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Spectrophotometric Determination of Metoclopramide Hydrochloride in Pharmaceutical Formulations Using Diazotization Coupling Reaction

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Abstract

For the determination of metoclopramide hydrochloride (MCPD) in pharmaceutical formulations, a rapid and straightforward spectrophotometric method has been proposed. The method involves diazotizing the main amino group of MCPD with sodium nitrite followed by coupling reaction with reagent 1,7-Dihydroxynaphthalene (1,7-DHN) to form a stable and colored compound in alkaline medium of sodium hydroxide which showed a maximum absorbance intensity at the wavelength 578 nm. The linearity of developed method has ranged from 1.0 - 15 $\mu g.ml^{-1}$ while the molar absorptivity $2.9867x10^4$ $l.mol^{-1}.cm^{-1}$, RSD% was less than 1.11%. While the LOD and LOQ were 0.059 $\mu g.ml^{-1}$ and 0.198 $\mu g.ml^{-1}$ respectively. The method is appropriate for the determination of MCPD in the presence of other substances that are typically included in dosage forms.

Keywords: Spectrophotometric, metoclopramide hydrochloride, 1,7-dihydroxynaphthalene diazotization, and coupling reaction

طريقة طيفية لتقدير هيدروكلوريد الميتوكلوبراميد في المستحضرات الصيدلانية عبر تفاعل الأزوتة والاقتران

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الخلاصة

لتقدير هيدروكلوريد الميتوكلوبراميد (MCPD) في مستحضراتة الصيدلانية تم اقتراح طريقة طيفية سرعة ومباشره. تضمنت الطريقة تفاعل أزوتة مجموعة الامين الريسية في MCPD باستخدام نتريت الصوديوم ثم الأقتران مع الكاشف
1,7–Dihydroxynaphthalene (1,7–DHN) لتكوين صبغة الآزو مذابة في الوسط المائي ومستقرة وبوجود وسط قلوي من هيدروكسيد الصوديوم والصبغة المتكونة تعطي أعلى امتصاص عند الطول الموجي 578 نانومتر وكانت العلاقة الخطية للطريقة المطورة في مدى من التركيز من 1 الى 15 مايكروغرام. مل–1 ومعامل الامتصاص المولاري 2.9867 × 104 لتر/.مول. سم ، وكان الانحراف

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القياسي النسبي أقل من 1.11% بينما كان حد الكشف وحد التقدير الكمي 0.059 ميكروغرام / مللتر و 0.198 مايكروغرام / مللتر على التوالي. الطريقة الحالية مناسبة لتقديرهيدروكلوريد الميتوكلوبراميد في مستحضرات صيدلانية مختلفة بوجود مواد أخرى يتم تضمينها عادة في المستحضرات الصيدلانية.

1. Introduction

Metoclopramide hydrochloride (MCPD) is Benzamide, 4-amino-5-chloro-N-[2-(diethylamino)ethyl]-2-methoxy-, monohydrochloride, monohydrate with $C_{14}H_{22}ClN_3O_2.HCl.H_2O$ (molecular formula) and the molecular weight is 354.3 g /mol, Figure 1 [1]. MCPD is a white crystalline powder or crystal that dissolves with decomposition at 183 ˚C and has a high solubility in distilled water, is readily soluble in alcohol, and is soluble in methylene chloride [2].

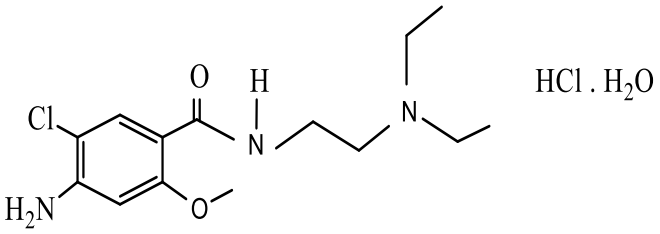


Figure 1: The chemical structure of metoclopramide hydrochloride

In addition to being a gastroprokinetic and an antiemetic, metoclopramide is primarily a dopamine receptor antagonist with 5HT3 receptor antagonist and 5HT4 receptor agonist activity. It also blocks dopamine D2 in the chemoreceptor trigger zone of the medulla, having strong antiemetic and antinausea effects [3,4]. It is frequently used to treat digestive problems, as an anti-emetic and anti-nausea from chemotherapy, migraine, and post-operative [5]; it is also regarded as a first-line treatment for nausea and vomiting during the first trimester of pregnancy [6] and is used to treat diabetic gastroparesis [7].

The most used analytical techniques for MCPD measurement using various reagents are spectrophotometric approaches. Many studies have published techniques employing various reagents such as 3,5-Dimethylphenol [8], 4-Nitrophenol [9], 1-Naphthol [10], p-Nitroaniline [11], Orcinol [12], Iminodibenzyl, and 3-Chloroiminodibenzyl [13] for the majority of the reactions utilized for the detection of MCPD in pharmaceuticals.

Along with other spectrophotometric techniques, including oxidative-coupling reactions [14–16], oxidation-reduction reactions [17], charge transfer complexes [18], ion-pair complexes [19], Schiff's bases [20,21], complexes after oxidation of metoclopramide [22,23], UV method [24], and interaction between the amino groups in MCPD and 1,2-naphthoquinone [25]. Numerous additional methods, including HPLC [26], LC-MS [27], LC-MS/MS [28], flow injection [29], electrochemiluminescence [30]and capillary electrophoresis [31], volumetric oxidation [32], potentiometric sensor [33], molar refraction and polarizability [34], atomic absorption [35], quenched continuous fluorescence [36] and spectrofluorometric [37]., have also been employed to assess MCPD. The majority of these techniques are sensitive and selective, but they may also be costly, necessitate the use of organic solvents, and occasionally require cleaning.

In the current research, a spectrophotometric technique has been developed for the estimation of MCPD using the diazotization and coupling reaction, which is used in the estimation of various drug compounds [38,39]. The current method is based on the diazotization of MCPD and coupling with 1,7-dihydroxy naphthalene in the presence of an alkyl group. Some of the prior methods may have required the use of organic solvents, extraction, or heating, and some of them required expensive equipment.

2. Experimental part

2.1Apparatus

A double-beam Jasco-Japan V-630 UV-VI spectrophotometer was used to measure the absorbance of the product, and the pH of solutions was measured using pH meter type BP3001.

2.2. Chemicals reagents

All the chemicals used in this study were of analytical-reagent grade and high degree of purity.

2.2.1. Sample preparation

Diazotized metoclopramide hydrochloride solution (D-MCPD) (100 µg/mL, $2.822x10^{-4}$M)

The following steps are performed in a dark flask: first, dissolve 0.0100 g of MCPD, which has the molecular formula $C_{14}H_{25}C_{l2}N_3O_3$, in 80 mL of distilled water; next, add an equivalent amount of sodium nitrite, which is dissolved in 10 mL; this produces $2.822x10^{-3}$M ($NaNO_2$ in final volume); finally, add 4.0 mL of hydrochloric acid (1.0 M) and complete to the mark with distilled water.

Diazotized Pharmaceutical Solutions

Tablet solution 100 µg/mL

As each tablet contains 10 mg of metoclopramide hydrochloride, ten tablets (from the pharmaceutical preparation metoclopramide, Darnitsa-Ukraine) were cautiously weighted, smashed, and mixed. The equivalent of 0.0100 g of pure metoclopramide was then weighed and dissolved in 80 ml of distilled warm water, with decent stirring. After that, filtering was performed. Then addition of an equivalent amount of sodium nitrite, which is dissolved in 10 mL; this produces $2.822x10^{-3}$M ($NaNO_2$ in final volume); finally, add 4.0 mL of hydrochloric acid (1.0 M) and complete to the mark with distilled water.

Meclobran injection (10 mg, Brawn, India) was diluted by adding 80 mL of distilled water to it, diazotizing the mixture in the same manner as the standard solution, and then completing the volume to 100 ml with the same solvent in a volumetric flask.

2.2.2. Reagents preparation

Sodium nitrite solution ($2.822 x 10^{-3}$ M) (w/v%)

It was prepared by mixing 100 mL of distilled water with 0.0194 g of sodium nitrite, which was dissolved in the least quantity of distilled water. This mixture was then placed in a volumetric flask.

Reagent solution 1, 7-dihydroxynaphthalene (0. 1 % 1, 7-DHN)

The solution was prepared each day by dissolving 0. 1000 g of the reagent in a few drops of ethanol, diluting it to 100 mL in distilled water, and then placing it in a volumetric flask.

Hydrochloric acid solution (1 M approximately) (v/v %)

A volumetric flask of 100 mL was filled to the desired level with distilled water after adding 8.4 mL of concentrated acid (11.9 M) to a small amount of the liquid.

Sodium hydroxide solution (0.1 M) (%v/v)

An ampoule of NaOH (10 M) was diluted with distilled water to make 1000 mL of the solution. From there, 10.0 mL of the produced solution was taken out and diluted to the level of a 100 mL volumetric flask before being kept in a plastic bottle.

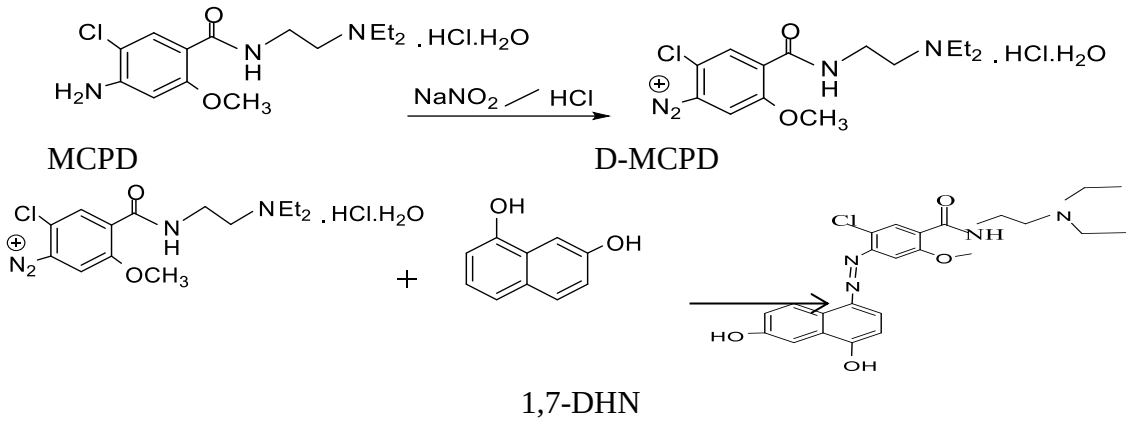
Interferences (1000 µg/mL)

The solutions of the interferences were prepared via dissolving 0.1 g of each interference (Acacia gum, Glucose, Lactose, and Starch) in distilled water using a 100 mL-volumetric flask.

3. Results and discussion

3.1. General Procedure

The main reactions include the formation of the diazonium salt of MCPD, followed by coupling with the 1,7-DHN reagent in an alkaline medium to give a colored azo dye that has a maximum absorbance at 578 nm (Scheme 1).



1,7-DHN

Scheme 1: The proposed mechanisms to produce the colored azo dye

3.2. Studying the optimum conditions

The following factors influencing the response of the production of the azo dye generated from coupling D-MCPD with 1,7-DHN in the presence of the basic medium were explored in order to achieve the highest absorbance intensity and stability of the formed azo dye are:

3.2.1. The effect of acid type

To investigate the impact of various types of acids used in the diazotization process, metoclopramide was first diazotized as previously described (MCPD and $NaNO_2$) with the addition of 4 mL at a concentration (1.0 M) from various types of acids, and the remaining components were fixed. Next, 0.5 mL of the diazotized solutions were reacted with 1 mL of reagent 1.7-DHN at a concentration (0.1%), and 0.5 as shown in Table 1.

Table 1: Effect of the type of acid used in diazotization

Acid used(4ml,1M)	HCl	HNO_3	H_2SO_4	H_3PO_4	CH_3CO_2H
Absorbance	0.288	0.278	0.280	0.255	**0.232**

Because HCl acid generated a maximum absorbance intensity of the formed azo dye, as shown in Table 1's data, this acid was used in the future studies.

3.2.2. Study the optimal concentration of the acid

The identical quantities and sequences of $NaNO_2$ were added to various volumes of HCl (1 M) used in the MCPD diazotization procedure, and the diazotized was employed as previously

indicated in the preparation of azo dye. According to Figure 2, the absorbance of the colored azo dye was measured at 578 nm in comparison to the blank solution.

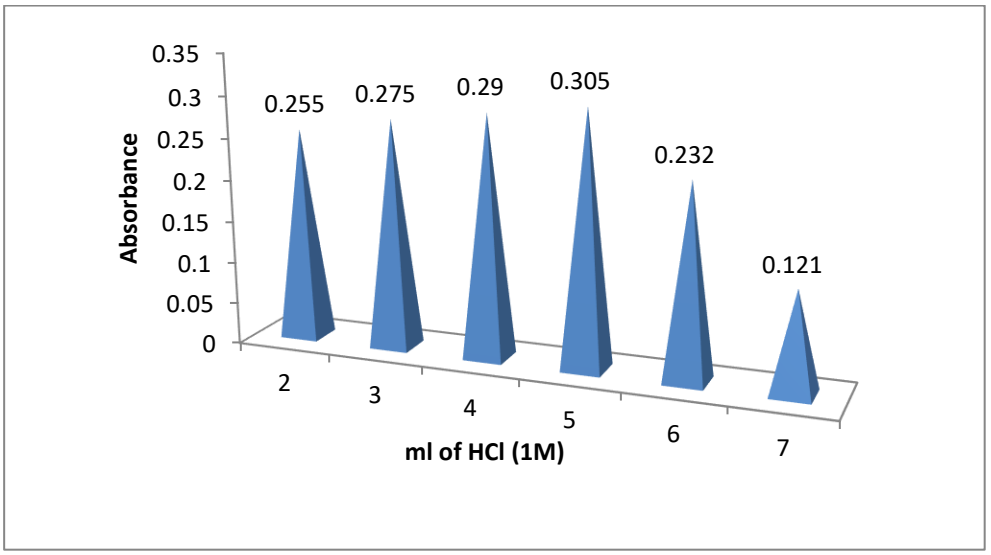


Figure 2: The effect of the amount of acid used in diazotization

According to Figure 2, 5 mL of HCl (1 M) provided the colored azo dye with the maximum absorbance intensity. As a result, this amount was used to produce D-MCPD.

3.2.3. Study the effect of the quantity of the reagent

The effect of different amounts of 1,7-DHN reagent was studied by adding various volumes of D-MCPD to a series of 10 mL volumetric flasks and then adding different volumes of a coupling reagent (0.1 %), followed by adding of 0.5 mL of NaOH (0.1 M), then the solution mixture was diluted with distilled water to the mark. The obtained results are shown in Figure 3.

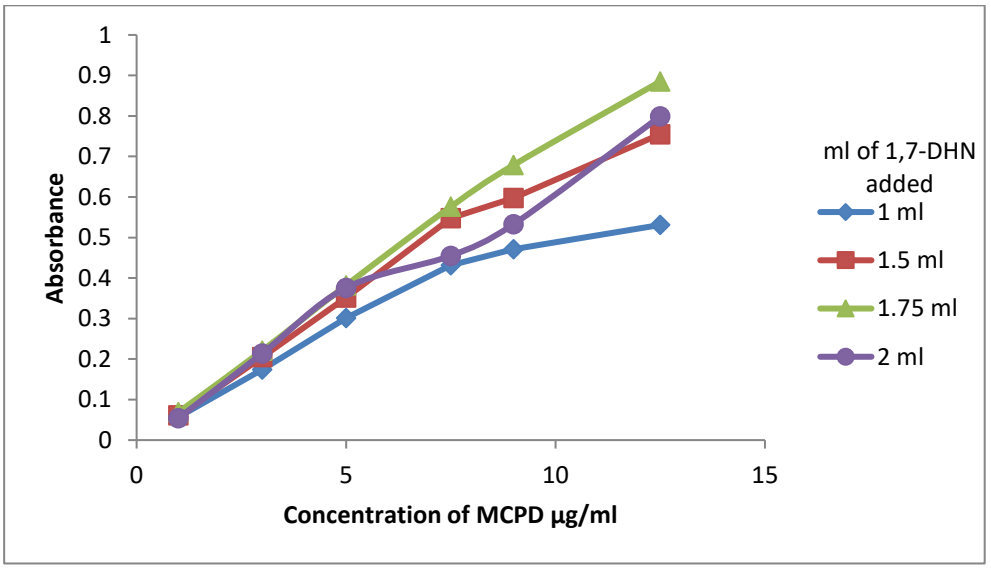


Figure 3: The effect of using variable amounts of reagent 1,7-DHN

According to Figure 3, 1.75 ml of the coupling reagent (1,7-DHN) solution at a concentration of (0.1%) produced the highest azo dye absorbance intensity as well as the highest

determination coefficient (0.9955). For this reason, this amount of coupling reagent was used in the experiments that followed.

3.2.4. Studying the effect of the base type

In an alkaline media, the coupling reaction between the reagent 1,7-DHN and the D-MCPD actually occurs. Accordingly, the effect of various bases and basic salts was investigated to determine which of them produced the highest absorbance. To this end, 0.5 mL of D-MCPD, 1.75 mL of reagent 1.7-DHN, and then 0.5 mL of various bases (0.1 M) were added to each sample were added to several volumetric flasks of 10 mL. According to the findings in Figure 4, sodium hydroxide provided the colored azo dye's best absorbance, hence this base was continued to be used.

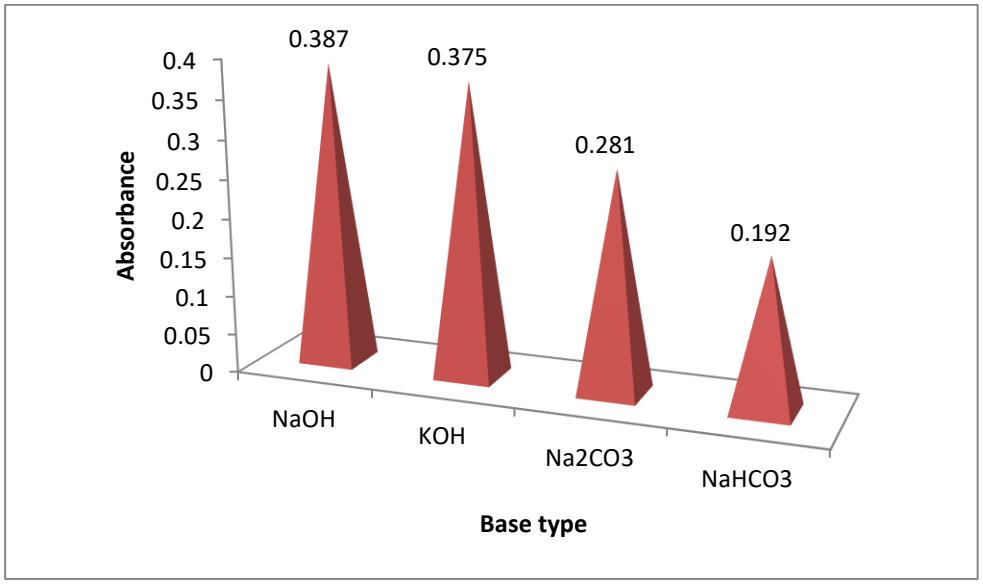


Figure 4: The effect of the applied bases used during the coupling reaction

3.2.5. Study of the amount of base

To achieve the maximum adsorption intensity from the azo dye, the optimum volume of NaOH was investigated. The same prior processes were used to add various base volume amounts. It was discovered that 1 mL of NaOH (0.1 M) is the ideal volume, thus it was used in the tests that followed. The outcomes are shown in Figure 5.

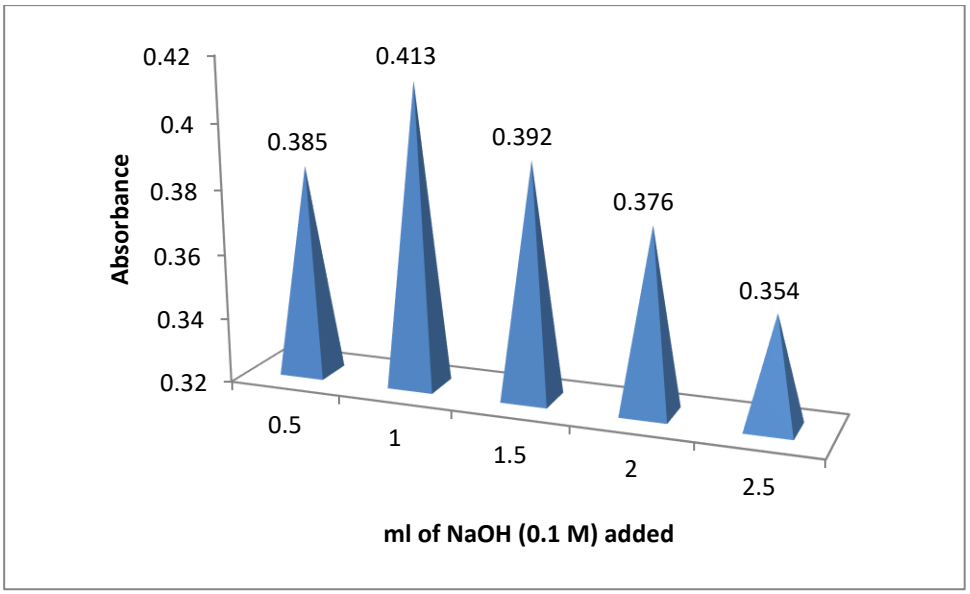


Figure 5: The optimum amount of the NaOH used in the experiment

3.2.6. Study the effect of interferences

By examining the impact of a few pharmaceutical additives, the selectivity of this approach and its usefulness in pharmaceutical formulations were put to the test. In this investigation, a 10 mL volumetric flask containing 0.5 mL D-MCPD was filled with increasing amounts of the additives (100, 500, and 1000) µg, and the remaining chemicals were added to them in their ideal volumes and by the final dilution to the mark with distilled water. The results of Table 2 show that the interfering has no significant influence on the recovery% of the pharmaceutical compound when measuring the absorbance at wavelength 578 nm against the blank solution and comparing the results with a standard solution that is devoid of any of the interfering. MCPD.

Table 2: The effect of interferences

Interferences compounds	Recovery (%) of 5 µg MCPD /µg Interferences compounds		
	100	500	1000
Acacia	99.0	96.7	101.9
Glucose	102.5	98.2	103.2
Lactose	103.1	98.6	104.0
Starch	98.1	95.7	101.8

3.2.7. Study the effect of the dilution solvent

Different types of solvents were used in the final dilution to obtain the optimal and suitable solvent. A sequence of 10 mL volumetric flasks were prepared, each containing 0.5 mL of the D-MCPD solution and with other additions from the reagent 1,7-DHN and NaOH in the same volumes that were previously added, then it is diluted with different organic solvents (as well as water). The results are cited in Figure 6 and Table 3.

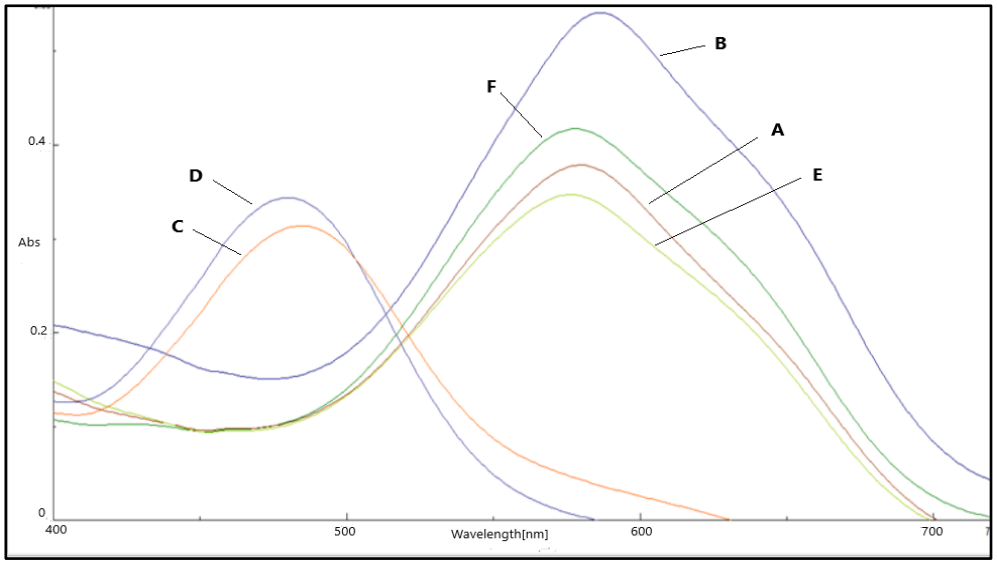


Figure 6: Spectra of colored azo dye in various solvents

Table 3: Effect of solvents

	Solvent	Absorbance	λ_{max} (nm)	ε(x10 $^{-4}$) l.mol^{-1}.cm^{-1}
A	Ethanol	0.377	580	2.672
B	Methanol	0.538	586	3.813
C	n-Butanol	0.312	485	2.211
D	Acetic acid	0.342	480	2.423
E	Formic acid	0.346	576	2.452
F	Water	0.416	578	2.948

The absorption spectra of the formed azo dye (Figure 6) showed that the highest absorption was obtained during use of methanol as a solvent, however the water was preferred in the final dilution due to its abundance, cheapness, and ease of handling compared to the rest of the solvents. Therefore, distilled water was kept as a solvent used in subsequent experiments.

3.2.8. Studying the stability of the formed azo dye

The stability of the formed dye was investigated by studying the effect of time on absorbance of two different concentrations (2.5 and 5.0 µg/mL) of metoclopramide was studied according to the procedure of proposed method and the results are listed in Table 4.

Table 4: Effect of time on the stability of the azo dye

Standing time	Absorbance/µg of MCPD ml^{-1}	
	2.5	**5**
Immediately	0.210	**0.409**
5	0.212	**0.415**
10	0.212	**0.416**
15	0.215	**0.413**
20	0.211	**0.412**
25	0.211	**0.412**
30	0.215	**0.413**

35	0.215	**0.415**
40	0.214	**0.410**
45	0.216	**0.419**
50	0.213	**0.421**
55	0.216	**0.423**
60	0.217	**0.426**

The results illustrated in Table 4 show that the formed azo dye is stable for 60 mints, above that the dye stars to decomposing and the measurements will not be accurate, therefore, it is highly recommended to conducting the measurements before that time.
Table 5 shows a summary of the optimal conditions that have been studied and established.

Table 5: The optimum conditions of the developed method

Parameters	Optimum conditions
Reagent used	1,7-Dihydroxynaphnthalene
The concentration of reagent, %	0. 1
Amount of reagent used (mL)	1.75
Base used	NaOH
Molarity of base used	0.1
Amount of acid used in diazotization (mL)	5
Medium	Aqueous
Solvent	Water
λ_{max} (nm)	578

3.3. Final absorbance spectrum

The optimal amount (1.75 mL) of 1.7-DHN reagent fixed in Table (5) was added to a 10 mL volumetric flask containing 0.5 ml (100 µg/mL) of diazotized metoclopramide solution (D-MCPD), followed by the addition of 1.0 mL of sodium hydroxide solution (0.1 M), then the volume was diluted with distilled water. Figure 7 shows the absorption spectrum of the azo dye versus the blank solution and both the azo dye and the blank solution versus the distilled water.

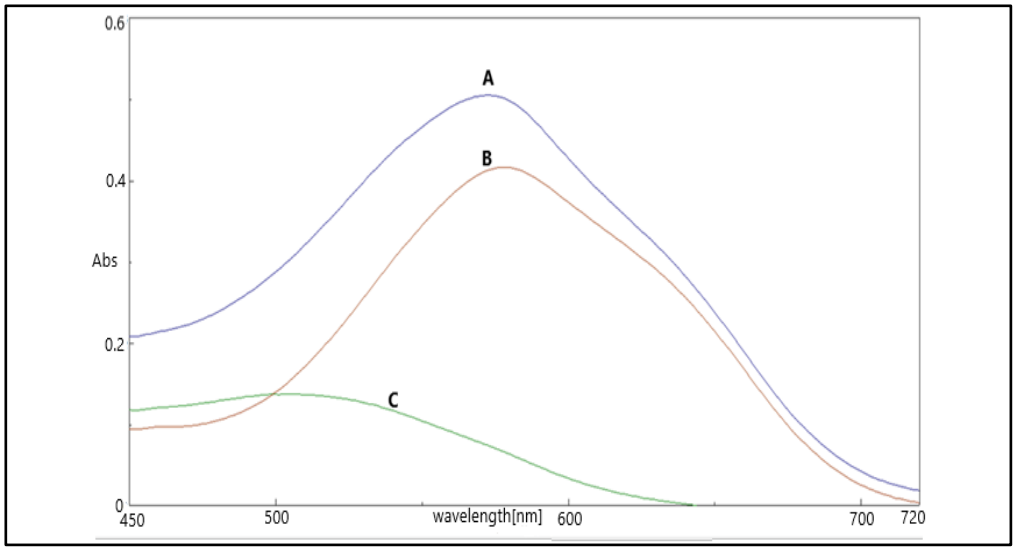


Figure 7: The final absorption spectra of 5 µg/mL of MCPD against distilled water (A); MCPD against blank solution (B), and Blank against distilled water (C)

3.4. Calibration graph

To a set of volumetric flasks of 10 mL, different volumes (0.1-1.5) mL of diazotized metoclopramide (D-MCPD) solution (100 µg/mL) were added. These volumes cover the concentrations of 1.0 to 15.0 µg/mL, then 1.75 mL of 1.7-DHN organic reagent (0.1%) was added followed by the addition of 1 mL of sodium hydroxide (0.1 M), then the volume was completed to the mark with distilled water. The absorbance of the solutions is measured against the blank at 578 nm. Figure 8 shows that the calibration curve follows Beer's law in the range of 1.0 to 15.0 µg/mL. The molar absorptivity was 2.9867 x 10^4 l. $mol^{-1}.cm^{-1}$ and Sandall's index value is 0.01186 µg. cm^{-2}.

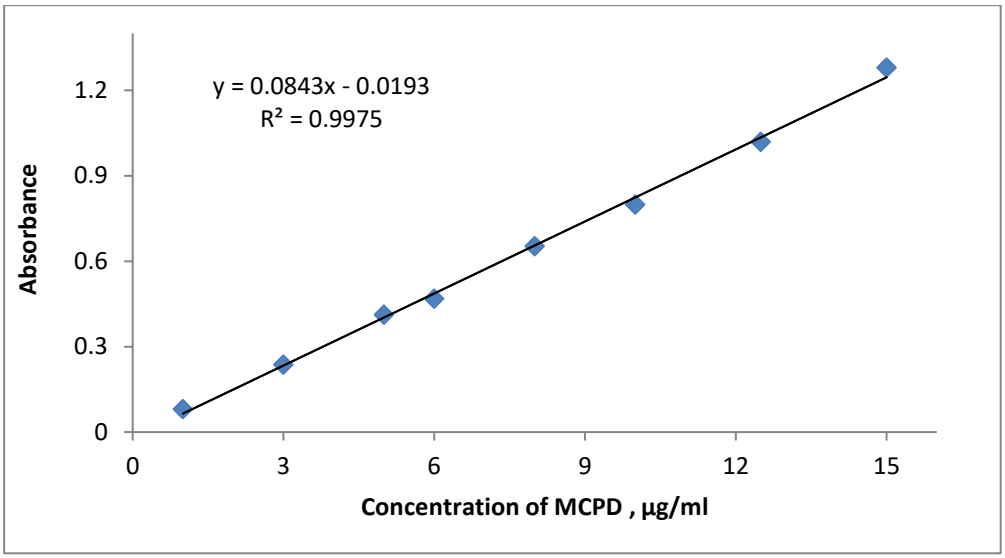


Figure 8: The linear curve for determination of MCPD using the proposed method

3.5. Accuracy and precision

The accuracy and precision of the present method for determination MCPD was calculated by applying the optimum conditions. From calculated recovery value, relative error (expressing accuracy), and relative standard deviation (expressing precision), three different concentrations of D-MCPD were employed (4, 7, and 12 µg/mL) with four repeated measurements for each concentration. The results in the Table 6 indicated that the recovery% values have ranged from 98.90 to 102.10 % while the error% (Er%) between -1.1 to +2.1% and the relative standard deviation gave a value that did not exceed 1.11 %, meaning that the method has good accuracy and precision for the determination of MCPD see Table 6.

Table 6: The accuracy and precision vlaues of the proposed method

Amount of MCPD µg/ml	Recovery* %	Er %	RSD %
4	102.10	+2.1	**1.11**
7	101.20	+1.2	**0.85**
12	98.90	-1.1	**0.72**

* Average of four determinations.

3.6. Studying the ratio of MCPD and 1,7-DHN in formed azo dye

Since equivalent amounts of the reagent 1,7-DHN and the drug molecule MCPD were applied, the Job's approach was used to determine their molar interaction ratios. The total volume of the drug ingredient MCPD and reagent 1.7-DHN was 0.5 mL in a final volume of 10 mL, with a concentration of 2.8x 10^{-4} M for both for various quantities of solutions. According

to the mole ratio diagram, increasing volumes of 1.7-DHN (0.25-3) mL at a concentration of 2.8x 10^{-4} M are added to 1 mL of D-MCPD solution with the same concentration of the used reagent, diluted to a volume of 10 mL, and then the absorption of each solution is measured at 578 nm in comparison to the blank solution.

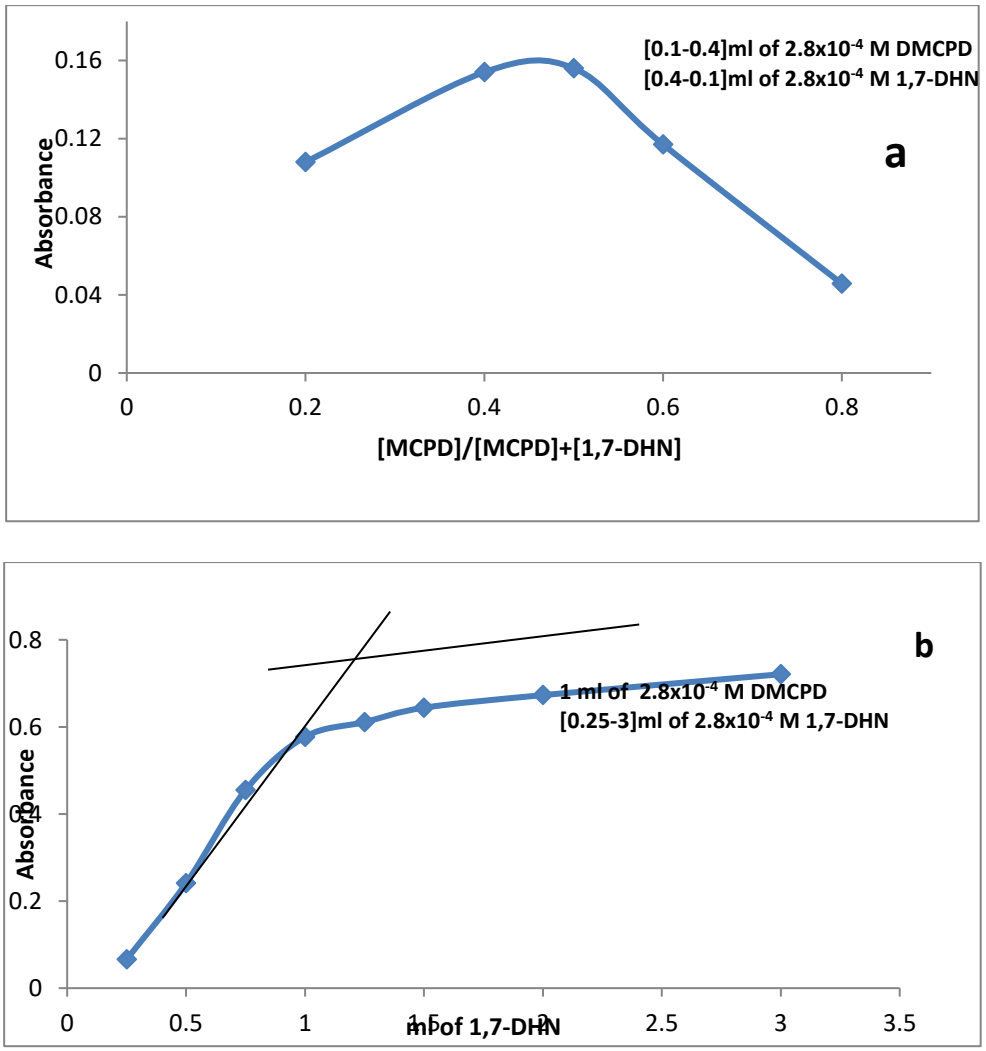


Figure 9: The continuous variation method curve (a) and the mole ratio method curve (b) for a reaction product MCPD with 1,7-DHN using Job's method

From the obtained results in Figure 9, it was found that the reaction ratio is 1:1. Therefore, Figure 10 below shows the proposed formula for the azo dye formed by the reaction of D-MCPD with the reagent 1,7-DHN in the basic medium

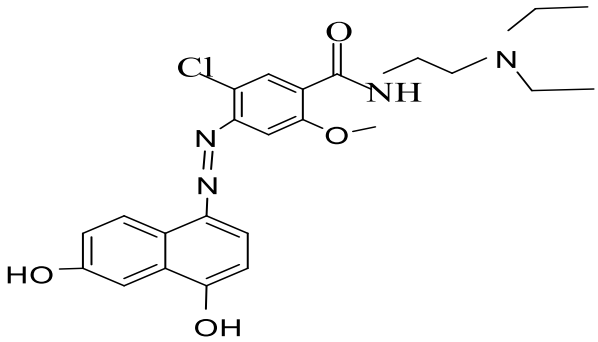


Figure 10: The proposed chemical structure of blue colored azo dye(D-MCPD-1,7-DHN)

3.7. Application of proposed method in real samples

The proposed method has been applied for the determination of MCDP in the pharmaceutical preparations (Tablets and injections) supplied from different commercial sources at three different concentrations of 5, 7, and 10 µg/mL of (D-MCPD). The obtained results are shown in Table 7.

Table 7: The obtained results for the determination of MCPD in pharmaceutical samples

Drug content	Amount taken (µg/ml)	Amount measured (µg/ml)	Recovery* %	RE %	Drug content measured (mg)	t_{cal}
Metoclopramide 10mg/tablet (Darnitsa / Ukraine)	5	5.05	101.0	1.0	10.10	**1.52**
	7	6.80	97.2	-2.8	9.72	
	10	9.88	98.8	-1.2	9.88	
Meclobran 10mg/2ml/injection (Brawn/India)	5	5.15	103.1	3.1	10.31	**0.97**
	7	6.93	99.1	-0.9	9.91	
	10	10.19	101.9	1.9	10.19	

* Average of four determinations (*n=4*), $t_{cal.}$ = $t_{calculated}$.

Through the recovery values and from the value of t_{cal} for the concentration of 7 of the tablets and the injection (Table 7), which is less than the tabulated value and with degrees of freedom of three and at a confidence level of 95% [41], which indicates the success of the present method in estimating metoclopramide hydrochloride in its pharmaceutical preparations.

3.8. Standard addition method

The standard addition was employed using two different concentrations, 3 µg /mL and 6 µg /mL, from tablets and injection samples in order to demonstrate the effectiveness and success of the current method for the determination of MCPD by the diazotization-coupling method and that it is free of additives and interferences. Figure 11 and Table 8 show the agreement of the standard addition method with the proposed method and which did not exceed the permissible values in terms of the analytical variables for both recovery % and % RSD.

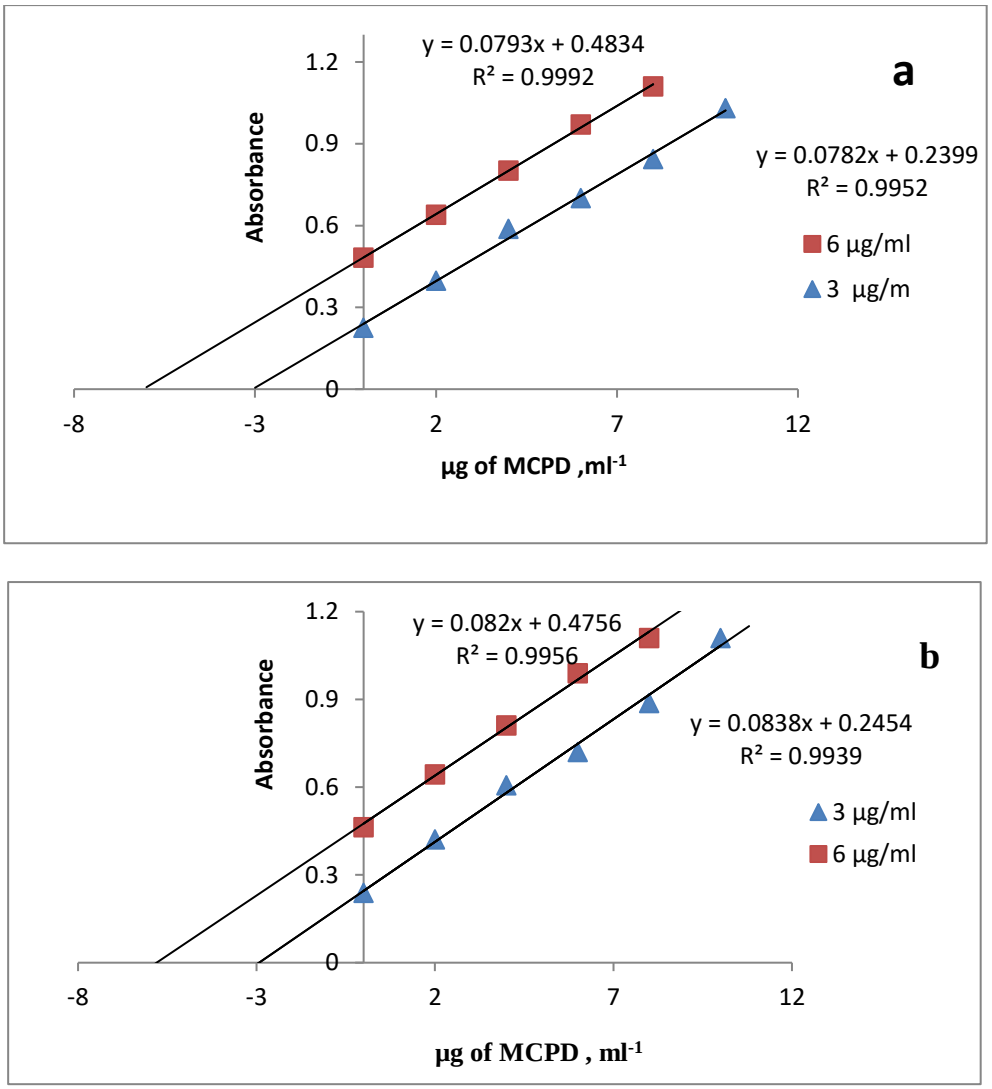


Figure 11: The standard addition curve for MCPD determination: a - tablets, b - injection

Table 8: The results of standard addition method for the determination of MCPD

Drug content	Amount taken (µg/ml)	Recovery* %	RE %	RSD* %	Drug content measured(mg)
Metocloramide 10 mg/tablet (Darnitsa/Ukraine)	3	102.00	2.00	1.44	**10.20**
	6	101.50	1.50	1.08	**10.15**
Meclobran/injection 10 mg/2ml (Brawn/India)	3	97.33	-2.66	1.10	**9.73**
	6	96.66	-3.33	0.78	**9.66**

* Average of four determinations.

3.9. Statistical analysis

The t-test was applied to find out the efficiency of the proposed method for estimating MCPD by comparing it with previous reported method and the results are shown in the Table (9).

Table 9: The comparison study between the proposed and the reported methods

Drug content	Recovery * %		t_{exp}
	Present method	**Reported method [42]**	
Metocloramide 10mg/tablet/Darnitsa/Ukraine	96.8	98.65	1.29
Meclobran (10mg/2mL) injection/Brawn/India	102.3	102.54	1.08

* Average of 5 determinations.

The results of Table (9) show that the values of t_{cal} are less than the values of $t_{tabulated}$ at a confidence level of 95% and for eight degrees of freedom. This indicates that the difference is not significant between the proposed method and the approved method. A comparison was also made for the analytical variables of the proposed method for the determination of MCPD with some variables of other spectrophotometric methods used in the literature, as the proposed method considered as an important, sensitive, and acceptable results compared to other methods (Table 10).

Table 10: The comparison study between the proposed with reported methods

Analytical parameters	Present method	Literature Method [43]	Literature Method [44]
Reagent	1,7-Dihydroxy naphthalene	1-Naphthol	**9-Chloroacridine**
Type of reaction	Diazotization coupling	Diazotization-coupling	**Nucleophilic substitution**
$\lambda_{max\ (nm)}$	578	550	**470**
Linearity, µg/ml	1-15	0.4-18	**2-50**
Media	Aqueous	Aqueous	**Organic**
Molar absorptivity ($l.mol^{-1}.cm^{-1}$)	2.9867×10^4	3.4969×10^4	**0.8500×10^4**
Dye's color	Blue	0range	**-----**
Sandell's Index ($\mu g.cm^{-2}$)	0.01186	0.0101	**0.0417**
RSD%	≤ 1.95	0.8140	**≤0.456**
Determination coefficient	0.9975	0.9971	**0.9960**
Nature of the dye	1:1	1:1	**1:1**

Conclusion

A rapid and simple method has been proposed for the quantitively determination of metoclopramide hydrochloride in pure and in its pharmaceutical formulations through the diazotization and coupling reaction with the 1,7-Dihdroxynaphthalene reagent in the alkaline medium to produce colored azo dye. The proposed method was successfully applied for the determination of MCPD in real pharmaceutical samples (Tablets and injections). The relative standard deviation and recovery values did not exceed 1.95 % and 103.1%, respectively.

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