were added. The reaction mixture was allowed to stand for 5 min after mixing thoroughly. A 0.3 ml of 3% sulphamic acid solution was added with occasional shaking for 4 min followed by addition of 2.5 ml of 0.2 % 8-hydroxyquinoline, the solutions were left for 3 min at room temperature and 3 ml of 1M potassium hydroxide was added and the contents were diluted to the mark with distilled water and mixed well. The absorbance of the formed coloured azo dye was measured at 528 nm against the corresponding reagent blank. A linear calibration graph was obtained over the concentration range of (5-300) µg of MCP/25ml. Higher concentrations show a negative deviation from Beer's law (Fig.1). The apparent molar absorptivity has been found to be 3.1×10^4 $l.mol^{-1}.cm^{-1}$.

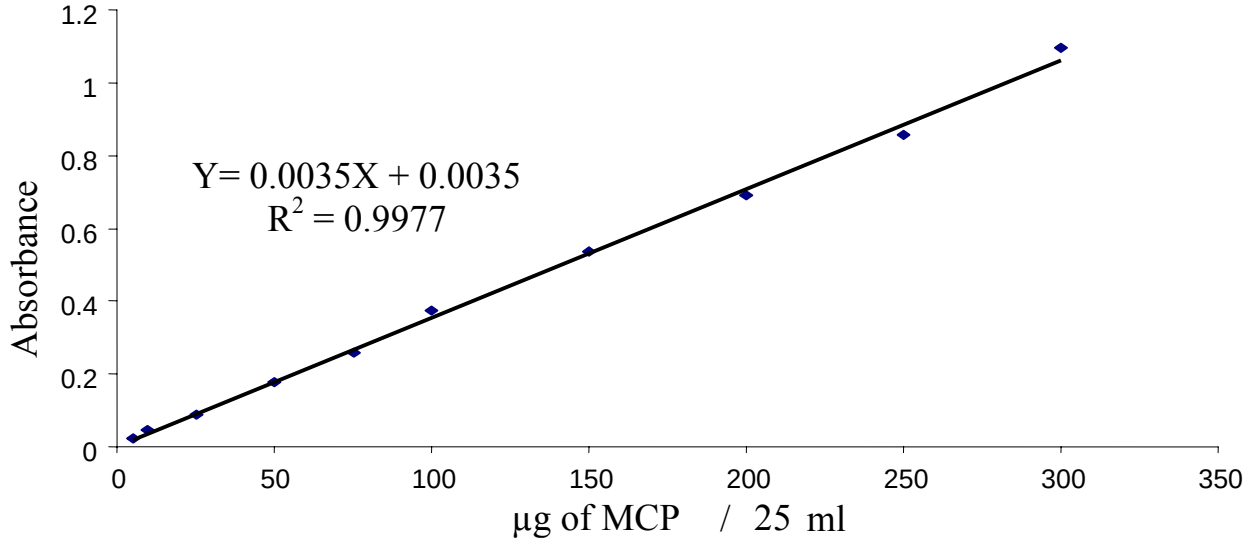


Fig. 1. Calibration graph for MCP determination

Procedure for dosage forms

For tablets: A ten tablets (5 mg MCP-HCl / tablet) of the drug were weighed, powdered and mixed well. A portion equivalent to 0.01 g was weighed and dissolved in 50 ml of distilled water, shaken well, filtered and diluted with water to 100 ml in a volumetric flask. An aliquot of the diluted drug solution was then treated as done in a recommended procedure.

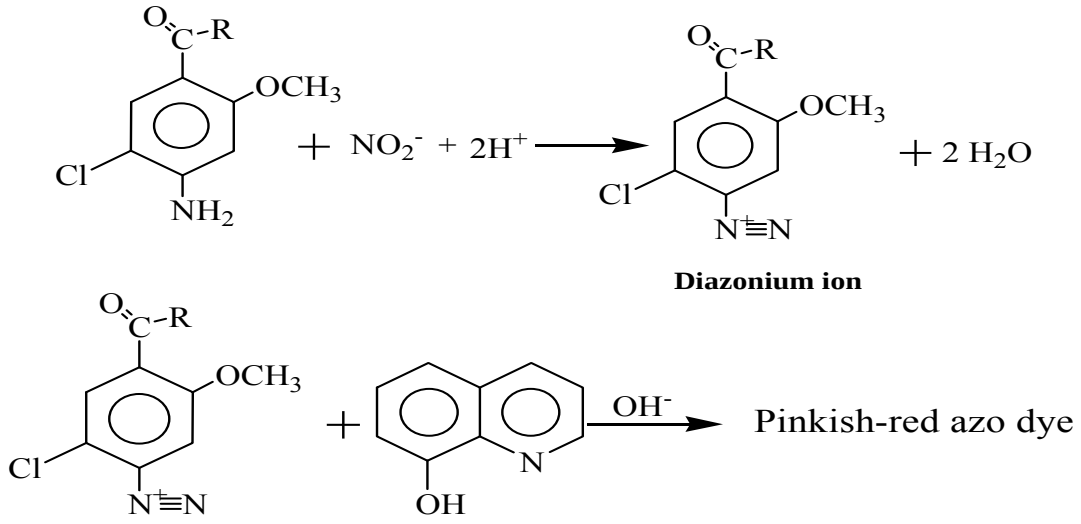
For syrups: The content of the container of MCP syrup (5 mg MCP-HCl/5 ml) was mixed well and 2 ml of the syrup was quantitatively transferred into 100 ml volumetric flask and completed to the work with distilled water. An aliquot of the diluted drug solution was then treated as done in recommended procedure.

For drops: An accurate volume 2.5 ml of MCP drops (4 mg MCP-HCl / ml) was transferred into a 100 ml volumetric flask and completed to the mark with distilled water, then it was proceeded as described under recommended procedure.

RESULTS AND DISCUSSION

Principle of the colour reaction

Under the reaction conditions, metoclopramide was treated with nitrite solution in acidic medium, which undergoes diazotization reaction to give the diazonium salt. The diazonium salt was coupled with 8-hydroxyquinoline as a coupling agent in a basic medium to form an intensely-coloured azo dye :



R= $-NH(CH_2)_2N(C_2H_5)_2$

The formed coloured dye exhibited absorption maxima at 528 nm against reagent blank solution. The intensity of the formed dye has been found to be proportional to the amount of metoclopramide originally present in solution.

Effect of diazotization acid

Different amount of various acids such as HCl, CH_3COOH, HNO_3 and H_2SO_4 have been studied in diazotization of MCP for the purpose of producing intense coloured dye, strong colour contrast and lower blank value. The experimental results showed that 1 ml of 1M HNO_3 solution was selected for the reaction because it gave high intensity for the dye with a corresponding low reagent blank absorbance.

Effect of sodium nitrite amount and time

The effect of different amount (0.1-2.0) ml of 1% sodium nitrite with time on the absorbance of the resulting azo dye has been investigated. The results in Table 1 show that 0.5 ml of 1% sodium nitrite solution with 5 min reaction time was optimum and it was recommended for the subsequent experiment .

Table 1: Effect of sodium nitrite amount and time on absorbance.

ml of $NaNO_2$ solution (1%)	Absorbance / min standing time						
	0	**1**	**2**	**3**	**4**	**5**	**7**
0.1	0.210	0.215	0.215	0.200	0.232	0.256	0.251
0.3	0.222	0.242	0.239	0.239	0.239	0.254	0.243
0.5	0.249	0.249	0.247	0.256	0.225	0.305	0.300
0.7	0.264	0.242	0.255	0.250	0.243	0.258	0.257
1.0	0.285	0.271	0.256	0.279	0.266	0.261	0.234
2.0	0.237	0.254	0.258	0.249	0.265	0.268	0.221

Effect of sulphamic acid amount and time

It was found from the experimental results that 0.3 ml of 3% sulphamic acid with 4 min standing time have been incorporated for the development of the formed coloured azo dye (Table 2).

Table 2: Effect of sulphamic acid amount and time on absorbance.

ml of 3% sulphamic acid	Absorbance / min standing time						
		0	**1**	**2**	**3**	**4**	**5**
0.1	S	0.214	0.295	0.239	0.202	0.298	0.274
	B	0.008	0.004	0.010	0.008	0.000	0.003
0.3	S	0.219	0.248	0.258	0.369	0.378	0.273
	B	0.003	0.006	0.000	0.004	0.000	0.004
0.5	S	0.222	0.274	0.271	0.279	0.278	0.278
	B	0.008	0.007	0.000	0.004	0.000	0.004
0.7	S	0.192	0.298	0.254	0.279	0.282	0.247
	B	0.008	0.010	0.000	0.003	0.000	0.003

Effect of 8-hydroxyquinoline amount

The effect of 8-hydroxyquinoline amount on the absorbance of the azo dye has been studied (Table 3). It was observed from the results that 2.5 ml of 0.2 % 8-hydroxyquinoline solution and 3 min of reaction time was the more suitable to give the highest intensity value for the azo dye.

Table 3: Effect of 8-hydroxyquinoline amount.

ml of 8-hydroxyquinoline (0.2%) solution	Absorbance / min standing		
	0	1	3
0.25	0.199	0.234	0.264
0.5	0.195	0.204	0.229
1.5	0.242	0.246	0.264
2.0	0.227	0.239	0.298
2.5	0.307	0.318	0.321
3.0	0.087	0.063	0.046
4.0	0.067	0.043	0.034

Effect of base

The preliminary investigations showed that the coupling of 8-hydroxyquinoline with diazotized metoclopramide to produce the coloured azo dye was developed only in a basic medium. Therefore, different amounts (1-3 ml of 1M solutions) of various bases have been examined for the purpose of producing intense coloured dye with a strong colour contrast and lower blank value. The results indicate that the formation of the coloured azo dye needs a strong basic medium (Table 4). Sodium carbonate and ammonium hydroxide exhibited weak colour contrast which is apparently due to pH variation. Therefore, 3 ml of 1M KOH has been recommended for the subsequent experiments.

Table 4: Effect of base on absorbance.

Base used (1M)	Absorbance / ml of base added		
	1	2	3
NaOH	0.015	0.293	0.216
Na_2CO_3	0.039	0.033	0.036
NH_4OH	0.018	0.011	0.012
KOH	0.022	0.356	0.360*

* pH of the final solution =12.6

Effect of surfactants

The presence of surfactants in a coloured reaction mixture solution may frequently lead to an increase in the absorbance and a shift in the wavelength to higher values. In this respect, sodium dodecyl sulphate (SDS) (anionic surfactant), cetyltrimethylammonium bromide (CTAB) (cationic surfactant) and Triton X-100 (non-ionic surfactant) have been

introduced. The results indicated that addition of surfactants gave no useful effect. Therefore, they were omitted in this study.

Development time and stability period

To test the effect of time on the absorbance of the coloured dye at 528 nm, the coloured dye has been prepared from different amounts of metoclopramide under the optimal experimental conditions, and the absorbance were measured at different intervals of time up to 60 min. The experimental results shown in Table 5 indicate that the coloured dye develops immediately and the absorbance remains maximum and constant for at least 30 minutes.

Table 5: Effect of time and concentration on absorbance.

µg of MCP	Absorbance / min									
	0	**5**	**10**	**15**	**20**	**25**	**30**	**40**	**50**	**60**
5	0.020	0.023	0.023	0.024	0.023	0.024	0.023	0.042	0.037	0.032
25	0.092	0.093	0.092	0.091	0.092	0.090	0.090	0.088	0.118	0.099
50	0.180	0.181	0.183	0.182	0.184	0.183	0.181	0.172	0.164	0.165
100	0.373	0.377	0.374	0.371	0.368	0.362	0.357	0.340	0.325	0.309

Absorption spectra

Under the above optimized conditions , a pinkish-red coloured chromophore was formed by coupling of diazotized metoclopramide with 8-hydroxyquinoline in alkaline medium. This coloured dye exhibited an absorption maxima at 528 nm against reagent blank as shown in Fig.2. The corresponding reagent blank shows a negligible absorbance at this wavelength .

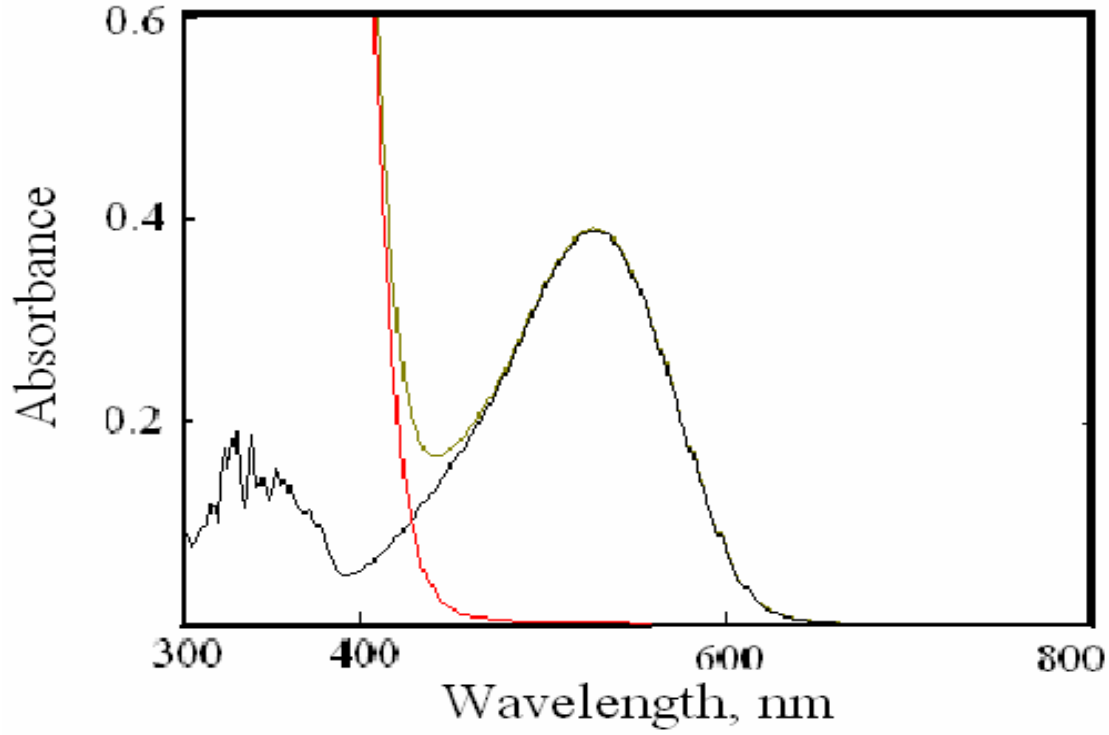


Fig. 2: Absorption spectra of 100 µg of MCP/25 ml measured against (A) blank, (B) distilled water, and (C) blank measured against distilled water.

Nature of the azo dye

The stoichiometry of the product formed from the reaction of diazotized metoclopramide with 8-hydroxyquinoline was investigated by applying the continuous variations method (Job's method) Fig.3.

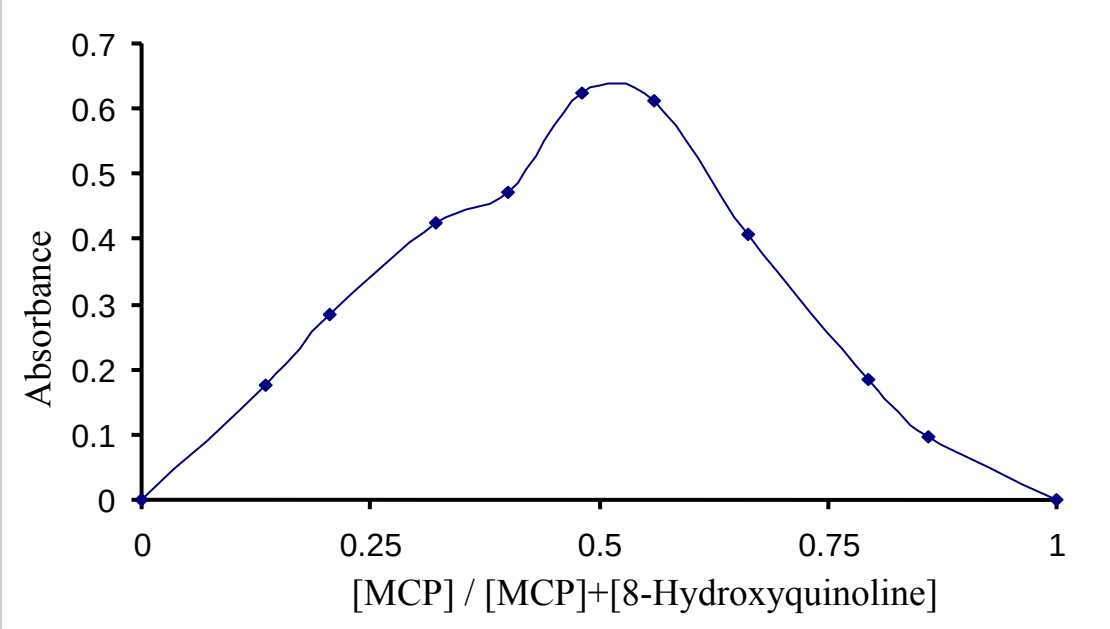
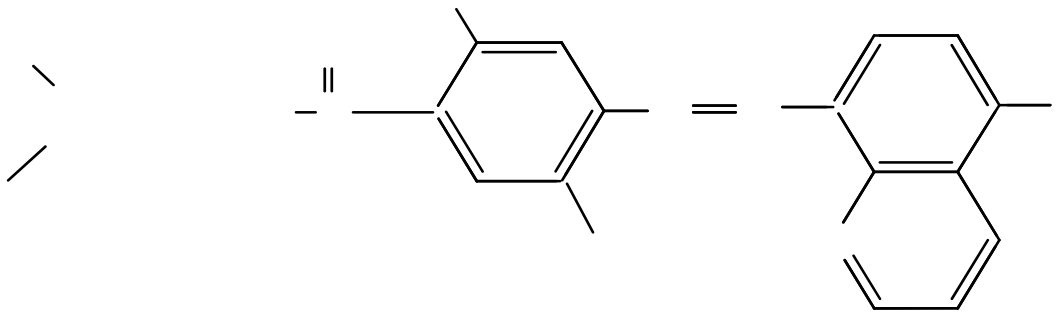


Fig. 3: Job's plot for diazotized MCP - 8-hydroxyquinoline azo dye.

The results indicate that the azo-dye was formed in a ratio of 1:1 indicating a mono azo dye with probably of the following structure.



Pinkish - red azo dye

Accuracy and precision

To check the accuracy and precision of the proposed method , metoclopramide was determined at three different concentrations. The results shown in Table 6 indicate, that the method is satisfactory.

Table 6**:** Accuracy and precision of the proposed method.

Amount of metoclopramide taken, µg	**Recovery, % ***	**Relative standard deviation, % ***
50	100.0	± 0.64
100	98.9	± 0.38
200	100.0	± 0.50

*Average of five determinations.

Effect of organic solvents

Different organic solvents are examined to evaluate their effects on the intensity of the resulting azo dye and the data are shown in Table 7 .

Table 7: Effect of water and organic solvents on the optical properties of the azo dye.

Solvent	Colour		λmax,(nm)	ε ,l.mol^{-1}.cm^{-1}
	Sample	Blank		
Acetic acid	Yellow	Colourless	400	0.8×10^3
Acetone	Pink	Yellow	560	0.68×10^3
1,4-Dioxane	Pink	Colourless	536	1.5×10^3
Ethanol	Pink	Pale Yellow	534	1.4×10^3
Formic acid	Yellow	Colourless	400	0.5×10^3
Methanol	Yellow	Colourless	442	0.6×10^3
n-Butanol	Orange	Pale Yellow	478	1.6×10^3
Water	Pinkish-red	Colourless	528	3.1×10^4

Water is still being the choice in the subsequent experiments due to its availability, non-toxicity as
well as from the sensitivity point of view.

Effect of interferences

In order to test the efficiency and selectivity of the proposed method , the effect of some foreign substances (e.g., acacia, glucose, lactose, lindocaine, menthol and starch), that usually present in dosage forms were studied by adding different amounts of foreign substances to 100 µg metoclopramide / 25 ml. It was observed that the studied foreign species did not interfere in the present method (Table 8).

Table 8: Effect of additives and excipients on the determination of 100 µg of MCP.

Interferences	**Recovery(%) of 100 µg metoclopramide / µg of interfere added**		
	100	**500**	**1000**
Acacia	98.6	97.1	95.6
Glucose	96.8	94.2	95.6
Lactose	96.3	96.3	94.8
lindocaine	95.6	96.8	101.4
Menthol	98.6	99.1	100.8
Starch	99.3	96.2	97.5

Application of the method

The proposed method was successfully applied to the determination of Metoclopramide -HCl in its pharmaceutical preparations (tablet, syrup and drop). The results which are shown in Table 9 indicate that a good recovery was obtained.

Table 9: Analytical applications.

Metoclopramide amount, µg	**Recovery(%) of metoclopramide***		
	Meclodin (5mg/ tablet) NDI-Iraq	**Meclodin syrup (5mg/5ml) NDI-Iraq**	**Meclodin drops (4mg/ml) NDI-Iraq**
5	95.8	100.0	95.8
50	95.0	95.0	100.0
100	101.6	98.9	103.7

* Average of five determinations.

The performance of the proposed method was assessed by calculating the student's t-test and F-test compared with the literature method (Khalil, 2010). The results in Table 10 show that the calculated values of t and F did not exceed the theoretical values at the 95% confidence level for eight degrees of freedom indicating that there is no significant difference between the proposed method and the literature method.

Table 10: Determination of metoclopramide in pharmaceutical preparations.

Drug	MCP amount, (µg)	Pharmaceutical preparation	Recovery, * %			
			Present method	Literature method (Khalil , 2010)	t-exp	F-exp
Meclodin (5mg/ tablet) SDI-Iraq	100	Tablet	101.36 ± 0.56	101.24 ± 0.4	0.4	3.9944
Meclodin (5mg/5ml) SDI-Iraq	100	Syrup	99.24 ± 0.5	98.62 ± 0.37	2.3	4.0062
Meclodin (4mg/ml) NDI-Iraq	100	Drops	103.7 ± 0.5	103.48 ± 0.39	1.6	1.8548

* Average of five determinations.

Comparison of the methods

Table 11, shows the comparison between some of analytical variables for the present method with that of another literature spectrophotometric methods.

Table 11: Comparison of the methods.

Analytical parameters	Present method	Literature method (Khalil, 2010)	Literature method (Al-Talib and Mohammed, 1996)
Coupling condition	Alkaline medium	Alkaline medium	Acidic medium
λmax (nm)	528	450	612
Reagent	8-Hydroxyquinoline	2,4-Hydroxyacetophenone	Phenothiazine
Type of method	Azo coupling	Azo coupling	Oxidative coupling
Beer's law range, ppm	0.2 - 12	0.4-12	0.1-16
Molar absorptivity , $l.mol^{-1}.cm^{-1}$	3.1×10^4	2.48×10^4	1.65×10^4
Application of the method	Tablets , syrup and drops	Tablets , syrup and injection	Tablets

The results indicate that the proposed method is more sensitive than the literature methods .

CONCLUSIONS

The developed spectrophotometric method for the assay of MCP is simple, sensitive, selective, inexpensive and exhibits a fair degree of precision and accuracy. Beer's law was obeyed over the concentration range of 5-300 μg / 25 ml . with a molar absorptivity 3.1×10^4 $l.mol^{-1}.cm^{-1}$and a relative standard deviation of ±0.38 to ±0.64% depending on concentration level .The method does not involve any critical reaction conditions and can be compared favorably with other existing methods. The proposed method can serve as an alternative method for the analysis of MCP in pure form and in pharmaceutical formulations.

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