

Spectrophotometric determination of metoclopramide hydrochloride in pharmaceutical tablets, by diazotization-coupling method with 1-naphthol as the coupling agent*Raghad Sinan**

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Abstract

Simple, rapid and sensitive spectrophotometric method was proposed for the analysis of metoclopramide hydrochloride (MPH) in pure form as well as in pharmaceutical tablets. The method is based on the diazotization reaction of MPH with sodium nitrite in hydrochloric acid medium to form diazonium salt, which is coupled with 1-naphthol in sodium hydroxide medium to form azo dye, showing absorption maxima at 550 nm. Beer's law is obeyed in the concentration range of 0.4 – 18 $\mu\text{g mL}^{-1}$ of MPH with detection limit 0.5448 $\mu\text{g mL}^{-1}$. The molar absorptivity and Sandell's sensitivity are $3.4969 \times 10^4 \text{ L mol}^{-1} \text{ cm}^{-1}$ and $0.0101 \mu\text{g cm}^{-2}$, respectively. The method was successfully applied to the determination of MPH in pharmaceutical tablets without any interference from common excipients used as additives in tablets. The results agree favorably with the official British Pharmacopoeia method.

Keywords: Spectrophotometric; Diazotization; Metoclopramide hydrochloride; 1-Naphthol; Pharmaceutical tablets.**Introduction**

Metoclopramide hydrochloride (MPH), 4-amino-5-chloro-N-[2-(diethylamino)ethyl]-2-methoxybenzamide hydrochloride, is a white crystalline powder [1]. It is widely used in the treatment of patients with delayed gastric emptying due to postsurgical disorders (vagotomy, antrectomy) and diabetic gastroparesis. MPH is sometimes administered in hospitalized patients to promote advancement of nasogastric feeding tubes from the stomach into the duodenum [2]. In this perspective, the wide applications of MPH in both clinical and experimental medicine have prompted extensive interest in its determination.

A number of the analytical techniques available in the literature for the quantification of MPH involve amperometric and potentiometric

titrations [3], potentiometry [4], voltammetry [5-7], reversed phase high performance liquid chromatography [8, 9], spectrophotometry [10-13], second derivative synchronous fluorometry [14] and chemiluminescence [15].

The British Pharmacopoeia (BP) reported a potentiometric method for the determination of MPH powder and UV method for tablets [16]. The potentiometric method requires about 250 mg MPH. The UV method is liable to interferences from tablet excipients and requires pre-extraction of MPH with chloroform.

Diazotization and coupling reactions were used for determination of MPH by diazotization reaction of MPH and coupling with different coupling agents as shown in Table (1). These reactions required removing of excess of sodium

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nitrite by sulfamic acid [21, 23] or ammonium sulfamate [18, 19], also required diluting the azo dye by methanol [21] or hydrochloric acid [23], heating step [22], high concentration of sodium hydroxide as alkaline medium for coupling reaction [21, 22] and low range of determination [20, 23].

These deficiencies have encouraged proposing a safe, simple, rapid sensitive, selective and accurate method using spectrophotometric detection at 550 nm for determination of MPH in pharmaceutical tablets. The method is based on the diazotization reaction of MPH with sodium nitrite in hydrochloric acid medium; the formed diazonium salt is then coupled with 1-naphthol in sodium hydroxide medium to form a purplish violet water-soluble mono azo dye. This method does not need to get rid of excess sodium nitrite (by addition sulfamic acid or ammonium sulfamate) because of the low concentration of sodium nitrite used in equimolar solution of MPH and sodium nitrite. The proposed method has been successfully applied to the determination of MPH in pharmaceutical tablets.

Table (1): Spectrophotometric methods for determination of MPH using diazotization and coupling reactions

Reagent	λ_{max} nm	Linear range, μg mL^{-1}	Ref.
NED	525	0.4 – 11	17
Terbutaline sulfate	440	0.5 – 10	18
1-naphthylamine	510	0.1 – 11	
Thymol	495	1 – 11	19
Resorcinol	415	1 – 6	20
DBM	440	1 – 12	21
Aniline	410	0.5 – 12	22
Imipramine	570	0.5 – 5	23

NED = N-(1-naphthyl)ethylenediamine dihydrochloride, DBM = Dibenzoyl methane, Ref. = Reference

Material and Methods:

Apparatus

A Shimadzu UV-VIS 260 (Tokyo, Japan) digital double-beam recording spectrophotometer was used for all

spectral and absorbance measurements with matched 1-cm quartz cells.

Reagents

All chemicals were of analytical reagent grade.

- 1- MPH stock standard solution $1000 \mu\text{g mL}^{-1}$ was prepared by dissolving 0.1000 g of pure MPH (SDI) in distilled water and diluting to the marked in 100 mL volumetric flask. Working standard solution $100 \mu\text{g mL}^{-1}$ was prepared by diluting 10 mL of this stock standard solution with distilled water in 100 mL volumetric flask.
- 2- Sodium nitrite solution $5 \times 10^{-3} \text{ M}$ was prepared by dissolving 0.0690 g of sodium nitrite (Merck) in distilled water and diluting to the marked in 200 mL volumetric flask. Then, $2.82 \times 10^{-4} \text{ M}$ was prepared by diluting 14.1 mL of sodium nitrite solution ($5 \times 10^{-3} \text{ M}$) with distilled water in 250 mL volumetric flask.
- 3- Hydrochloric acid solution 1 M was prepared by diluting 43 mL of 11.64 M of concentrated hydrochloric acid (BHD) with distilled water in 500 mL volumetric flask.
- 4- 1-Naphthol solution 0.1% w/v was prepared by dissolving 0.1000 g of 1-naphthol (BHD) in ethanol (BHD) and diluting to the marked with same solvent in 100 mL volumetric flask.
- 5- Sodium hydroxide solution 4 M was prepared by dissolving 16.0000 g of sodium hydroxide (BHD) in distilled water and diluting to the marked in 100 mL volumetric flask.

Pharmaceutical preparations of metoclopramide hydrochloride

Pharmaceutical preparations were obtained from commercial sources.

- 1- Meclodin tablets (SDI, Iraq): 5 mg metoclopramide hydrochloride for each tablet.

- 2- Meclodin tablets (SDI, Iraq): 10 mg metoclopramide hydrochloride for each tablet.
- 3- Metoclopramide tablets (Ajanta Pharma Limited, India): 10 mg metoclopramide hydrochloride for each tablet.

Analytical procedure for calibration

An aliquot of a standard solution ($100 \mu\text{g mL}^{-1} = 2.82 \times 10^{-4} \text{ M}$) containing 0.1 – 4.5 mL of MPH was transferred into a series of 25 mL calibrated flasks. To this solution was added equimolar of sodium nitrate solution ($2.82 \times 10^{-4} \text{ M}$) and the acidity was adjusted with 3 mL of 1 M hydrochloric acid solution. The solution was shaken thoroughly. Then, 3 mL of 0.1% 1-naphthol and 2 mL of 4 M sodium hydroxide solutions were added and the contents were diluted to the mark with distilled water and mixed well. After 5 min, the absorbance of the colored azo dye was measured at 550 nm against the corresponding reagent blank.

Procedure for the assay of tablets solution ($1000 \mu\text{g mL}^{-1}$)

The average tablet weight was calculated from the contents of 20 tablets that had been finely powdered and weighed. A portion of this powder, equivalent to 100 mg of MPH, was accurately weighed. The sample was dissolved in distilled water and filtered into a 100 mL volumetric flask, the residue was washed and finally the volume was diluted to the marked with distilled water.

Further appropriate solution ($100 \mu\text{g mL}^{-1}$) was made by using distilled water. Two different concentrations of this tablets solution were analyzed in five replicate by analytical spectrophotometric procedure.

Results and discussion

Preliminary studies

Throughout the preliminary study on the diazotization reaction of MPH, with sodium nitrite in hydrochloric acid medium; the formed diazonium salt is then coupled with 1-naphthol in sodium hydroxide medium, a purplish violet water-soluble azo dye was obtained with a maximum absorbance at 550 nm [Fig. (1)]. The absorbance of the azo dye solution measured versus reagent blank which has negligible absorbance at this wavelength.

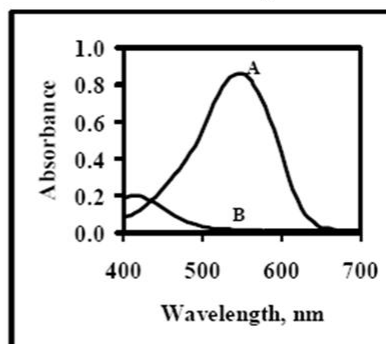


Fig. (1): Absorption spectra of the azo dye against reagent blank (A) and reagent blank against distilled water (B)

Optimization of the experimental conditions

The effect of various variables on the color development was studied to establish the optimum conditions for the determination of MPH.

In the subsequent experiments, 2 mL of MPH solution ($100 \mu\text{g mL}^{-1} = 2.82 \times 10^{-4} \text{ M}$) with equimolar of sodium nitrite solution (2 mL of $2.82 \times 10^{-4} \text{ M}$) was taken in 25 mL final volume and the absorbance of a series of solutions were measured by varying one and fixing the other parameters at 550 nm versus reagents blanks.

This method does not need to get rid of excess sodium nitrite (by

addition of sulfamic acid or ammonium sulfamate) because of the low concentration of sodium nitrite used in equimolar solution of MPH and sodium nitrite.

The effect of different volumes of 1 M hydrochloric acid solution (0.3 – 5.0 mL) (used in diazotization reaction of MPH), 0.1% 1-naphthol solution (0.3 – 6.0 mL) and 4 M sodium hydroxide solution (0.5 – 5.0 mL) were examined on the maximum absorbance of the azo dye. Fig. (2) shows that 3 mL of hydrochloric acid solution (1 M), 3 mL of 1-naphthol solution (0.1% w/v) and 2 mL of sodium hydroxide solution (4 M) were enough to obtain the maximum absorbance.

The purplish violet azo dye was only formed in alkaline medium. Therefore, the effects of different alkaline solutions were studied such as sodium carbonate, potassium hydroxide, sodium hydroxide and ammonium hydroxide. It was found that sodium hydroxide is the most suitable alkaline medium to produce a maximum absorbance and was used in all subsequent experiments.

To obtain optimum results, the order of addition of reagents should be followed as given under the analytical procedure, otherwise a loss in color intensity and stability were observed.

The stability of the dye was studied for 2 h following the mixing of the reagents. The colored azo dye developed rapidly after mixing and attained maximum absorbance about 2 min at room temperature. The color was stable for a period of 2 h.

The effect of temperature on the diazotization and coupling reaction show that the absorbance of the azo dye remains constant in the range 0 – 30°C and decrease up to 30 °C. Therefore, it has been recommended to carry out reaction at room temperature

(25°C) and cooling to 0 – 5°C was not necessary.

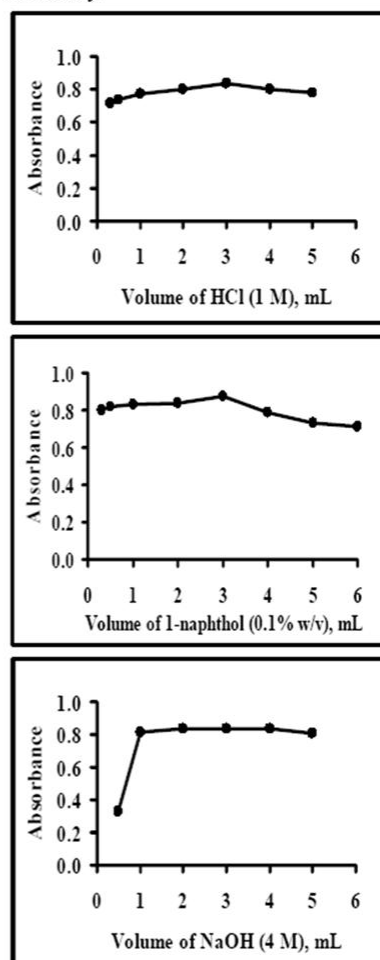


Fig. (2): Optimum conditions for determination of MPH

The stoichiometry of the product was studied applying the continuous variation method. Volumes of 1 – 6 mL of 2.82×10^{-4} M portions of MPH (V_D) were diazotized and coupled according to analytical procedure with the corresponding complementary volume of 2.82×10^{-4} M 1-naphthol solution (V_R) to give a total volume of 6 mL for $V_D + V_R$. The results obtained in Fig. (3) shows that a 1 : 1

azo dye was formed between diazotized MPH and 1-naphthol.

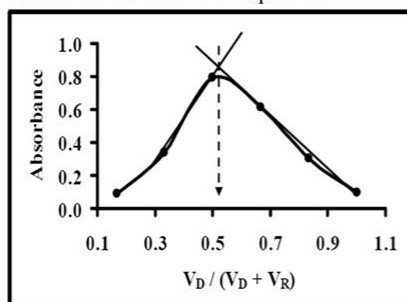
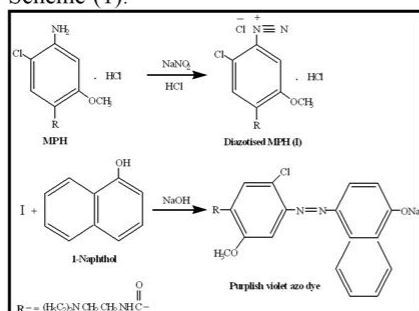


Fig. (3): Continuous variation plot

For the diazotization process; it would be expected that NH_2 group in MPH would be readily diazotized in a hydrochloric acid medium, and that diazonium group would then react with a molecule of 1-naphthol by electrophilic substitution at the 4-position of the coupling agent to produce an intense purplish violet azo dye in sodium hydroxide medium. An investigation of the continuous molar variation of diazotized MPH and 1-naphthol showed that diazotized MPH interacts with 1-naphthol in the ratio of 1 : 1. A reaction sequence based on the above results is shown in Scheme (1).



Scheme (1): Reaction sequence

The formation constant of the reaction product (K_f) was calculated adopting the following formula [24]:

$$K_f = (A / A_m) / [(1 - A) / A_m]^{n+1} C^n n^n$$

Where A is maximum absorbance, A_m is the absorbance corresponding to intersection of the two tangents of the curve in Fig. (3), C is the concentration corresponding to maximum absorbance, n is the amount of the MPH in reaction product. Using this equation, K_f was found to be equal to $4.502 \times 10^5 \text{ L mol}^{-1}$.

The Gibbs free energy of the reaction (ΔG) was also calculated adopting the following equation [24]:

$$\Delta G = -2.303 R T \log K_f$$

Where R is the universal gas constant and T is the absolute temperature.

The value of ΔG was found to be $-32.27 \text{ KJ mol}^{-1}$. The negative sign of ΔG points out to the spontaneous nature of the reaction.

In order to assess the possible analytical applications of the proposed method. The effect of some common excipients frequently found with MPH in pharmaceutical tablets such as lactose, starch, talc, magnesium stearate and polyvinylpyrrolidone (PVP) was studied by analyzing synthetic sample solutions containing $8 \mu\text{g mL}^{-1}$ of MPH and excess amounts (10-fold excess) of each excipient, none of these substances interfered seriously [Table (2)].

Table (2): Determination of $8 \mu\text{g mL}^{-1}$ of MPH in the presence of excipients

Excipient, $80 \mu\text{g mL}^{-1}$	Concn. of MPH, $\mu\text{g mL}^{-1}$	Erel. ^a , %	Rec. ^b , %	RSD ^c , %
	Found ^a			
Lactose	7.933	0.838	99.162	0.933
Starch	7.911	1.113	98.887	0.688
Talc	8.093	1.163	101.163	0.471
Mg stearate	7.951	0.613	99.387	0.891
PVP	8.104	1.300	101.300	0.747

^a Average of five determinations.
^b Erel. is relative error. ^c Rec. is recovery,
^c RSD is relative standard deviation

Analytical characteristics of the proposed method

The calibration graph was obtained by the analytical procedure described previous and a series of standard solutions were analyzed in triplicates to test the linearity. The molar absorptivity (ϵ), the Sandell sensitivity (S), the intercept (a), the slope (b), the correlation coefficient (r), the correlation of determination (r^2), were evaluated by a least-squares regression analysis and are included in Table (3). Beer's law plot ($n = 11$) was linear with very small intercept and good correlation coefficient in the concentration range in Table (3).

Statistical evaluation [25] of the regression line gave the values of standard deviations for residuals ($S_{y/x}$), intercept (S_a) and slope (S_b) at 95% confidence are shown in Table (3). These small figures point out to the high precision of the proposed method.

The limit of detection (LOD) and limit of quantitation (LOQ) were determined using the formula: LOD or $LOQ = k S_a / b$, where $k = 3$ for LOD and 10 for LOQ. The LOD and LOQ values are shown in Table (3).

Table (3): Data for the calibration graph for MPH using the proposed method

Parameter	Value
Linearity range, $\mu\text{g mL}^{-1}$	0.4 – 18
r	0.9986
r^2	0.9971
ϵ , $\text{L mol}^{-1} \text{cm}^{-1}$	3.4969×10^4
S, $\mu\text{g cm}^{-2}$	0.0101
a	0.0011
b, $\text{mL } \mu\text{g}^{-1}$	0.0987
$S_{y/x}$	3.4382×10^{-2}
S_a	1.7924×10^{-2}
S_b	1.7598×10^{-3}
LOD, $\mu\text{g mL}^{-1}$	0.5448
LOQ, $\mu\text{g mL}^{-1}$	1.8160
Erel. %*	-0.0507**
RSD ^o *	0.8140**

* For $8 \mu\text{g mL}^{-1}$ of MPH.
** Average of five determinations.

Accuracy and precision of the proposed method

The accuracy and precision of the proposed method were tested by analyzing five replicate samples of MPH by analytical procedure. The low value of the percentage error (Erel.%) are summarized in Table (3). The percentage relative standard deviation (RSD%) was found to be low. These values indicate the high accuracy and precision of the proposed method.

Pharmaceutical applications

In order of demonstrate the applicability of the proposed method to the determination of MPH, the method was applied to the analysis of MPH in various samples of tablets.

The proposed method where successfully applied to the analysis of different tablets containing MPH and the results are summarized in Table (4). When different tablets of MPH were analyzed by the proposed method, interference from the sample matrix posed no problem. For all the tablets examined, the assay results of proposed method were in good agreement with the declared content.

Table (4): Pharmaceutical applications for MPH using the proposed method

Pharmaceutical preparation	Concn. of MPH, $\mu\text{g mL}^{-1}$		Erel. %	Rec. %	RSD, %
	Present	Found*			
Meclodin Tablets- 5	4.000	3.935	-	98.375	0.932
	10.000	9.970	0.250	99.750	0.678
Meclodin Tablets-10	4.000	3.956	-	98.900	1.109
	10.000	9.899	1.010	98.990	1.006
Metoclopramide Tablets	4.000	4.081	+	102.025	0.810
	10.000	10.099	0.990	100.990	0.787

*Average of five determinations.

The results obtained by the proposed method were compared with BP method [16] [Table (5)] by applying the F-test and the t-test at 95% confidence level.

Table (5): Comparison of the proposed method with BP method for determination of pharmaceutical tablets

Pharmaceutical tablets	Rec.*%	
	Proposed method	BP method
Pure MPH	100.000	100.000
Meclostin-5 Tablets	99.063	98.900
Meclostin-10 Tablets	98.945	99.400
Metoclopramide Tablets	101.508	99.520

***Average of five determinations.**

The calculated values for F-test (6.871) and t-test (0.669), did not exceed the critical values of $F_{3,3} = 9.277$ and $t = 2.447$ ($n_1 + n_2 - 2 = 6$). These confirming that there are no significant differences between the proposed method and BP method with respect to precision and accuracy in the determination of MPH in tablets.

Conclusions

The proposed method was found to be simple, rapid, economical, selective, sensitive and good color stability.

It can be concluded that, the present method has the advantages of high sensitivity over the BP method, since the minimum quantifiable limit was taken as $0.4 \mu\text{g mL}^{-1}$ for MPH by the proposed method. Concerning the published UV methods, necessitate pre-treatment procedures involving extraction of the active ingredient to avoid interference from tablet excipients. However, the present method is simple as there is no need for solvent extraction or separation steps before the analysis, since no interferences were observed from tablet excipients.

Additionally to these advantages, the proposed method is accurate and precise as indicated by the good recoveries of MPH and low RSD values. There is no significant difference between the proposed method and BP method with respect to precision and accuracy.

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التقدير الطيفي لهيدروكلوريد الميتوكلوبراميد في الأقراص الصيدلانية بطريقة الأزوتة و الازدواج مع 1 نفثول كعامل الازدواج

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الكلمات المفتاحية: التقدير الطيفي، الأزوتة، هيدروكلوريد الميتوكلوبراميد، 1- نفثول، الأقراص الصيدلانية.

الخلاصة

أُقتُرحت طريقة بسيطة و سريعة و حساسة لتحليل هيدروكلوريد الميتوكلوبراميد في الشكل النقي و كذلك في الأقراص الصيدلانية. تعتمد الطريقة على تفاعل الأزوتة لهيدروكلوريد الميتوكلوبراميد مع نترتيت الصوديوم في وسط حامض الهيدروكلوريك لتكوين ملح الديازونيوم الذي يزدوج مع 1- نفثول في وسط هيدروكسيد الصوديوم لتكوين صبغة أزو تعطي أقصى امتصاص عند طول موجي 550 نانومتراً. و التي تطيع قانون بير عند مدى التركيز 0.4-18 مايكروغرام مل⁻¹ هيدروكلوريد الميتوكلوبراميد و بحد كشف 0.5448 مايكروغرام مل⁻¹. و إن قيمة الامتصاصية المولارية و حساسية ساندل 2.42×10^4 لتر مول⁻¹ سم⁻¹ و 0.0015 مايكروغرام سم⁻² على التوالي. طبقت الطريقة بنجاح في تقدير هيدروكلوريد الميتوكلوبراميد في الأقراص الصيدلانية بدون تداخل من قبل المواد المعروفة التي تستعمل كمضافات للأقراص. كانت نتائج الطريقة متوافقة معنوياً مع الطريقة القياسية المعتمدة في دستور الأدوية البريطاني.