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A New Spectrophotometric Azo-Coupling Method for the Determination of Metoclopramide

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This study presents a new, simple, and sensitive spectrophotometric method for the determination of metoclopramide in both pure form and pharmaceutical preparations. The method is based on an azo-coupling reaction between metoclopramide and α-naphthol under optimized experimental conditions. The influence of various factors, such as acid type and concentration, base type, reagent volume, reaction time, solvent, and temperature, was investigated to achieve maximum color intensity and stability of the formed product. The absorbance of the colored complex was measured at 613 nm, and Beer's law was obeyed in the range of 1–12 µg/ml. The molar absorptivity and Sandell's sensitivity were 28840.76 $L \cdot mol^{-1} \cdot cm^{-1}$ and 0.013699 $\mu g/cm^2$, respectively. The detection and quantification limits were 0.0137 µg/ml and 0.0186 µg/ml. The proposed method showed excellent accuracy, precision, and recovery (about 101%), and can be successfully applied for the determination of metoclopramide in pharmaceutical dosage forms.

Keywords: Azo coupling, metoclopramide, pharmaceutical analysis, spectrophotometry

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Metoclopramide hydrochloride (MCH) is a benzamide compound that appears as a mostly white powder, melts between 182.5 and 184 °C, is odorless, and dissolves in water [1]. It is commonly used as an antiemetic following surgery and radiation therapy [2], has neuroprotective effects against vomiting [3], and acts as a dopamine receptor antagonist in crystalline solid form. The compound may appear colorless or slightly yellow [4], tends to darken upon exposure to light [5], and has a faint phenolic odor. It dissolves sparingly in water, alcohol, chloroform, and ether [6]. In 1858, Peter Kress reported that diazo nitrogenous ortho-aminophenol reacts with nitrous acid to form diazonium salts [7]. Typically, diazonium salts are prepared by reacting aromatic amines with nitrous acid in the presence of a mineral acid [8]. Aromatic amines are stable enough to undergo diazotization because of the resonance within the benzene ring. This reaction usually proceeds efficiently at low temperatures, often below freezing, to stabilize the diazonium intermediate [9]. Several researchers have developed new and sensitive methods for the detection of metoclopramide in biological and pharmaceutical samples [10]. For example, metoclopramide has been determined in blood plasma using a reversed-phase HPLC technique at 275 nm, achieving a detection limit of 5 ng mL^{-1} and a linear range of 5–1000 ng mL^{-1}. This method was successfully applied to pharmaceutical formulations [11]. Similarly, a spectrophotometric method was proposed based on the diazotization reaction between nitrite and ethylene as a coupling reagent, with an absorption maximum at 410 nm [12]. Optimal conditions such as NaOH concentration, reagent volume, and acidity were investigated, showing linearity between 0.5–12 µg mL^{-1}. This approach was effectively used for drug determination in pharmaceutical formulations without interference [13]. Moreover, an indirect flame atomic absorption spectroscopic technique for metoclopramide hydrochloride determination was developed based on its reaction with ammonium to form a pink complex. Detection was carried out at 358 nm with a linear range of 20–120 mg mL^{-1} and a recovery of 99.36% [10]. However, despite the availability of several analytical techniques, most existing methods require expensive instruments or involve multiple extraction and preparation steps. Therefore, there is still a need for a simple, accurate, and cost-effective spectrophotometric method that can be applied to both pure drugs and pharmaceutical dosage forms [14, 15]. The main objective of this study is to develop a new spectrophotometric method based on the azo-coupling reaction for the determination of metoclopramide in its pure form and pharmaceutical formulations.

EXPERIMENTAL

Materials

SDI, Merck, and BDH companies provided all of the chemicals used in this experiment.

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Devices Used

UV-visible spectrophotometric Shimadzu, 800, Japan. Water bath - Velp Scientific, made in Europe. Center fudge - Geemy Company plc-03, Taiwan. Electrical balance - Kern&SOHN GmbH, China.

Preparation of Standard Solutions

A stock solution of metoclopramide (purity 100%) (1000 µg/mL) was prepared by dissolving 0.1 g of the pure drug in distilled water and diluting to 100 mL in a volumetric flask.

A standard reagent solution of α-naphthol (1000 µg/mL) was prepared by dissolving 0.1 g of the compound in ethanol and diluting to 100 mL with distilled water [16].

The following 1 M acid and base solutions were freshly prepared by appropriate dilution of the concentrated reagents with distilled water in 100 mL volumetric flasks: phosphoric acid (6.22 mL of 16.07 M), sulfuric acid (5.44 mL of 18.38 M), acetic acid (5.74 mL of 17.43 M), nitric acid (6.97 mL of 14.34 M), hydrochloric acid (8.40 mL of 11.96 M), sodium hydroxide (4.0 g), potassium hydroxide (5.61 g), and ammonium hydroxide (5.34 mL of 18.70 M). Additionally, 1% (w/v) aqueous solutions of sodium nitrite and sulfamic acid were prepared by dissolving 1 g of each reagent in 100 mL of distilled water [17]. Carbonate buffer solutions (1 M) were prepared by dissolving 13.8 g of potassium carbonate, 10.59 g of sodium carbonate, and 7.2 g of sodium bicarbonate separately in 100 mL of distilled water [18]. All reagents used were of analytical grade, and distilled water was used throughout the work.

Azo Coupling Reaction in Spectrophotometric Determination of Metoclopramide in Aqueous Solution

In the first experiments, 1 ml of (100) mg/ml of metoclopramide was introduced into a 10-ml volumetric vial in an ice bath with 1 ml of acetic acid with a concentration of 1 M. This gave the product of the nitrification reaction. Shake 10 minutes with 1% sodium nitrite; add 1 ml of 100 sulfamic acid to remove all the nitrite. Then, after shaking in an ice bath for 5 minutes, add 1 ml of (100) mg/ml of the reagent, a-Naphthol directly. To the coupling reaction, we will add 1 ml of (1 M) sodium carbonate and incubate in an ice bath, and then we will fill in the volume with distilled water. To form a colorful complex that is different from the one that was formed by the blank solution prepared with the same ingredients and no medication. In order to determine which sensitivity and detection limit would give the best result in detecting the drug, several factors that affect the absorption of the resulting azo formulation were analyzed; these conditions were analyzed under a wavelength that was suitable for the substance under study [19].

RESULTS AND DISCUSSION

Metoclopramide Spectrophotometric Analysis in a Water Solution through the Use of the Azo Coupling Reaction

In the coupling reaction between the azo dye in the aqueous solution, the water solvent was used to prepare solutions with 100 parts per million (ppm) of metoclopramide, and the absorbance spectrum of metoclopramide was recorded for the items being studied. The absorbance of (0.674) of the solution of metoclopramide at the wavelength (613) nm was high, and the wavelengths were taken as the maximum wavelength at which all materials were further measured [20]. The drug was analyzed using visible and ultraviolet spectroscopy in the wavelength range of the wavelength (200-800 nm to obtain these solutions.

Study the Reaction's Appropriate Conditions

The influence of different parameters on the spectral analysis of the medicine used in this research paper has been studied using a set of analyses.

Effect of the Type of Acid

This study was performed through a series of experiments, and the acid solutions with a concentration of 0.5 M were prepared. The results were summarized in Table 1, which clearly shows that acetic acid of 0.5 M is the optimal acid to use with metoclopramide as it produced the greatest absorbance (0.552) [21].

Table 1. Absorption data for the Effect of the acid type.

1 ml from 0.5M different acids	HCl	H_2SO_4	HNO_3	H_3PO_4	CH_3COOH
Absorbance at λmax = 613 nm	0.442	0.161	0.203	0.126	0.552

Table 2. The effect of acid volume on the MCH colored product's absorbance.

V of 0.5M acids	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
Ab at λ max = 613	0.532	0.548	0.572	0.594	0.522	0.511	0.503	0.492	0.476	0.451

Acid Volume's Effect

To accomplish this investigation, several volumes of acetic acid were produced at a concentration of 0.5 M. The obtained results are summarized in Table 2, and it can be clearly seen that the best volume of acid to use in metoclopramide is 0.4 ml of acetic acid with a concentration of 0.5 M, as it yielded maximum absorption (0.594). The ideal volume for the highest absorption was proved in subsequent experiments (0.4) ml of acetic acid with metoclopramide [22].

The Influence of the Base Type

Base solutions were prepared with concentrations of 0.5 M. Table 3) clearly shows that the best base for metoclopramide is sodium carbonate with a concentration of M (0.5), as it gave the highest absorbance (0.604) [23].

The Effect of the Ideal Volume of (0.5 molars) of (Na_2CO_3)

Volumes of (1-10) ml of the base were prepared with concentrations of (0.5 M) of sodium carbonate. Table 4 summarizes the results and clearly indicates that the base volume of the medication Metoclopramide is 0.5 ml of sodium carbonate at a concentration of 0.5 M, as this was the best base volume to give the highest absorption (0.604).

The Effect of the Optimum Sodium Nitrite Volume of 1%

The sodium nitrite concentration of the solution was 1 percent, and various quantities were obtained from it. Table 5 presents a recap of results achieved and makes it clear that the most appropriate volume of sodium nitrite to use with metoclopramide is 0.6 ml at a concentration of 1%, as this gave the greatest absorption (0.618) [24].

Table 3. Effect of the type of base on the absorbance of the colored products of (MCH).

1ml from 0.5M base	NaOH	KOH	NH4OH	Na2CO3	K2CO3	NaHCO3
Ab at λ max = 613	0.387	0.175	0.104	0.597	0.438	0.249

Table 4. Effect of base size on Metoclopramide-stained product absorbance.

V of 0.5M bases	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
Ab at λ max = 613	0.493	0.511	0.532	0.589	0.604	0.599	0.596	0.593	0.592	0.591

Table 5. Effect of 1% sodium nitrite volume on the absorbance of the metoclopramide-colored product.

V of 1% Sodium Nitrite	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
Ab at λ max = 613	0.571	0.582	0.592	0.603	0.61	0.186	0.611	0.608	0.601	0.594

Table 6. Effect of 1% volume of sulfamic acid on metoclopramide.

V of 1% Sulfamic acid	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
Ab at λ max = 613	0.491	0.549	0.621	0.593	0.495	0.487	0.473	0.455	0.446	0.442

Table 7. The effect of the reagent volume at a concentration of 100 μg ml^{-1} on the absorbance of metoclopramide.

V of (100 μg ml^{-1}) Reagent	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
Ab at λ max = 613	0.417	0.525	0.581	0.634	0.614	0.603	0.601	0.598	0.582	0.417

Perfect Size Effect 1% Sulfamic Acid

Variable volumes of sulfamic acid were taken from the solution, whose concentration was 1%. The table (6) summarizes the results retrieved, and it is clear that the ideal volume of sulfamic acid for metoclopramide is (0.3 ml) at a concentration of (1%), as it gave the highest absorption (0.621).

Reagent Volume (100 μg ml^{-1}) Effect

Variable volumes of α-Naphthol reagent were taken at a concentration of 100 μg ml^{-1} with metoclopramide. The obtained results were summarized in Table 7, which clearly shows the best ideal volume of α-Naphthol reagent (0.4 ml) for metoclopramide, as it gave the highest absorbance (0.634). Absorption increases with increasing reagent volume, but absorption decreases when reagent volume is increased beyond the required limit because this volume is not suitable for conjugation with the drug [25, 26].

Reaction Time's Effect on the Product's Color Stability

The time range was 5-65 minutes of the reaction, depicted in Table 8. As the highest absorbance (0.659) was recorded with metoclopramide, 40 min was discovered to be the best period to complete the reaction.

Effect of Adding Sequence

As different sequences of additives were taken, Table 9 shows the result. It was observed that the best addition sequence is (1) for metoclopramide, as it gave the highest absorbance (0.652) [27].

Table 8. Reaction time's effect on the stability of the MCH colored product.

Time (min)	5	10	15	20	25	30	35	40	45	50	55	60	65
Ab λ max = 613	0.541	0.604	0.614	0.624	0.63	0.632	0.657	0.659	0.661	0.652	0.643	0.643	0.637

Table 9. Shows the Effect of the addition sequence.

No.	1	2	3	4	5	6
Addition	D+H+N+S+R +B	R+H+N+S+D +B	D+H+N+B+R +S	D+B+R+N+H +S	R+B+D+H+N +S	R+H+N+B+D +S
λmax=61 3	0.652	0.459	0.594	0.432	0.463	0.141

D: (metoclopramide), H: (Acid acetic), S: (sulfamic acid), N: (Sodium nitrite), R: (α-Naphthol), B: (Sodium carbonate).

Table 10. Effect of the solvent on the absorption of the colored product of metoclopramide.

No.	1	2	3	4	5	6
Solvent	Water	Ethanol	Methanol	Acetonitrile	1-Propanol	Acetone
λ_{max}=613	0.652	0.511	0.481	0.577	0.142	0.187

Table 11. Effect of temperature on the absorption of Metoclopramide.

Temp. C°	5	10	15	20	25	30	35	40	50	60
Abs of MCH	0.490	0.552	0.587	0.657	0.674	0.535	0.521	0.511	0.503	0.481

Solvent Effect

Some of the solvents that were used included water, ethanol, methanol, acetonitrile, 1-propanol, and acetone. It is increasingly clear, due to Table 10, which presents a summary of the obtained results, that water is the best solvent of metacloxyl (0.652). Water is considered one of the best solvents because it is easy to obtain and cheap. It is also considered one of the safest and most environmentally friendly solvents [28].

Tempe Literature's Effect on the Development and Durability of the Colored Product

This study was conducted using a series of experiments at different temperatures. The obtained results were summarized in Table 11, which clearly shows that the best temperature (25 °C) for the drug Metoclopramide, which gave the highest absorption (0.526). When the temperature rises, the absorption begins to decrease, which is attributed to product dissociation, since the intensity of the color indicates [29].

Table 12. Data of the continuous change method for metoclopramide α-Naphthol.

Volume of Drug/ml	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
Volume of Reagent/ ml	0.9	0.8	0.7	0.6	0.5	0.4	0.3	0.2	0.1
Abs of MCH	0.091	0.186	0.254	0.341	0.421	0.361	0.255	0.212	0.102

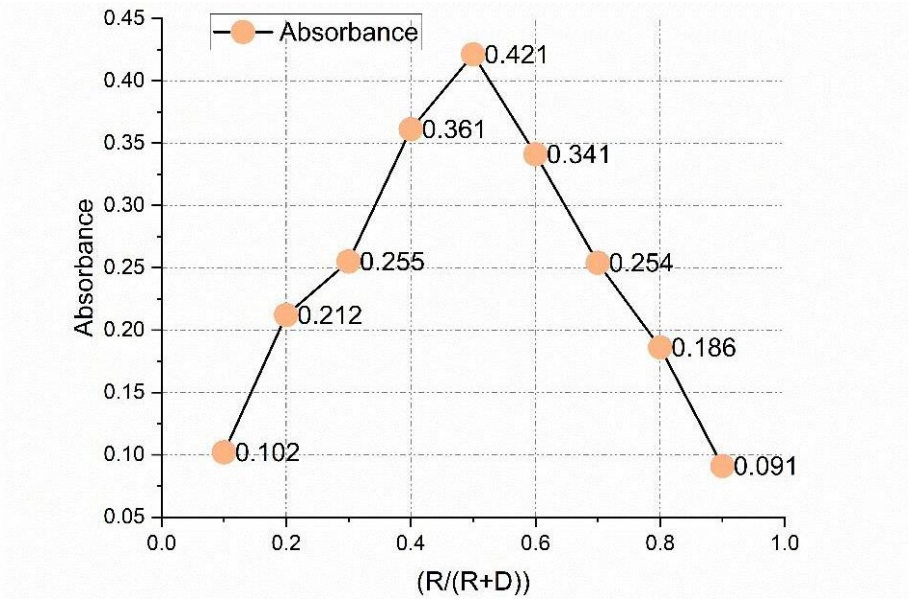


Figure 1. The method of continuous changes (JOB) for metoclopramide.

The Nature of the Produced Product

Method of Continuous Variation (Job's Method)

The results were summarized in Table 12 and Figure 1, which clearly showed that metoclopramide (0.5 ml) was the best choice due to the fact that it gave the highest absorbance (0.198) [30].

Molarity Method

As seen in Table 13 and Figure 2, which is a summary of the results, it becomes very clear that the greater the size of the reagent, the greater the absorbance of metoclopramide, as it gave the highest absorbance (0.414) [31].

Table 13. Absorbance values for the results of the molar ratios method for metoclopramide: α-Naphthol.

Volume of Reagent/ ml	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5
Ab at λmax =613nm	0.114	0.282	0.332	0.351	0.369	0.381	0.392	0.406	0.414

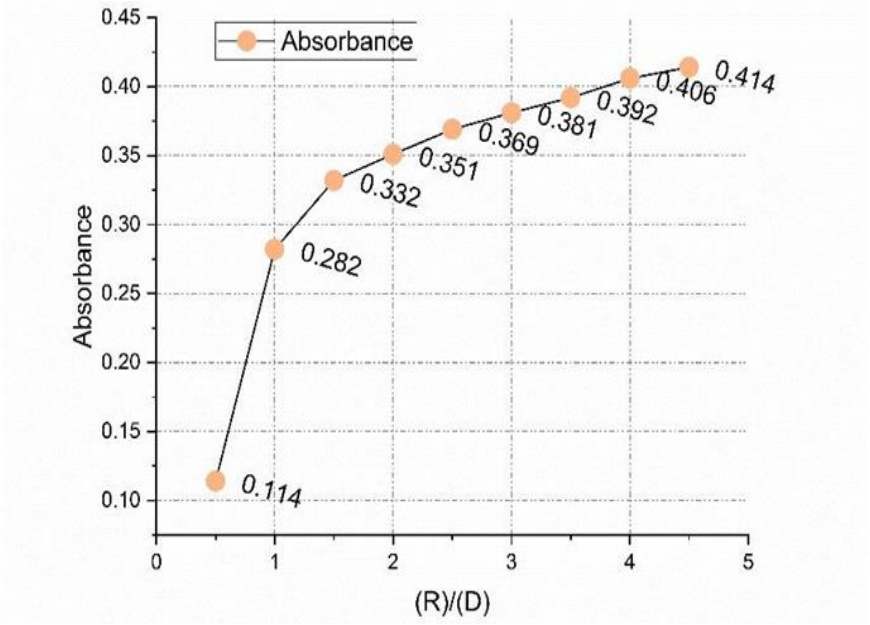
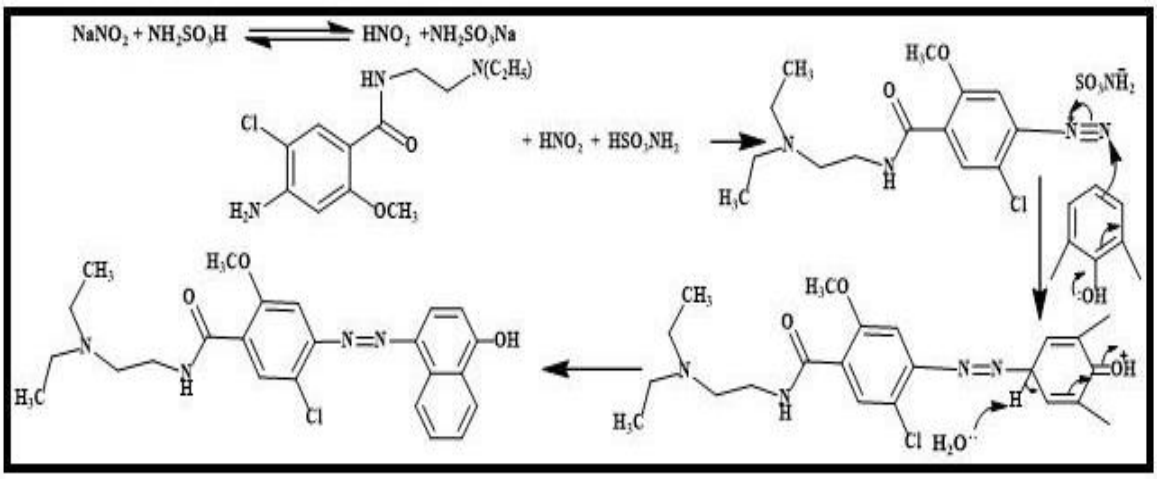


Figure 2. Curve of the MCHL drug molar ratios method.



Scheme 1. Proposed mechanism for the formation of the colored product of metoclopramide [32, 33].

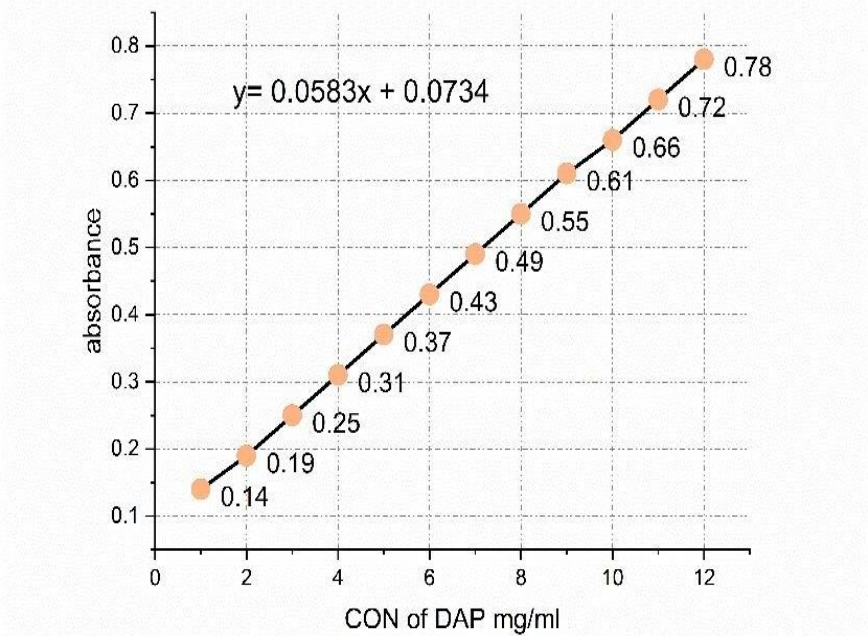


Figure 3. Calibration curve for (MCH drug.

Table 14. Effect of Interactions on the Absorption of Metoclopramide.

No.	100ppm interference	Abs.	Recovery %	Erel%
1	Lactose	0.653	96.884	-3.2159
2	Starch	0.662	92.284	-1.1812
3	Arabic Gum	0.664	98.516	-1.506
4	Glucose	0.671	99.554	-0.447
5	Talc	0.667	98.961	-1.049
6	Ca3(PO4)2	0.625	92.729	-7.84
7	MCH	0.642	95.252	-4.984
8	Trimethoprim	0.661	98.071	-1.966
9	COCl2	0.632	93.768	-6.645
10	CaCO3	0.660	97.922	-2.121
11	Without interference	0.0.675	100.14	0.148

Calibration Curve for Metoclopramide Complexed with α-naphthol

The 0.4 ml of acetic acid, 0.6 ml of sodium nitrite, 0.3 ml of sulfamic acid, 0.4 ml of a-naphthol, and 0.5 ml of sodium carbonate were placed in several 10-ml volumetric vials. The distilled water was added until the mark was reached, and the absorbance was measured against the blank solution at the greatest wavelength. Figure 3) shows that the calibration curve of the medication (MCH), whose values conform to Beer's law, is within the range of (1-12) mg ml^{-1}. The sensitivity of Sandal is 0.013699 mg/cm 2, and the molar absorption coefficient of the product is 21885.4 L/mol.cm. The regression equation was A = 0.073C + 0.157, with a correlation coefficient of R^2 = 0.999, confirming excellent linearity [34].

Interference Effect

To find out the effect of the interfering substances on the drug, each of the interfering substances (lactose, starch, talc, glucose, calcium phosphate, calcium carbonate, cobalt chloride, gum Arabic) was used (1 ml) at and concentration (1000 mcg/ml) with (1 ml), (100ppm) of each of the two drugs. The remainder of the additive is supplemented to its ideal volumes and then diluted with distilled water in a 10ml volumetric vial. Then the absorbance is measured at 613 nm for metoclopramide. The results of metoclopramide

are presented in Table 14. The information in this table shows that there are no effects of interactions on metoclopramide in pharmaceutical preparations [35].

Detection Limit and Quantitative Limit for Drugs

The detection and quantitative detection limits were calculated by taking ten iterations of the blank solution [38]. As shown in Table 15.

Colored Output Stability Constant

Depending on my method, molar ratios, and previous continuous changes, the ratio of [drug: reagent] is [1:1] and the stability constant of the complex. The value of the stability constant is large. Consequently, the dye that is formed is highly stable, as seen in Table 16.

Accuracy and Precision Testing

Metoclopramide's accuracy and precision test were calculated using four concentrations of the calibration curves (12, 9, 6, 3). Table 17 shows the effect of accuracy and precision. Five replicates were taken, and the optimal conditions of the method were applied. The metoclopramide recovery rate is 101.3808% which means that the findings of this technique are correct and precise.

Table 15. Calculating the detection limit and the quantitative limit for metoclopramide.

Parameters	$\overline{x}_B$	$SB = [(Xi-\overline{x})^2/n-1]^{1/2}$	$LOD = \overline{x}_B+3SB$	$LOQ = \overline{x}_B+10\ SB$
Metoclopramide	0.0239	0.0007	0.0137	0.0186

Table 16. Data on stability constants for the colored product of (MCH).

V $4x10^{-4}$M of MCH / ml	Final con. MCH /M	As*	Am*	α	K(L..Mol^{-1})	Mean of K (L.Mol^{-1})
0.3	1.2×10^{-5}	0.380	0.376	0.0342	2487.1209	590438.4501
0.5	2×10^{-5}	0.540	0.538	0.0037	1249410.41623	
0.7	2.8×10^{-5}	0.671	0.665	0.0089	519417.8134	

Table 17. Metoclopramide determination accuracy and precision data for the proposed method.

Amount of MCH / µg mL^{-1}	*Found	Recovery %	Average Recovery %	Erel%	Average Erel%	RSD%
12	12.123	101.025	101.3808	1.0250	1.8095	0.1498
9	9.1388	101.5422		1.5422		0.4629
6	6.1094	101.8233		1.8233		0.7370
3	3.034	101.133		1.1333		0.4419

Table 18. Data for determining Metoclopramide in the pharmaceutical preparation (Primosan).

Amount of MCH / µg mL^{-1}	*Found	Recovery %	Average Recovery %	Erel%	Average Erel%	RSD%
12	11.828	98.5667	98.2336	-1.4333	-1.7993	0.110
9	8.8192	97.9911		-2.008		0.101
6	5.9142	98.57		-1.4300		0.074
3	2.9342	97.8067		-2.1933		0.106

Table 19. Data for the determination of Metoclopramide in the pharmaceutical preparation (Placell).

Amount of MCH / $\mu g\ mL^{-1}$	*Found	Recovery %	Average Recovery %	E_{rel}%	Average E_{rel}%	RSD%
12	11.943	99.525	99.14375	-0.475	-0.85625	0.6282
9	8.952	99.4667		-0.5333		0.0996
6	5.963	99.3833		-0.6167		0.04654
3	2.946	98.2		-1.8		0.12926

Table 20. Statistical results of the proposed spectral method for drug estimation (MCH).

Parameter	Metoclopramide & α-Naphthol
Colour of Product	Auburn
λ max	613 nm
Regression equation	y = 0.073 X + 0.157
Standard deviation of regression	0.26415
Correlation coefficient (r)	0.999
C.L for slop ($b \pm tS_b$) at 99%	0.073 ± 0.0311023
C.L for Intercept ($b \pm tS_a$) at 99%	0.15777 ± 0.2289069
Concentration range ($\mu g\ ml^{-1}$)	(1-12) $\mu g\ ml^{-1}$
Limit of Detection ($\mu g\ ml^{-1}$)	0.0137
Limit of Quantitative ($\mu g\ ml^{-1}$)	0.0186
Sandals Sensitivity ($\mu g\ ml^{-1}$)	0.013699
Molar absorbance ($L.mol^{-1}.cm^{-1)}$	21885.4
Composition of product	1:1
Recovery %	101.808
RSD% n=5	0.4479
C.L for con.12($\mu g\ ml^{-1}$)	12.123±0.03739
C.L for con.9($\mu g\ ml^{-1}$)	9.1388 ±0.0871
C.L for con.6($\mu g\ ml^{-1}$)	6.1094 ±0.09276
C.L for con.3($\mu g\ ml^{-1}$)	3.034±0.02761

Applications of the Proposed Method to Medicines

Two pharmaceutical preparations were used (Emirati Julphar Company and the French Sanofi Company), which contain 10 mg of Metoclopramide every 1gm, and the sample is prepared. The results shown in Tables 17, 18, and 19 are confirmed. The proposed method's success in determining Metoclopramide in the used preparation.

CONCLUSION

In this study, a novel spectrophotometric analysis method was developed for the identification of pharmaceuticals through nitration reactions of the drugs under investigation. The results obtained were promising, accurate, and efficient. Novel reagents were used to determine metoclopramide via azo conjugation, and the optimal reaction conditions were thoroughly investigated. This method proved to be simple, fast, and economical, and it is also more sensitive and selective than other available methods. It can be reliably applied to the identification of drugs, both in their pure form and in pharmaceutical formulations, even when used in very small quantities.

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