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NEW SPECTROPHOTOMETRIC METHOD FOR THE DETERMINATION OF METOCLOPRAMIDE HYDROCHLORIDE IN PHARMACEUTICAL PREPARATIONS BASED ON COUPLING WITH DOXYCYCLINE HYCLATE

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ABSTRACT

A new simple, rapid, sensitive, selective, and accurate method for the spectrophotometric determination of metoclopramide hydrochloride (MCP-HCl) in different pharmacetical preparations has been developed. Metoclopramide hydrochloride is widely used in the treatment nausea and vomiting. The spectrophotometric method is based on diazotization of primary amine group of (MCP-HCl) with sodium nitrite and hydrchloric acid followed by reaction with other drug doxycycline hyclate (DOX-HYC) as coupling agent in alkaline medium to form a stable yellow azo dye, showed amaximum absorption at 452 nm. Beers law was obyed in the concentration range of 0.1-10 $\mu g.mL^{-1}$ with amolar absorptivity (3.81×10^4) $L.mol^{-1}.cm^{-1}$, and sandell's sensitivity 0.009 $\mu g.cm^{-2}$, respectively. The analytical parameters were optimized as the fallowing: The best temperature is 1-30°C), the best time to complete reaction is 15 min and the best volume of doxycycline hyclate (DOX-HYC) solution is 1.5 mL. Limit of detection (LOD), and limit of quantification (LOQ) are 0.012 ppm, and 0.043 ppm, respectively, the recoveries range 98.58%-100.61%. The method was successfully applied to the analysis of the (MCP-HCl) in its pharmaceutical preparations (tablets, syrup, injection and orals drop).

Key words: Drugs, Metoclopramide, HCl, Doxycycline hyclate, Diazotization coupling method, Pharmaceutical preparation.

INTRODUCTION

Metoclopramide hydrochloride (MCP-HCl) is a dopamine recepter antagonst, the chemical name of it 4-amino-5-chloro-N-[2-(diethylamino)ethyl]-2-methoxybenzamide

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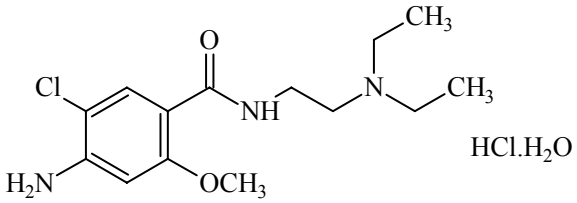
hydrochloride ($C_{14}H_{22}ClN_3O_2$, HCl, H_2O) Fig. 1 and the molecular weight is 354.3 g/mol, it is white crystalline powder, easy soluble in water but freely soluble in alcohol, middly souble in methylene chloride, the melting point of this drug about 183°C (British Pharmacopoeia 2013).



$C_{14}H_{22}ClN_3O_2.HCl.H_2O$

MW = 354.3 g.mol^{-1}

Fig. 1: Chemical structure of metoclopramide hydrocloride

Metoclopramide is used as antiemitic and used for treatment of poor stomach empting (the musles of stomach don't function normally) and nausea, vomiting that happened after the chemotherapy or infection, migrain headache and gastroesophageal relux disease (in that disease the food remain in the esophagus and not transmitted to the stomach). Metoclopramide is available in varios trade names such as Reglen, Degen and Maxolon[1]. Several methods have been used for determination of metoclopramide in pharmaceutical dosage forms and biological fluids such as spectrophotometric[2-9], high-performance liquid chromotography[10-12], spectrofluroimetric[13,14], solid-phase extraction[15], electrochemical[16,17], flow-injection analysis[18]. The present method is based on the reaction of metoclopramide HCl by diazodization coupling with doxycycline hyclate. The aim of method develop a simple, sensitive and inexpensive method for determination of metoclopramide in pure form and in pharmaceutical preparations (tablet, syrup, injection and drop).

EXPERIMENTAL

Apparatus

UV-Visible Spectrophotometer, double-beam, Shimadzu model UV-1800 PC (Japan) with quartz cell of 1 cm path length was used for all spectral and absorbance measurements.

Reagents

All reagents and chemicals used without futher purification and freshly prepared.

Standard solution of metaclopramide hydrocloride solution (Semara drugs iraq SDI) (MCP-HCl) 250 µg.mL^{-1}

Standard stock solution was prepared by accurately dissolving 0.025 g of metoclopramide hydrochloride in 100 mL calibrated volumetric flask and made up the volume with distilled water. The other standard solution of pure (MCP-HCl) drugs were prepared daily by suitable dilution of stock standard solution in water.

Sodium nitrite solution ($NaNO_2$) 0.01 mol.L^{-1}

A solution was prepared by dissolving accurate weighing of 0.069 g of ($NaNO_2$) in 100 mL calibrated volumetric flask and made up to the volume with distilled water.

Sulfamic acid solution 0.2 mol.L^{-1}

A stock solution was prepared by dissolving accurate weighing of 1.94 g of sulfamic acid in 100 mL calibrated volumetric flask and made up to the volume with distilled water.

Doxycycline hyclate solution (Semara Drugs Iraq SDI) (DOX-HYC) 0.01 mol.L^{-1}

A solution was prepared by dissolving accurate weighing of 0.512 g of (DOX-HYC) in 100 mL calibrated volumetric flask and made up to the volume with distilled water.

Sodium hydroxide solution (NaOH) 1 mol.L^{-1}

A solution was prepared by dissolving accurate weighing of 4 g from (NaOH) in 100 mL calibrated volumetric flask and made up to the volume with distilled water.

Interferences solution 1000 mol.L^{-1}

A solution was prepared by dissolving accurate weighing of 0.1 g from (excipents) in 100 mL calibrated volumetric flask and made up to the volume with distilled water.

Pharmaceutical preprations of metoclopramide hydrochloride

(i) Meclodin tablets (Samara Drug Iraq SDI): 5 mg metoclopramide hydrochloride for each tablet.

(ii) Metoclopramide tablets (Actavis-uk): 10 mg metoclopramide hydrochloride for each tablet.

(iii) MECLODIN Oral Drops (Samara Drug Iraq SDI): 4 mg/1 mL metoclopramide hydrochloride for each continer.

(iv) Primperan Injection (Sanofi aventis-France): 10 mg/2 mL metoclopramide hydrochloride for each ampoule.

(v) CLOPRAM Syrup (APM-Jordan): 5 mg/5 mL metoclopramide hydrochloride for each continer.

Recommended procedure

A liquot solution of pure (MCP-HCl) 0.1-16 $\mu g.mL^{-1}$ were transferred into series of 25 mL volumetric flasks then 0.5 mL of 1 M HCl solution was added, followed 1 mL of 0.01 M $NaNO_2$ solution and 2 mL of 0.2 M sulfamic acid were mixed and then left side for 2 min at 0-5°C. A series of tubes were taken, then 1 mL of 0.01 M NaOH was added to each tube, followed mixed with 1.5 mL of 0.01 M (DOX-HYC), the contents of these tube were mixed with previous contents of 25 mL of volumetric flask, complete to 25 mL of distilled water and then allowed to stand at room temperature for 15 min. The absorbance of each solution was measured at 452 nm against a blank solution prepared by the same way without (MCP-HCl).

Procedure of pharmaceutical preprations (tablet, syrup, oral drop and injection)

Tablets

A five tablets 5, 10 mg/table of (MCP-HCl) were weighted and pulerized, A portion g of these tablets which equivalent to 0.01 g of MCP. HCl was weighed and dissolved in distilled water and transferred into volumetric flask capacity 100 mL, the volume was completed with water to the mark. This solution was shaked well and filetred for using in the procedure.

Syrup

The content of two container of (MCP-HCl) syrup (5 mg/5 mL syrup) were mixed well and 10 mL of the syrup was quantitatively transferred into 100 mL volumetric flask and compeleted to the mark with distilled water, then calculated the concentration of (MCP-HCl) depending on the standard calibration curve.

Oral drops

The content of three container of (MCP-HCl) oral drops 4 mg/mL were mixed well and 2.5 mL of oral drops was quantitatively transferred into 100 mL volumetric flask and compeleted to the mark with distilled water, then calculated the concentration of (MCP-HCl) depending on the standard calibration curve.

Injections

The content of five container of (MCP-HCl) ampouls 10 mg/2 mL were mixed well and 2 mL of injections was quantitatively transferred into 100 mL volumetric flask and compeleted to the mark with distilled water, then calculated the concentration of (MCP-HCl) depending on the standard calibration curve.

RESULTS AND DISCUSSION

Preliminary studies

In this study, the diazotization reaction of metoclopramide hydrochloride (MCP-HCl) wih sodium nitrite ($NaNO_2$) in the presence of hydrochloric (HCl) acid was formed diazonium salt, then coupling with doxycycline hyclate (DOX-HYC) in sodium hydroxide medium to form a yellow water souble azo dye that showed a maximum absorbance at 452 nm Fig. 2 against the blank solution.

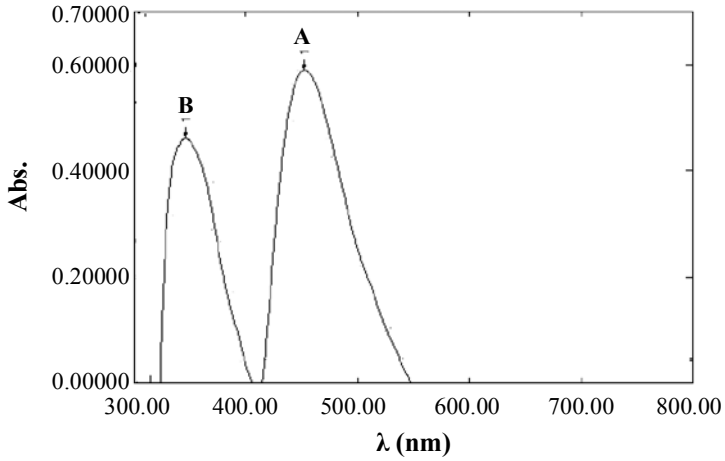
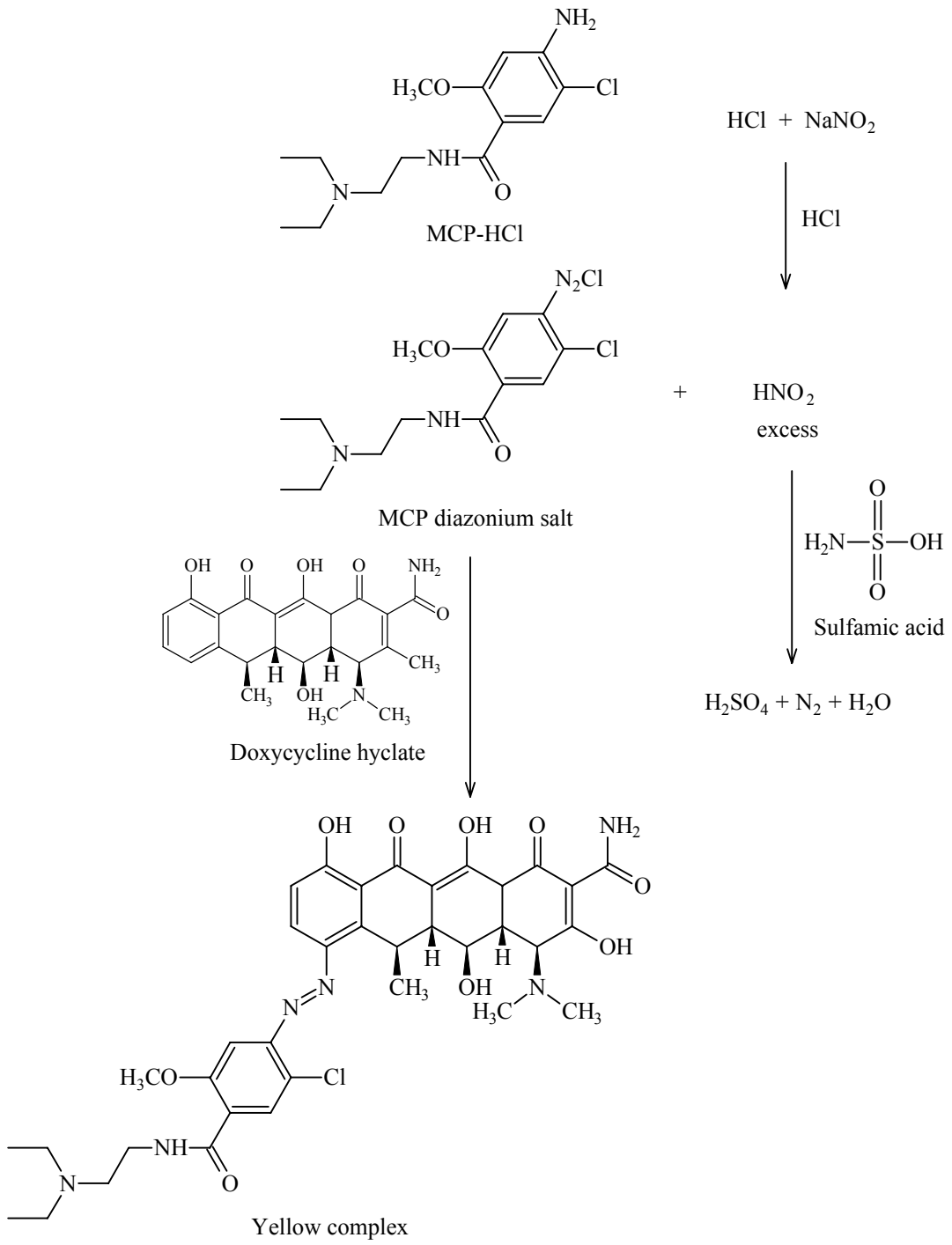


Fig. 2: Absorption spectra of A: (6 ppm) of MCP-HCl treated according to the procedure and measured against DOX-HYC reagent blank, B: the DOX-HYC reagent blank measured against distilled water. The suggested reactions equations are described in the following equation (Scheme 1)



Scheme 1: Proposed mechanism of the reaction between MCP-HCl and DOX-HYC

Optimization of reaction conditions

Effect of sodium nitrite volumeand time

The effect of sodium nitrite amount was studied by using diffirent volumes 0.3-3.5 mL of 0.01 M $NaNO_2$ solution. The results are shown in Fig. 3. 1 mL of $NaNO_2$ solution was selected as preffered volume that required 2 min reaction for diazotization process.

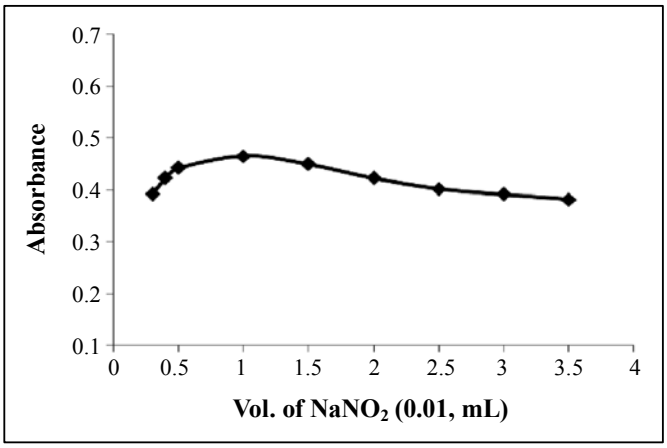


Fig. 3: The effect of sodium nitrite volume on the diazotization process

Effect of hydrochloric acid volume

Different volume of hydrochloric acid were used 0.2-3 mL. The results showed (Fig. 4) that 0.5 mL of HCl solution gave the maxiumam absorption.

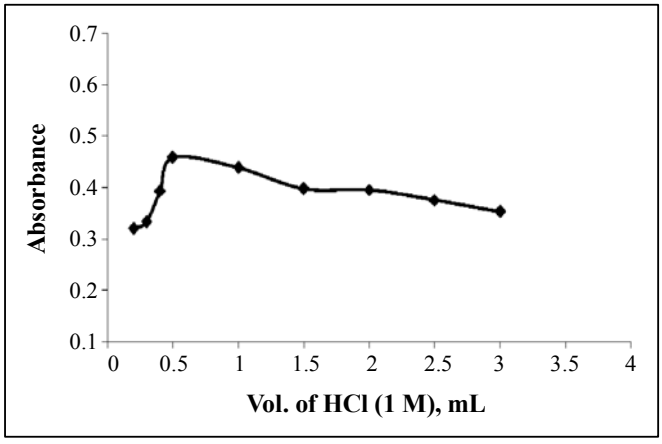


Fig. 4: The effect of hydrochloric acid volume that required for diazotization process

Effect of sulfamic acid volume and time

The effect of sulfamic acid volume was tested by using different volume 0.4-4 mL and the results are shown in Fig. 5. 2 mL of sulfamic acid was selected as perffered volume that required 2 min reaction time to remove the excess amount of nitrous acid.

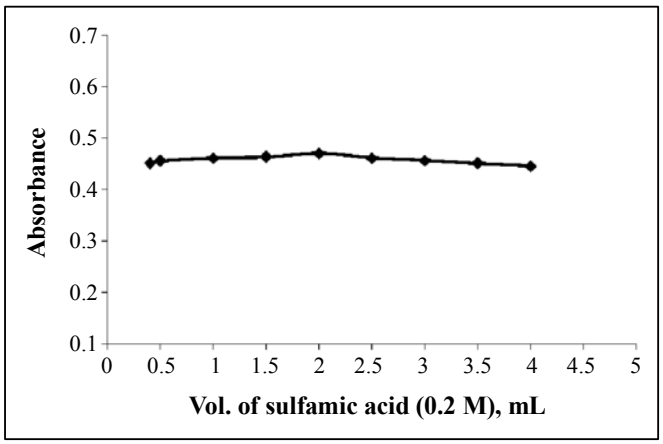


Fig. 5: The effect of sulfamic acid acid volume that required to remove of excess amount of nitrous acid

Effect of reagent (DOX-HYC) volume

Different volume of doxycycline hyclate were tested 0.3-3 mL and the results are shown in Fig. 6. 1.5 mL of it was used for coupling with metoclopramide hydrochloride to give color azo.

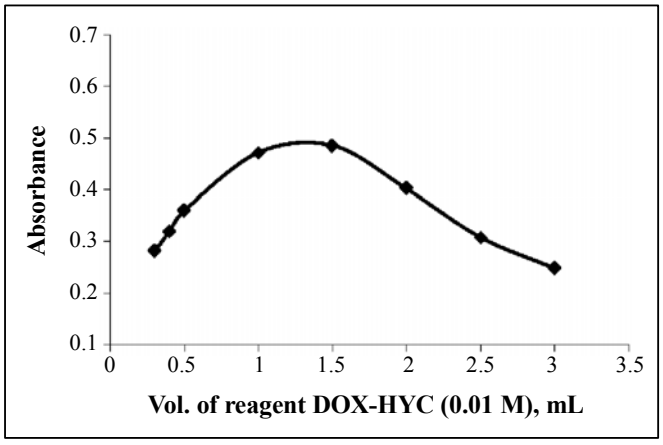


Fig. 6: The effect of reagent (DOX-HYC) volume

Effect of time

The results given in Fig. 7 show that, the azo-dye gave a maxiumam absorption after 15 min and remains stable for 24 hr, this means the complex is high stability.

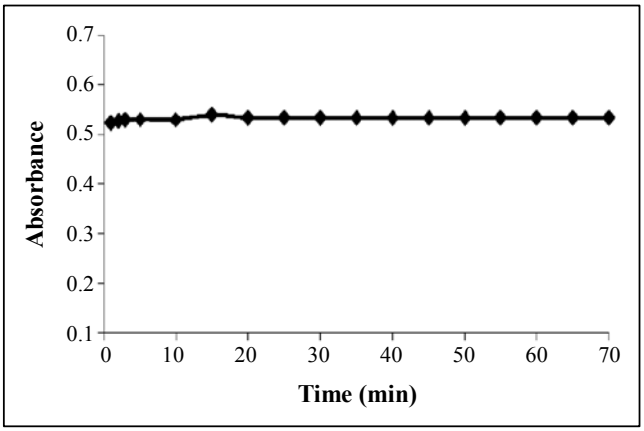


Fig. 7: The effect of time on stablitiy of product

Effect of temperature

The effect of temperature was tested by using different temperature 1-60°C. The results are shown in Fig. 8. The azo-dye was remained constant between 1-30°C and gave a maximum absorption but in high temperature the absorbance was decreased due to dissociation of azo-dye. This behavior may be explained on the basis that by increasing dyes concentration, higher dissociation of these dyes was observed.[19,20]

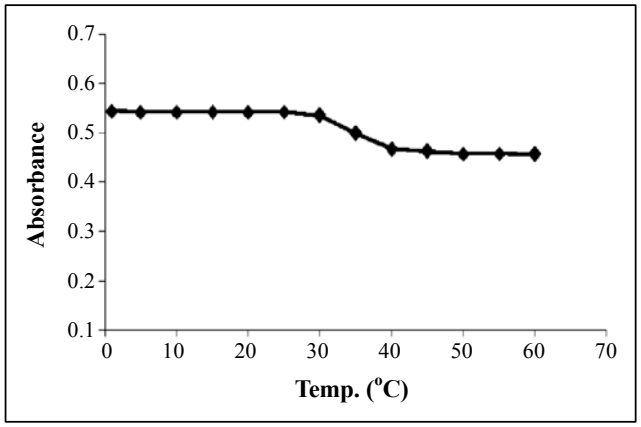


Fig. 8: The effect of time on stability of product

Calibration curve and sensitivity

Fig. 9 explain the calibration caurve of complex that compliant to beer law in the rang 0.1-10 ppm from concentration of metoclopramide hydrochloride (MCP-HCl) at 452 nm and other parameters are shown in Table 1.

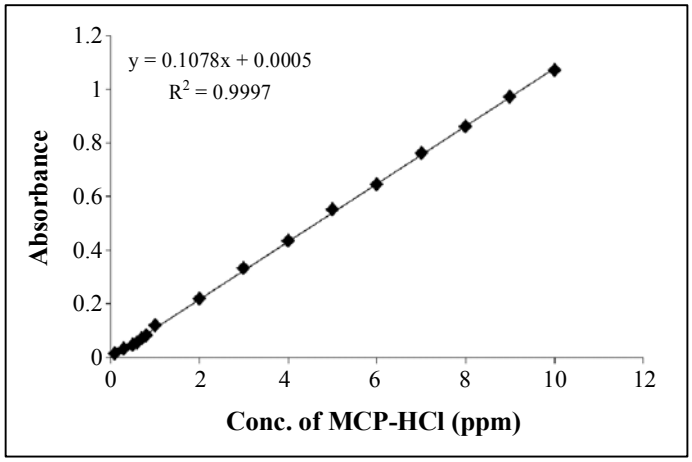


Fig. 9: Calibration curve of metoclopramide hydrochloride (MCP-HCl)

Table 1: Analytical characteristics of proposed method

Parameter	Proposed method
Regression equation	Y = 0.1078x + 0.0005
Slope	0.1078
Correlation coeficient	0.9997
Linear range (ppm)	0.1-10
Molar absorpivity ($L.mol^{-1}.cm^{-1}$)	3.81×10^{4}
Limit of detection (LOD) (ppm)	0.012
Limit of quantification (LOQ) (ppm)	0.043
Sandell's sensitivity, S ($\mu g\ cm^{-2}$)	0.009

Nature and stability constant of the complex

The stoichiometry of the product was studied by appling the continuous variation method. The results are shown in Fig. 10 for the ratio between the metoclopramide hydrochloride to doxycycline hyclate is 1:1. The stability constant of the complex is (1.1×10^{8}) L.mol $^{-1}$.cm^{-1}.

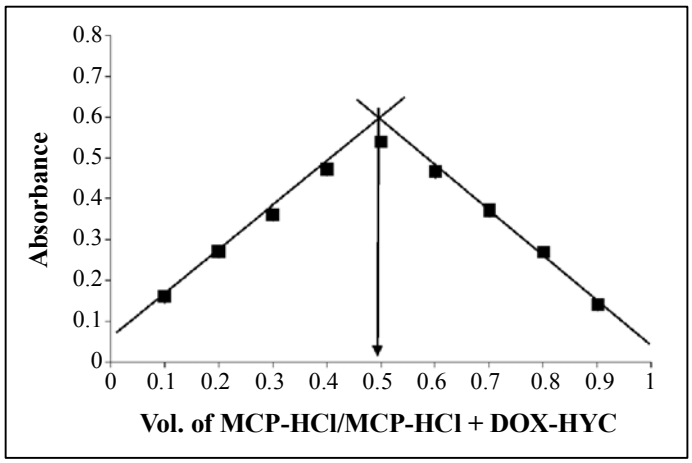


Fig. 10: The continuous variation of complex

Accuracy and precision of the proposed method

The accuracy and precision were tested by using metoclopramide hydrochloride in pure from at different concentration. The results are shown in Table 2, which indicate the high accuracy and precision of the proposed method.

Table 2: Accuracy and precision of proposed method

S. No.	Conc. of MCP-HCl (µg.mL^{-1})		Error (%)	Recovery (%)	R.S.D (%) n = 5
	Taken	Found			
1	0.7	0.69	-1.42	98.58	0.739
2	5	5.03	+0.61	100.61	0.225
3	7	6.98	-0.28	99.72	0.175

Interference study

The effect of some excipients that present with metoclopramide hydrochloride (MCP-HCl) in pharmaceutical preparations such as lactose, starch, talc and polyvinylpirrolidone (PVP) were studies by using solution containing 7 μg mL^{-1} of (MCP-HCl) but excess amount (10-fold excess) of each excipient. The results are shown in Table 3 and none of these excipients interferened.

Table 3: Effect of interference

Interferences	Conc. of MCP-HCl (μg.mL^{-1}) Found	Error (%)	Recovery (%) n = 3
PVP	6.992	-0.101	99.899
Tween 80	6.98	-0.278	99.722
Mennitol	7.025	+0.362	100.362
Lactose	7.088	+1.268	101.268
Acacia	6.989	-0.145	99.855
NaCl	7.054	+0.782	100.782
Sucrose	7.042	+0.605	100.605
Aspartate	7.079	+1.136	101.136
Benzoic acid	7.104	+1.490	101.490
Talc	7.116	+1.666	101.666
Starch	7.070	+1.003	101.003
Mg Sterate	7.095	+1.357	101.357
Microcrystalline cellulose	7.085	+1.224	101.224

The conc. of MCP-HCl μg.mL^{-1}, which taken is 7 ppm

Pharmaceutical applications

The method was applied on different pharmaceutical preparations (tablet, injection, oral drop, syrup) by using three concentration of each one. The results are shown in Table 4. A good recoveries and the results of this method were compared with official method (British Pharmacopoeia. 2013)[21] in Table 5 that showed there is no significant different between the official method and the proposed method.

Table 4: Pharmaceutical applications for MCP-HCl using the proposed method

Drug	Pharmaceutical preparation	Conc. MCP-HCl (μg.mL^{-1})		Error (%)	Recovery (%)	R.S.D (%) n = 5
		Taken	Found			
Metoclopramide hydrochloride	MECLODIN tablets	4	4.027	+0.675	100.675	0.364
		6	6.081	+1.36	101.36	0.42
		8	7.957	-0.537	99.463	0.224
	Metoclopramide tablets	4	3.964	-0.88	99.12	0.74
		6	5.905	-1.5	98.5	0.622
		8	8.038	+0.48	100.48	0.258
	MECLODIN oral drops	4	3.918	-2.04	97.96	0.389
		6	5.987	-0.216	99.787	0.525
		8	8.020	+0.255	100.255	0.306
	Primperan Injection	4	3.990	-0.232	99.767	0.465
		6	5.988	-0.185	99.814	0.401
		8	7.964	-0.441	99.558	0.260
	CLOPRAM syrup	4	3.962	-0.92	99.072	0.844
		6	6.081	+1.36	101.36	0.423
		8	7.935	-0.81	99.19	0.492

Table 5: Application of the proposed and official methods to determination of (MCP-HCl) in pure and dosage forms

Pharmaceutical preparations containing (MCP)	Proposed method		Standard method		F Value	t Value
	Recovery % $(\bar{x}_i)_1$	$(X_{i1}-X_1)^2$	Recovery % $(\bar{x}_i)_2$	$(X_{i2}-X_2)^2$		
Pure MCP	99.636	0.01	99.90	0.160	1.23 9.605	0.78 2.31
MECLODIN tablets	100.499	0.579	100.75	0.2025		
Metoclopramide tablets	99.366	0.138	100.26	0.0016		
MECLODIN oral drops	99.334	0.162	100.25	0.0025		
Primperan injection	99.716	0.0004	100.75	0.2025		
CLOPRAM syrup	99.874	0.018	99.89	0.168		
	$\bar{X}_1 = 99.373$ E = 0.910		$\bar{X}_2 = 100.3$ E = 0.737			

CONCLUSION

A simple, sensitive, rapid spectrophotometric method for determination of metoclopramide hydrochloride (MCP-HCl) drug solution has been developed. It is based on diazotization process of metoclopramide hydrochloride (MCP-HCl) and coupling with doxycycline hyclate (DOX-HYC) to form azo-dye yellow coloured soluble in water that exhibits a maximum absorption at 452 nm. The proposed method was applied successfully to determination of metoclopramide hydrochloride (MCP-HCl) in pharmaceutical preparations.

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