The development of analytical methods to determine metoclopramide-hydrochloric acid in the standard raw and it compared with pharmaceuticals

Khawla Salman Abd-Alrassol[1], Qutaiba A. Qasim[2], Maitham Ali AL-Rikabi[3], H. N. K. AL-Salman[*1]

[1]Department of pharmaceutical chemistry, College of pharmacy, Basrah University, Iraq
[2]Department of Clinical Laboratory Sciences, College of pharmacy, Basrah University, Iraq
[3]Department of Clinical Pharmacy, College of pharmacy, Basrah University, Iraq

ABSTRACT

The three novel easy, to the prepare and sensitive spectral methods, were used to estimate metoclopramide in both standard and pharmaceuticals. The effective double–electron, was present in the metoclopramide compound helps to interact in an acidic medium with a reagent such as diazetide resorcinol and 8-hydroxyquinoline reagents. The present article was extended to find out three analytical methods with UV-V is the detector. In both A and B methods, two azo-dyes are formed, they are orange-red and red stable and have high water solubility, giving highest absorption values at 415 nm and 485 nm but the C method will depend on a complex colour configuration with the p-benzoquinone reagent, which has a maximum absorption at a wavelength of 285 nm. Beer's law was applied in a range of concentrations between 1 and 10 μg / ml, 2-20 μg / ml and 1-30 μg / ml. The values of the molar absorption factors were (4.1224×10^4, 3.0229×10^4 and 1.7373×10^4) L mol-1cm-1 with a sensitivity of Sandell's equal to 0.2606×10-4, 0.9834×10-4 and 0.2568×10 - 4 μg cm-2 to methods A, B respectively and LLOD values were 0.255, 0.553 and 0.158 μg / ml to methods A, B and C. LLOQ 0.512, 0.898 and 0.455 μg / ml to methods A, B, C respectively. The constant fixed Kf configuration was also calculated for the colored outputs of the reaction where it was found to be equal to 43.6435×10^8, 54.6261×10-8 and 17.29099×10^6 L2 mol-2 to all methods A, B, C respectively. The values of G were calculated based on -43.9293 KJ / mol, -44.3735 and -51.2019. G values, molar absorption factor, Sandell sensitivity, detection limit.

*Corresponding Author

Name: H. N. K. AL-Salman
Phone: +9647702683703
Email: hsennaserh@yahoo.com

INTRODUCTION

The chemical formula to metoclopramide hydrochloride, C_{14}, ΔH, Cl, N, O. HCl with molecular weight (354.3 gm /mol) the scientific name under the IUPAC system is 4-amino-5-chloro-N-(2-diethylamino) ethyl-2 ethlyI-2 ethyl-2). Figure 1 shows the structural form of hydrochloride metoclopramide. Metoclopramide hydrochloride is an odourless white crystalline powder. 1 mg of metoclopramide is soluble in 0.7 gm of water at 25 C, and 3 gm of it is soluble in ethanol (96%), 55 gm in chloroform (90%) and soluble in diluted hydrochloric acid which is practically soluble in

ether. Metoclopramide hydrochloride contains ionization constants with values of 0.42 (pK$_1$) and 9.71(pK$_2$) (Yuvaraja and Khanam, 2014; Sawale et al., 2016; Shakeel et al., 2014; . et al., 2014; Zhai et al., 2017) . Metoclopramide strengthens the oesophagal muscle of the oesophagus and reduces gastric acid reflux. Metoclopramide hydrochloride is used to reduce nausea and vomiting when combined with chemotherapy, and it speeds up gastric emptying of harmful intestinal and liquid meals. It is an alternative benzamide drug that is used, because of its Kinetic properties to reduce disorders of gastrointestinal degeneration, such as ileal motility, stomach, oesophagus and reduce indigestion, vomiting and nausea (Adegoke, 2012; Satyanary and Nagesara, 2012; Okram et al., 2012) . Metoclopramide hydrochloride has been used because of its pro-gastrointestinal effects through cholinergic stimulation of gastrointestinal diseases caused by radiotherapy, chemotherapy and post-operative nausea. Several analytical methods were used to determine metoclopramide hydrochloride, such as High–performance liquid chromatography, gas chromatography, voltage measurement, voltage measurement method, chemical fluorescence. Metoclopramide and aspirin can be estimated together in human plasma and in pharmaceutical preparations by using chemical fluorescence and phosphorescence (Neha et al., 2015; Khaleel et al., 2011a; Vandenplas and Hauser, 2015) .

Most widely used methods to metoclopramide in pharmaceuticals are spectral, in which the metoclopramide is classified within the easy complexes, which can be readily estimated by the ultraviolet spectral method. The conjugation reaction can also be used to determine metoclopramide in the alkali medium. However, the best methods are used to estimate that metoclopramide hydrochloride and pyridoxine hydrochloride in human plasma are HPLC-UV methods. The electrolysis method was used to estimate metoclopramide by using a modified and electrode carbon. A sequential flow injection analysis can be performed to determine metoclopramide. (Patil and Nandibewoor, 2015; Gulsu et al., 2012; Dusane et al., 2011; Elmansi et al., 2016) .

In this study, three spectral methods were used to determine metoclopramide hydrochloride using colour reagents such as diazotzil reaction with resorcinol, 8-hydroxyninol and p-benzoquinone as a coupling agent to form azo-dye in alkaline medium at room temperature (Alshirifi and Abbas, 2015; Aljarah and Obedagha, 2014) .

MATERIALS AND METHODS

Instrumentation:

Double beam UV-visible spectrophotometer (UV-Jenawa Model 1100) was used for absorbance with a 10 mm quarty cell.

Materials and reagents:

All reagents with a high degree of analytical purity, deionized water were also used. Metoclopramide hydrochloride was purchased from Merck. The pharmaceutical dosage used in this work Primperan tablets (metoclopramide tablets) with 10 mg of metoclopramide HCl / tablet contains 5 mg of metoclopramide (Sifar-Istanbul / Turkey) HCl / tablet and Metal Injection (Sanofi Aventis Egypt) contains 10 mg / 2 ml (Jawad and Kadhim, 2013) .
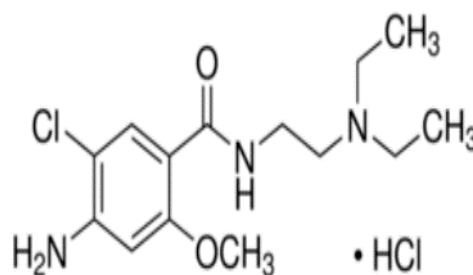

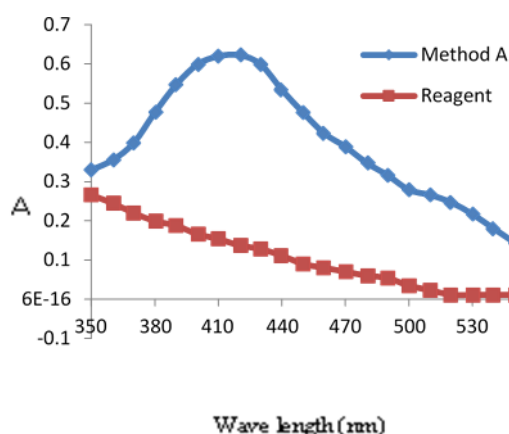**Figure 1: Structure of metoclopramide hydrochloride**

Figure 2: Absorption spectra of metoclopramide hydrochloride azo dye with the resorcinol reagent (5.0μg/mL)

0.5% sodium nitrite solution.

The sodium nitrite reagent was supplied by BDH Chemicals Ltd. The solution is prepared by dissolving 0.5 g of NaNO$_2$ in a volumetric flask and supplemented with 100 ml of deionized water.

Sodium hydroxide solution 0.5 N:

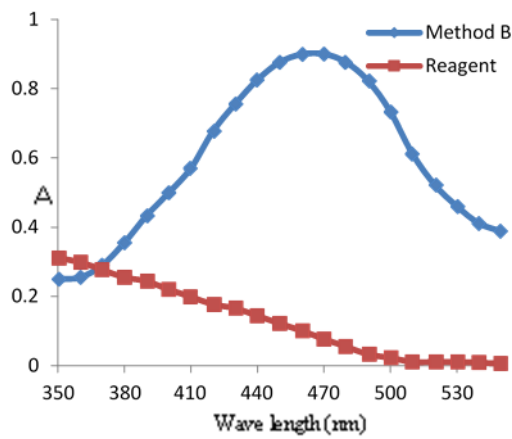This solution is prepared by taking the exact weight of the base and dissolving in 100 ml of deion-

Figure 3: Absorption spectra of metoclopramide hydrochloride azo dye with the 8-hydroxyquinaldine reagent (10.0 μgmL^{-1})
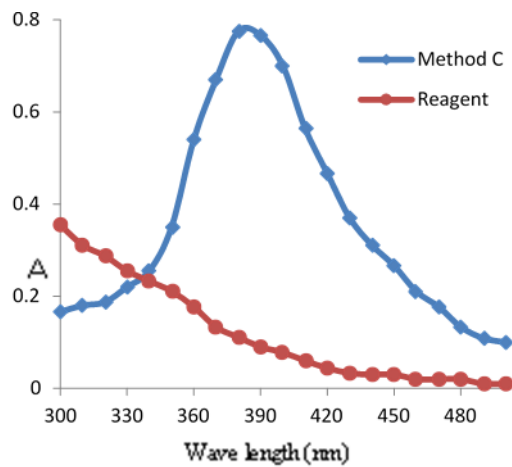

Figure 4: Absorption of metoclopramide hydrochloride with the p-benzoquinonere agent (15.0 μgmL^{-1})
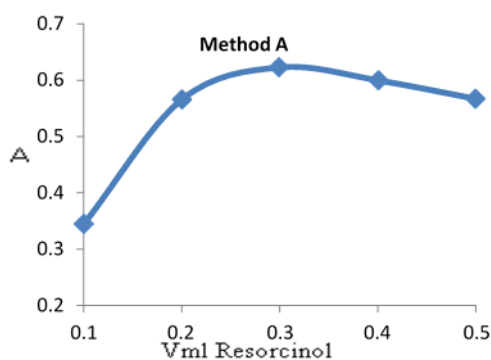

Figure 5: Effect of resorcinol reagent volume on absorbance
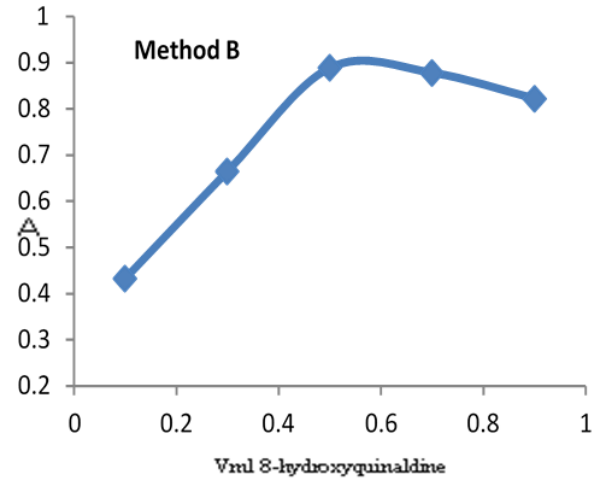

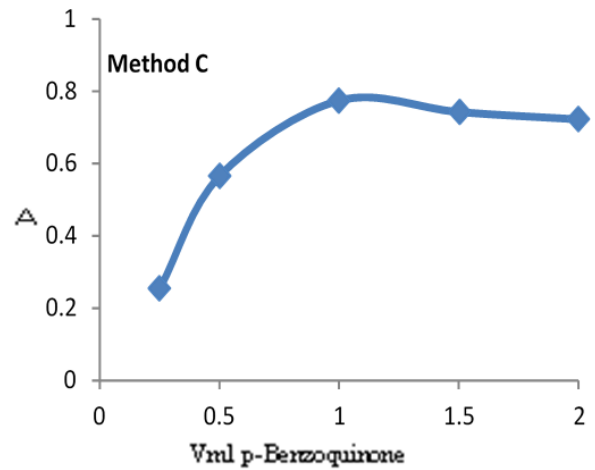**Figure 6: Effect of 8-hydroxyquinalidine reagent volume on absorbance**

Figure 7: Effect of p-benzoquinol volume on absorbance

ized water to prepare 0.5 N solution by dissolving 2 g of substance in 100 ml of deionized water [Deokate and Gorde, 2014].

8-hydroxyquinaldinereagent solution 0.5%.

Pure reagent supplied by BDH Chemicals Ltd. This solution was prepared by dissolving 0.5 g of 8-hydroxyquinoline reagent in a 100 ml volumetric flask [Okram *et al.*, 2012].

0.5% resorcinol.

0.5% resorcinol solution was prepared by dissolving 0.5 g of resorcinol (supplied by BDH Chemicals Ltd) in a 100 ml flask [Devi *et al.*, 2016].

1% p-benzoquinone solution.

1% of the p-benzoquinone solution was prepared by dissolving 1 g in a minimum amount of ethanol and making the volume to 100 ml with ethanol [Malih *et al.*, 2012].

Sodium hydroxide solution 0.5 N

This solution is suitably prepared by taking the exact weight of the base and dissolving it in 100 ml of deionized water to prepare a 0.5 N solution by dissolving 2 g of substance in 100 ml of distilled water (Al-Rufaie, 2016b) .

Hydrochloric acid solution 0,5 N

This solution is prepared by diluting appropriately a 36% concentrated solution of hydrochloric acid in a 250 ml graduated flask with deionized water (Al-Rufaie, 2016a) .

Metoclopramide hydrochloride standard solution

Metoclopramide hydrochloride was obtained from (SDI, Samara, Iraq).   A solution of 1,000 μg / ml metoclopramide hydrochloride was prepared by dissolved 100 mg of metoclopramide hydrochloride in 100 ml of deionized water and diluted for final concentrations [Hemalatha et al., 2011].
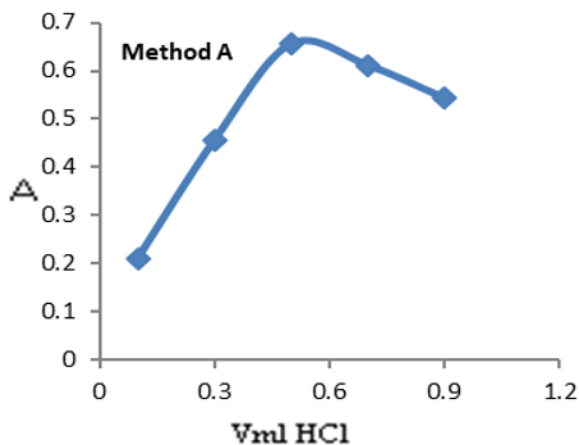

Figure 10: Effect of HCl (0.5N) volume on absorbance
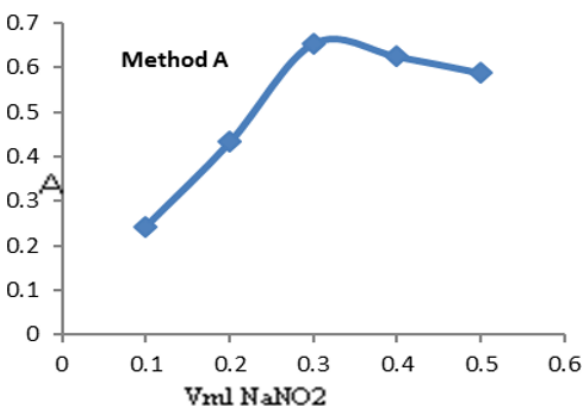

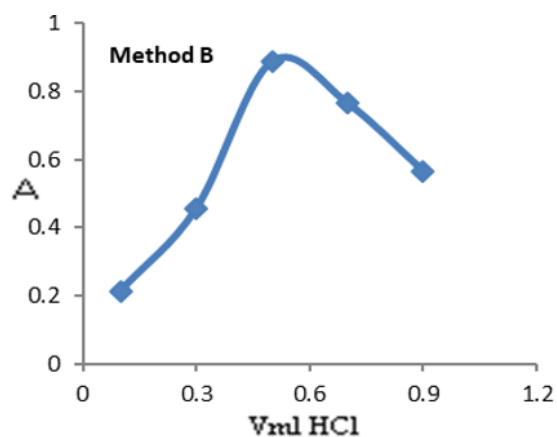**Figure 8: Effect of NaNO$_2$ volume on absorbance**

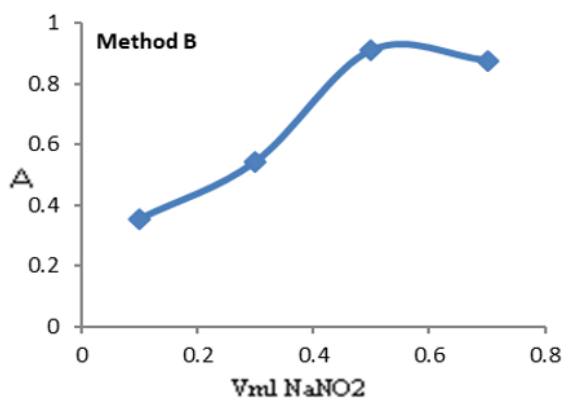**Figure 11: Effectof HCl (0.5N) volume on absorbance**

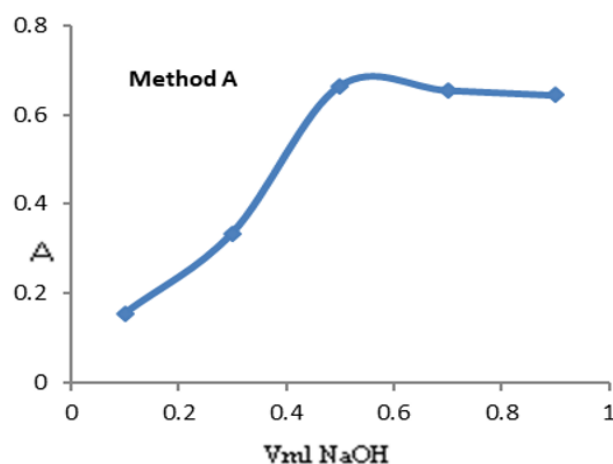**Figure 9: Effect of NaNO2 volume on absorbance**

Figure 12: Effect of NaOH (0.5N) volume on absorbance

Procedure:

The three spectral methods have been used to analysis of hydrochloric metoclopramide by using different coloured reagents:
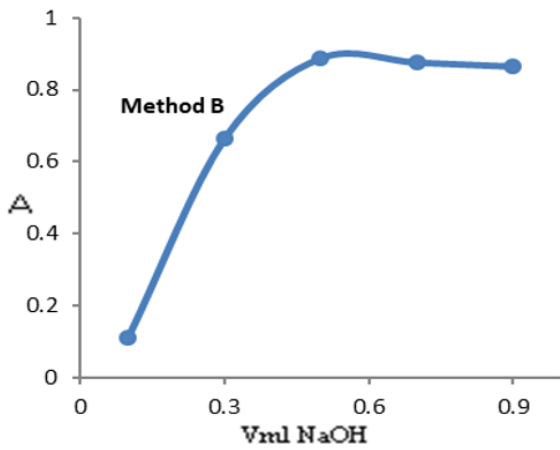
Method A

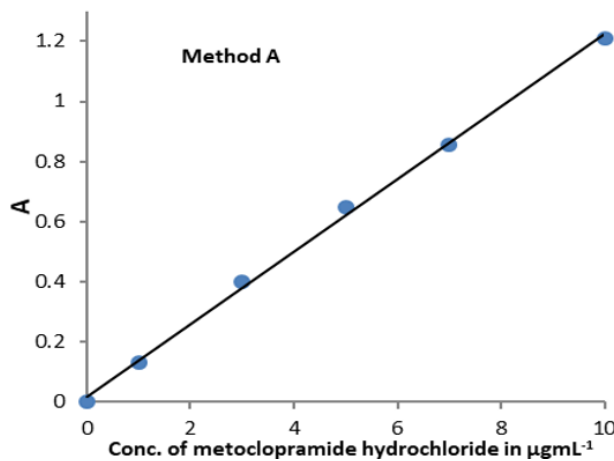**Figure 13: Effect of NaOH (0.5N) volume on absorbance**
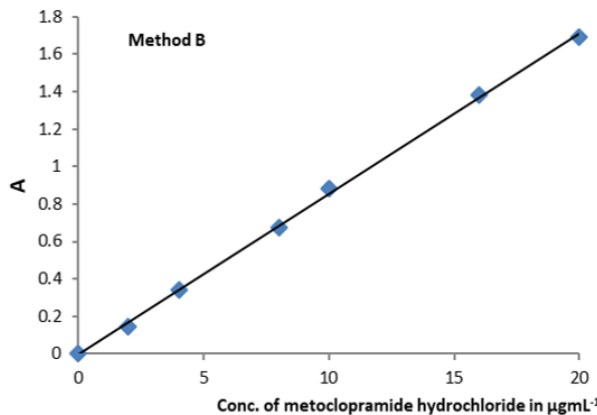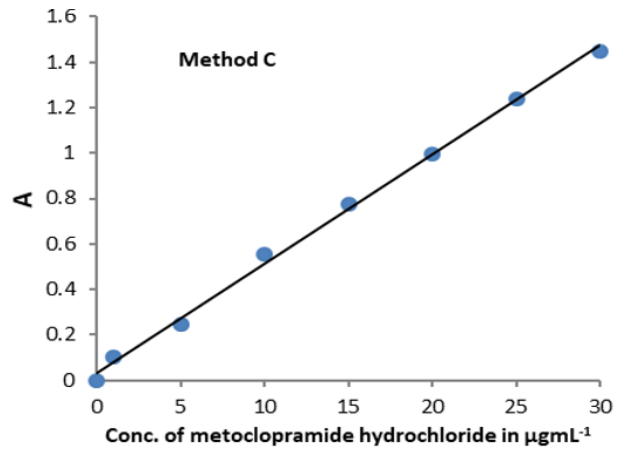

Figure 16: The calibration curve in method-C

Different concentrations in the range of 1-10 mg/ml (0.1 volumes, 0.3, 0.5 0.7, 0.9 and 1.0) ml of the standard solution of metoclopramide hydrochloride (100 μg / ml) were transferred and measured in the number of volumetric flasks with 10 ml volumes using a micro-pippet. To each flask were added 0.3 ml of 0.5% of NaNO2 and 0.5 ml of 0.5 N of HCl. After three minutes, 0.3 ml of resorcinol was added 0.5% and 0.5 ml of 0.5 N NaOH solution and added with deionized water. The absorbance of the coloured product was measured after 10 minutes, the colour absorbance at 415 nm against the corresponding white reagent.

Various concentrations were prepared in the range 2.0-20 mg / ml volume (0.2.0.4,0.6,0.8,1.0,1.2,1.4,1.6.1.8 and 2.0) ml of the standard solution of metoclopramide hydrochloride (100 mg / ml) in a series of volumetric flasks (10 ml) by means of a micro-pippet. For each flask, 0.5 ml of 0.5% NaNO$_2$ solution and 0.5 ml of 0.5 N solution of 8-hydroxyquinoline and 0.5 ml of 0.5% solution of 0.5 N NaOH and diluted to the mark with deionized water. The absorbance of the coloured product was measured at 485 nm against the solvent as blank after 10 minutes.

Method C

In the series of volumetric flasks (10 ml), transfer concentrations of the standard solution of 100 μg / ml of metoclopramide-HCl equivalent to 1.0-30 μg / ml, add one ml of p-benzoquinone solution, make up the volume to 10 ml with deionized water, then the absorbance was measured after 10 minutes at 385 nm against a blank. The calibration curve was constructed from the concentrations of metoclopramide hydrochloride (μg / ml) against absorbance.

The essay procedure to tablets of metoclopramide hydrochloride:

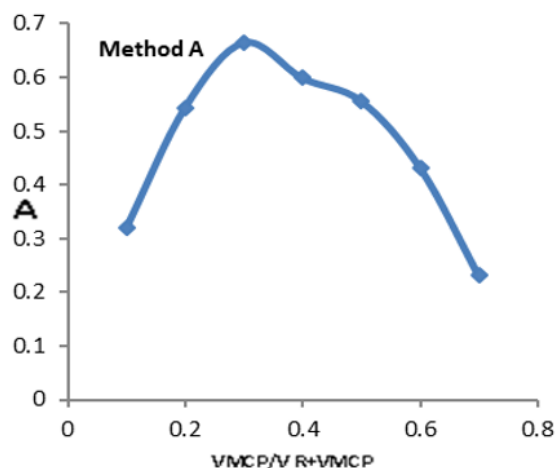**Figure 14: The calibration curve in method-A**

Figure 15: The calibration curve in method-B

Figure 17: Job's method for method A
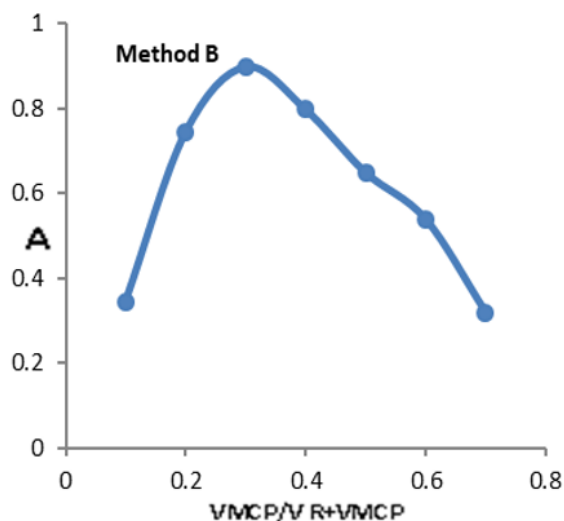

Figure 18: Job's method for method B
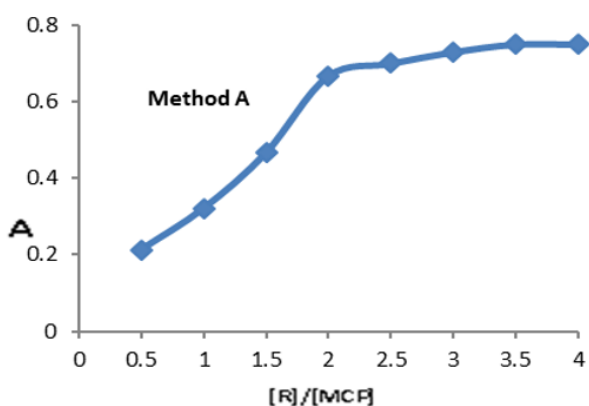
Figure 19: mole ratio method for method A
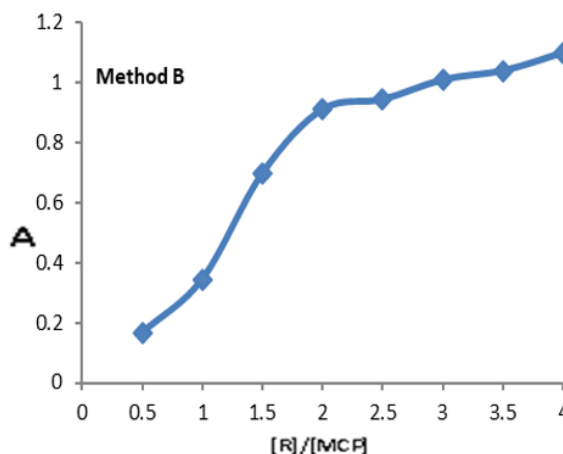
Figure 20: mole ratio method for method B

10 tablets were weighed and ground well, then mixed (5 mg and 10 mg). A fraction of the powder equivalent to 0.05 g of metoclopramide hydrochloride was weighed and dissolved in deionized water, mixed well and filtered using a filter paper. Then transfer to a 100 ml flask and complete to mark with deionized water. The solution was treated in the recommended way. The working solutions were prepared by diluting the resulting solution with deionized water.

RESULTS AND DISCUSSION

Determination of the Lambda max

The values of the absorption spectra of the coloured complexes of the reaction between the hydrochloride salt of metoclopramide and diazonium with the resorcinol or the 8-hydroxyquinoline reagent in acidic medium (in both methods A and B respectively) with respect to the reagent target. The sample shows the maximum absorption at 415 nm (method A) and 485 nm (method B). The reaction involved two steps to give a coloured product. Initially, metoclopramide hydrochloride is treated with sodium nitrite in an acid environment to give diazonium salt. In the second phase, the diazonium ion reacts with the coupling agent of resorcinol or 8-hydroxyquinoline (method A or B) to form an orange azo dye (method) and red colour (method B) in an alkaline medium. Method C, which includes the reaction between metoclopramide hydrochloride and p-benzoquinone, shows maximum absorption at 385 nm. The absorption spectra are shown in Figures 2, 3 and 4 .

Optimal conditions for the reaction

The effect of the various parameters on the absorption intensity, was optimized . all the experimental parameters were optimized by using 5.0, 10.0 and
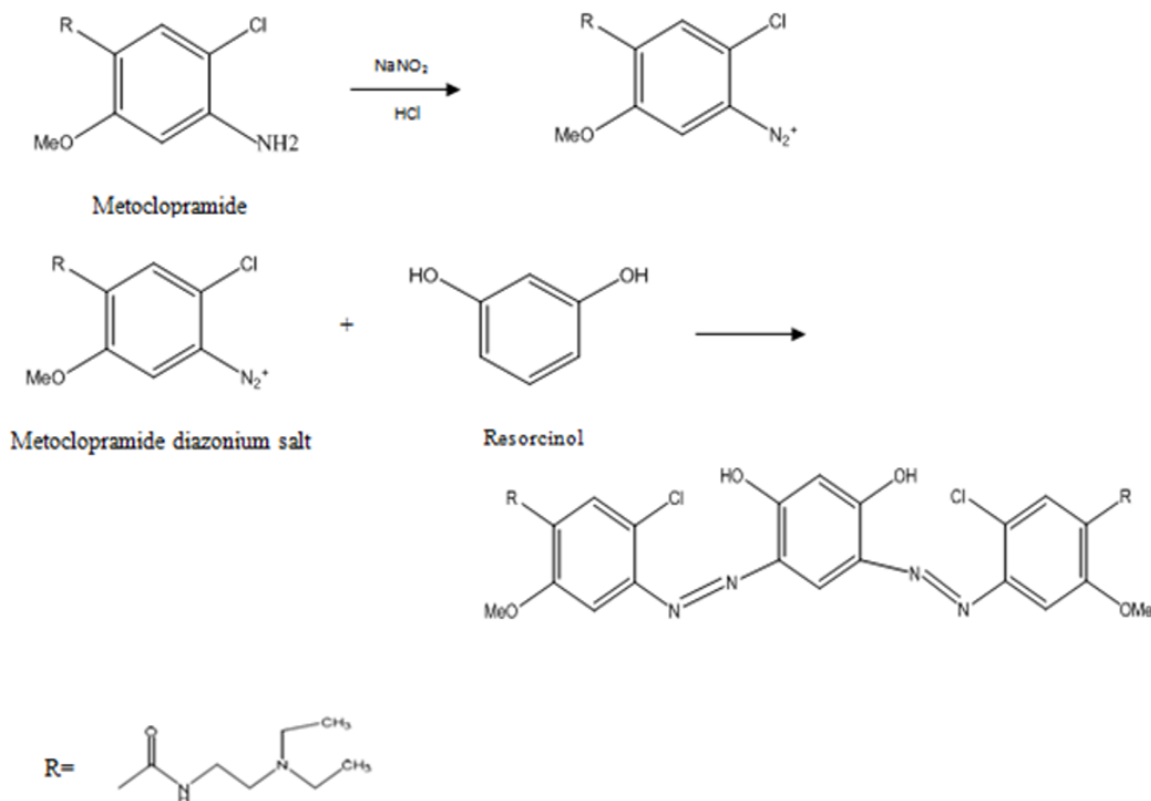
Figure 23: The proposed mechanisms of the products may be suggested as the following figures
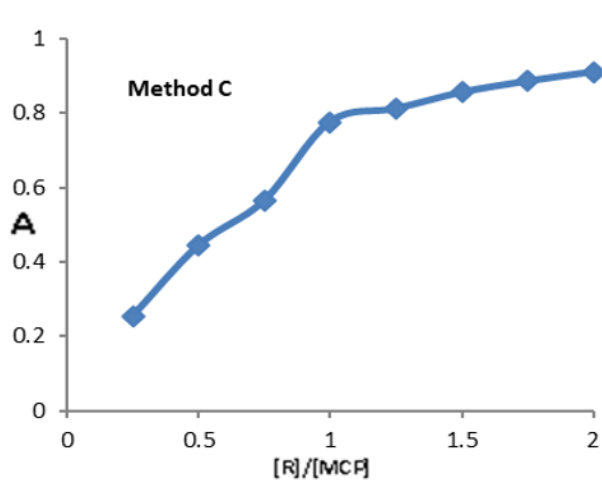
Figure 21: mole ratio method for method C
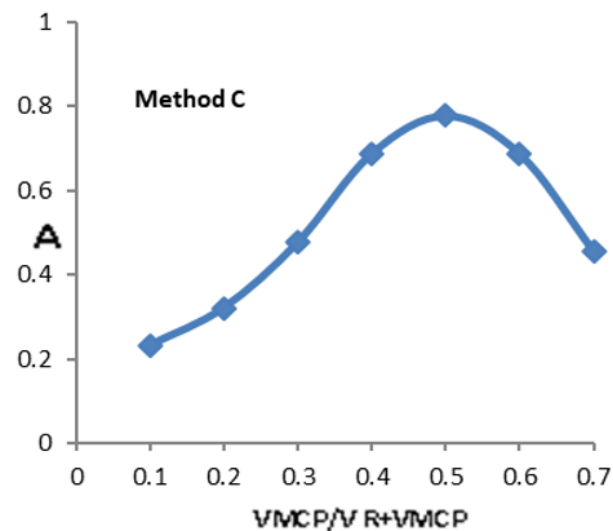
Figure 22: Job's method for method C

15.0 mg/ml metoclopramide hydrochloride with the three methods A, B, C respectively (Al-Rufaie *et al.*, 2013) (Figures 23, 24 and 25).

The effect of reagent volumes.

The reagent volumes were tested in the range of 0.1-0.5 mL and 0.5% resorcinol. The 0.3 ml were applied in subsequent experiments (method A) because they obtained the maximum absorption and the other 8-hydroxyquinoline in the range of 0.1-0.9 ml

at a concentration of 0.5%. The 0.5 ml volume was selected as the best volume that could be used for further studies due to this volume and focuses on the maximum absorption value (method B) as shown inFigure 5 and Figure 6 .

The quantities were tested within 0.25-2.0 ml of p-benzoquinone at a concentration of 1% (Al-Abbasi *et al.*, 2011; Khaleel *et al.*, 2011b; Menaka and
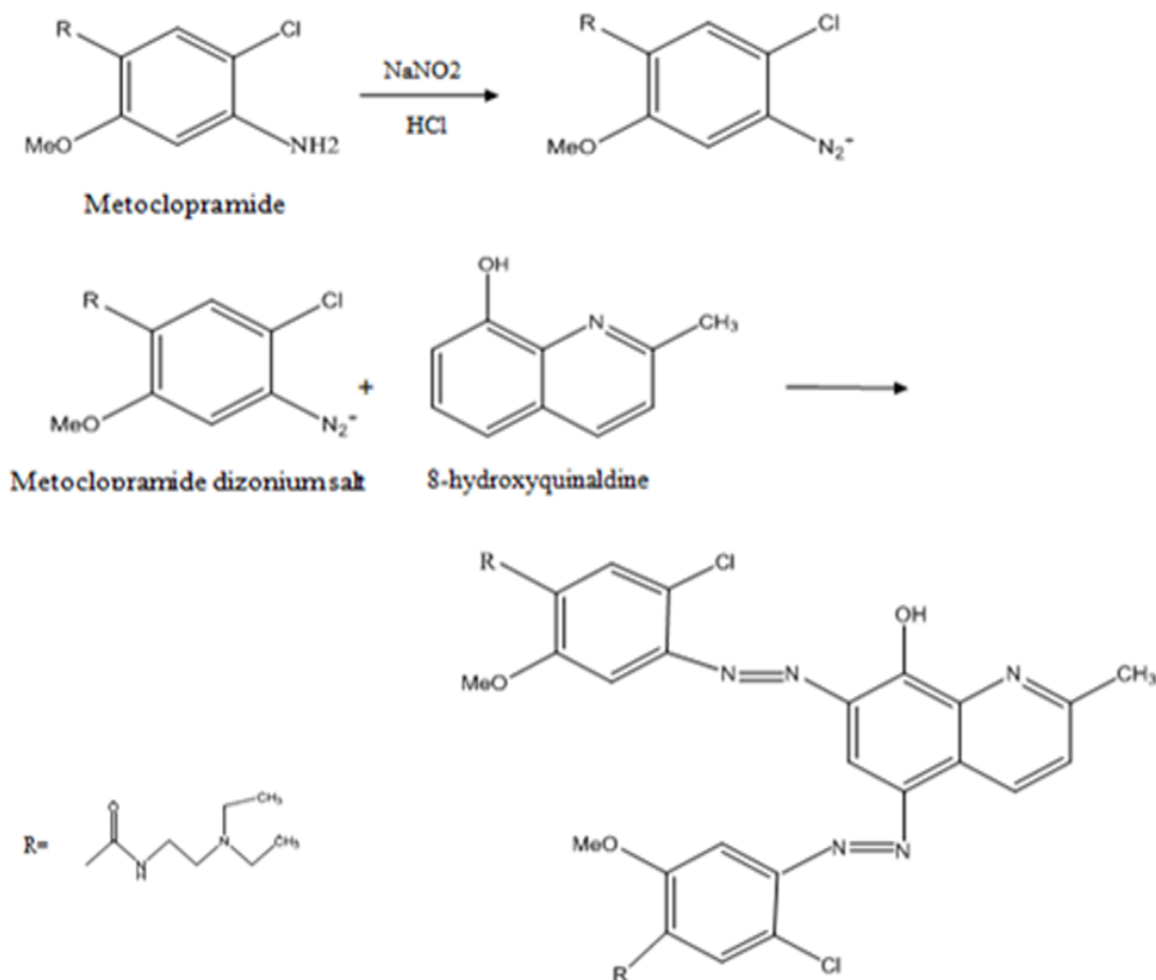
Figure 24: The probable reaction mechanism of the coupling reaction between metoclopramide and 8-hydroxyquinalidine (method-B)

Pandey, 2013) . It was found that 1.0 ml was appropriate for application in subsequent experiments (method C), Figure 7 .

Effect of sodium nitrite

The different volume of 0.5% in a range of 0.1-0.5 ml of NaNO2 was tested in the absorption density. It was observed that the volume of 0.3 ml of sodium nitrite was the optimal absorption volume (method A) (Figure 8). The NaNO2 volume of 0.5 ml was also selected for density absorption (method B) (Figure 9) (Rashmika *et al.*, 2013) .

Acid effect

Different acids such as H_2SO_4, HCl, HNO_3 and CH_3COOH were tested for absorption values in methods A and B. A 0.5 N concentration of 0.5 mL of hydrochloric acid was selected as this concentration gave the highest absorption of the measured product in both methods A and B (Jia *et al.*, 2010) (Figure 10 and Figure 11).

Effect of reaction time.

The azo coupling reaction was completed at 10 minutes and at 15 minutes for methods A and B. The coloured products were more stable at 24 hours in methods A and B, on the other hand, coloured products using p-benzoquinone and metoclopramide hydrochloride found completely in 10 minutes and stable for 24 hours (Poddar *et al.*, 2011) .

The effect of temperature

The effect of temperature on absorption intensity was studied at different temperatures in the range 5-45°C. The results indicate that the absorbance values decrease at higher temperatures, probably due to the dissociation of the compound. The maximum absorbance was found in the range of 20 to 35 °C. Therefore all studies were conducted at room temperature (Adegoke and Nwoke, 2008) .

The effect of Base volume :
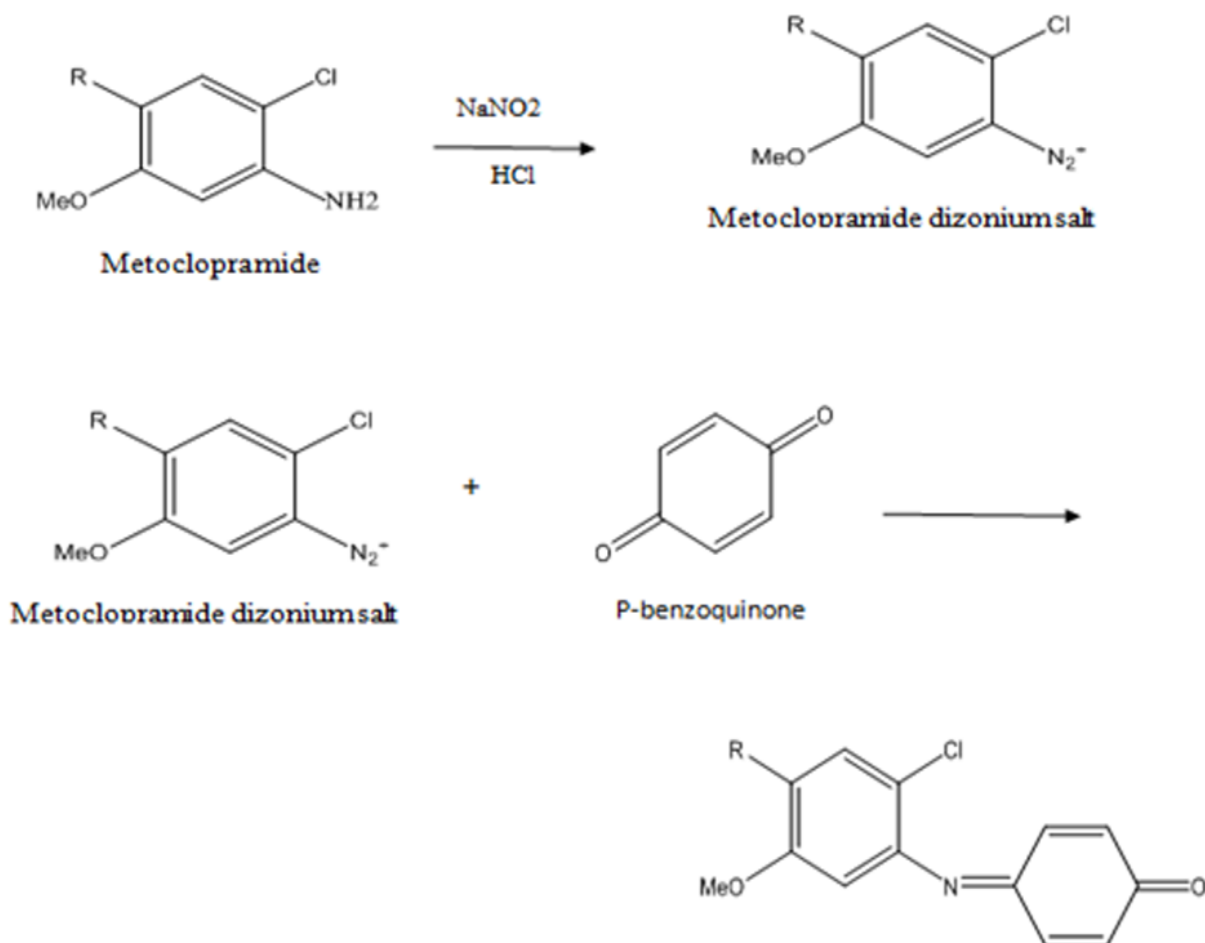
Figure 25: The probable reaction mechanism of the coupling reaction between metoclopramide and P-benzoquinone (methodC)

The effect of base concentration on the coloured product was tested by using different basic solutions, such as ammonium hydroxide, sodium acetate, potassium hydroxide, sodium carbonate and sodium hydroxide. The product of sodium hydroxide solution was given sensitivity and stability highly, so it was used in applied in subsequent experiments. different volumes of (0.1-0.9 ml) from 0.5 M NaOH solutions were tested. The results showed that 0.5 ml of sodium hydroxide solution is sufficient to the production of maximum reproducible and absorption intensity in both methods A and B as shown in Figures 12 and 13 . Partial decolonization of the product, maybe accruing in higher concentrations of the base (Annapurna *et al.,* 2009; Nancy *et al.*, 2018) .

The calibration curve:

Under optimal conditions studied, the metoclopramide-HCl calibration curves were designed for all methods A, B, C, illustrated in Figures 14 and 15 and Figure 16 , the linear relationship between the concentrations of metoclopramide HCl and absorbance and 1, 0-30 μg / ml to methods A, B, C, respectively, with a correlation coefficient of 0.988, 0.9999 and 0.9987 respectively to methods A, B, C. It was found that the molar absorption coefficients of the methods A, B, C are 4.1224 $\times$ 104 $\times$ 3.0229 $\times$ 1.7373 104 and 104 L mol-1 cm-1 for methods A, B, C, respectively (Yadav *et al.*, 2010) . The Sandell's sensitivity was 0, 3606 $\times$ 10 -4, 0.9834 $\times$ 10-4 and 0.2568 $\times$ 10-3μg.cm - 2 to methods A, B, C, respectively, all results are listed in Table 1 .

Stoichiometry

The stoichiometry of metoclopramide hydrochloride with diazonium salt and resorcinol or 8-hydroxyquinoline solutions was studied in methods A and B using the working method and the molar ratio method (Naggar *et al.*, 2009) as shown in Figures 17 and 18 and Figure 22 . the results showed that 1: 2 was formed at 415 nm and 485 nm respectively for methods A and B, instead, the results show

Table 1: The analytical parameter for methods A, B and C

Method-C	Method-B	Method-A	Parameters
385	485	415	λmax, nm
1.0-30	2.0-20	1.0-10	Linear range (μg/mL)
1.7373x104	3.0229x104	4.1224x104	Molar absorptivity coefficient (ε), (L mol-1cm-1)
0.2568x10-3	0.9834x10-4	0.3606x10-4	Sandell sensitivity (Ng cm-2)
0.033	0.003	0.018	Intercept (a)
0.048	0.085	0.120	Slope (b)
0.9979	0.9999	0.9988	correlation coefficient (R2)
0.158	0.553	0.255	LOQ(μg/mL)
0.455	0.898	0.512	LOD(μg/mL)

Table 2: Accuracy and precision of the proposed methods

%RSD*	%(Recovery $\pm$ SD)*	%Relative error*	The Amount was Found* (μg/mL)	Amount was taken (μg/mL)	Method
0.58	101.50±0.24	1.40	2.03	2	A
1.01	100.80±0.51	0.80	5.04	5	
1.09	101.30±0.33	1.30	10.13	10	
0.91	100.80±0.23	0.80	5.04	5	
0.89	100.20±0.49	0.20	15.03	15	
0.97	99.45±0.15	0.55	19.89	20	
0.83	101.20±0.14	1.20	10.12	10	C
0.96	99.67±0.22	0.33	14.95	15	
0.77	100.68±0.42	0.68	25.17	25	

that a 1: 1 complex was formed at 385 nm method C using the Labor and method of molar relations (Figures 19, 20 and 21).

The stability constant

The constant stability Kf of the colored products was calculated from the continuous variation data using the following equation (Wan *et al.*, 2012) :

$$K_f = \frac{A/A_m}{(1-A/A_m)^{n+1} \, C^n n^n}$$

Where: A and A_m are the maximum absorbance of the continuous variation curve and the absorbance corresponding to the union of the two tangents of the continuous variation curve, respectively. n is the number of reactant molecules in the reaction product, C is the molar concentration of metoclopramide hydrochloride at the maximum absorbance. K_f was found to be 43.6435 $\times$ 108, 54.6261 $\times$ 10-8 and 17.29099 $\times$ 106 L2 mol-2 for methods A, B and C respectively. This indicates a stable reaction product. The Gibbs free energy of the reaction ($\triangle$G) was also calculated using the following equation (Tyagi and Dhillon, 2012) :

$$\triangle G = -2.303 RT \log K_f$$

Where R is the universal gas constant (8.314 J mol-1 deg-1). T is the absolute temperature (273 + 25 $^\circ$ C), K_f is the reaction formation constant. It was found that ΔG values were -43.9293 kJ / mol, -44.3735 and -51.2019 for methods A, B and C, respectively (Figures 23 and 24 and Figure 25). The negative value of ΔG refers to the spontaneity of the reaction.

Precision and precision.

To study the accuracy and precision of the calibration curve, solutions containing three different concentrations of metoclopramide hydrochloride were designated in methods A, B and C (Suresh *et al.*, 2012) . The results obtained, which are summarized in Table 2 indicate a good precision and accuracy for all methods.

Interference

The methods developed were successfully applied to the determination of metoclopramide hydrochlo-

Table 3: The application the methods for determination of metoclopramide hydrochloride in pharmaceutical preparations

Drugs brand name									Conce. (μg/ml)	Proposed methods
METOCAL INGEC-TION 10mg/2ml			MECLODIN Tablets 5mg			Metocloprmide Tablets 10mg				
7.0	5.0	3.0	7.0	5.0	3.0	7.0	5.0	3.0	Taken conc. (μg/ml)	Method A
6.89	5.11	3.03	7.11	4.99	3.09	7.03	5.02	3.05	Found conc. (μg/ml)	
98.42	102.20	101.0	101.57	99.80	103.0	100.42	100.40	101.66	Recovery(%) n=3	
0.56	0.99	0.79	1.10	0.86	0.97	0.59	0.75	0.58	RSD(%),n=3	
99.73$\pm$0.08			100.05$\pm$0.04			101.22$\pm$0.02			(%Recovery $\pm$ SD) n=5	Reference method
15.0	10.0	5.0	15.0	10.0	5.0	15.0	10.0	5.0	Taken conc. (μg/ml)	Method B
14.89	10.04	5.09	14.77	10.05	5.12	15.02	10.12	5.04	Found conc. (μg/ml)	
99.26	100.40	101.80	98.46	100.50	102.40	100.13	101.20	100.80	Recovery (%) n=3	
0.98	0.76	0.64	1.01	0.89	0.77	0.91	0.57	0.66	RSD(%),n=3	
100.60$\pm$0.06			101.13$\pm$0.05			100.05$\pm$0.03			%Recovery $\pm$ SD n=5	Reference method
15.0	10.0	5.0	15.0	10.0	5.0	15.0	10.0	5.0	Taken conc. (μg/ml)	Method C
14.99	9.97	5.11	14.92	9.87	5.05	14.89	10.13	5.02	Found conc. (μg/ml)	
99.93	99.70	102.2	99.46	98.70	101.0	99.26	101.30	100.40	Recovery (%) n=3	
0.99	1.02	0.89	0.72	0.99	0.93	1.01	0.82	0.93	RSD(%),n=3	
100.72$\pm$ 0.01			99.9 2$\pm$ 0.05			101.22$\pm$ 0.04			%Recovery $\pm$ SD n=5	Reference method

ride in its pharmaceutical formulation, and the results are presented in Table 3 . The results obtained were compared statistically with the reference, the Student t-test values obtained with a 95% level of confidence and five degrees of freedom and did not exceed the theoretical tabulated value of t = 2.77, so it does not indicate a significant difference between the compared methods. The F value (19.01) has also shown that there is no significant difference between the accuracy of the proposed methods and the reference method. The proposed methods can be used for quality control and mass analysis of metoclopramide hydrochloride, as well as in its dosage forms (Al-Salman, 2018a, 2019).

Analytical applications

The methods developed were successfully applied to the determination of metoclopramide hydrochloride in the pharmaceutical formulation, and the results were presented inTable 3 . The results were statistically compared with the reference values of the Student's t-test were obtained with a confidence level 95% and five degrees of freedom and did not exceed the theoretical tabulated value t = 2.77, so it does not indicate a significant difference between the compared methods. The F value (19.01) has also shown that there is no significant difference between the accuracy of the proposed methods and the reference method. The proposed methods can be used for quality control and routine analysis of metoclopramide hydrochloride mass and in their

dosage forms (Al-Salman, 2018b) .

CONCLUSIONS

Simple, fast and precise spectrophotometric methods have been a determination of metoclopramide hydrochloride in standard and pharmaceutical preparations. Methods A and B depended on the diazotation coupling reaction to form an azo dye with resorcinol reagent and 8-hydroxyquinoline azo dye absorbed at 415 nm and 485 nm respectively. Method C contains the reaction between the drug metoclopramide hydrochloride with p-benzoquinone to form a dye-absorbed product at 385 nm. The completion of these procedures did not require the control of temperature, solvent extraction and even its precise and sensitive methods. The proposed methods are able to determine metoclopramide hydrochloride in pharmaceutical formulations without any interference of excipients such as starch and glucose and commonly used products, suggesting easy application in the analysis of standard materials. Furthermore, these methods are extremely accurate and do not require the use of expensive instruments, which makes them suitable for routine measurement methods in laboratories.

Expressions of gratitude

The authors thank the professors of pharmaceutical chemistry for helping us in this manuscript.

Contributions of the authors

This research was conducted individually in the laboratories of the Faculty of Pharmacy, University of Basrah. This investigation was completed during a 4-month period with serious and continuous work and, therefore, excellent results were obtained by finding an easy and sensitive method to estimate metoclopramide hydrochloride.

REFERENCES

., G., ., V., ., M., ., N., ., M., ., B., ., G., Rani, S. S., ., S. 2014. A Simple Rp-Hplc Method for Simultaneous Estimation of Paracetamol and Metoclopramide. HCl inTablet Dosage Form. IOSR Journal of Pharmacy and Biological Sciences, 9(6):69–78.

Adegoke, O. A. 2012. Chemical derivatization methodologies for UV-visible spectrophotometric determination of pharmaceuticals. International Journal of Pharmaceutical Sciences Review and Research, 14(2):2012–2018.

Adegoke, O. A., Nwoke, C. E. 2008. Spectrophotometric determination of hydralazine using p-dimethylaminobenzaldehyde. Journal of the Iranian Chemical Society, 5(2):316–323.

Al-Abbasi, K. M., Mohammed, S. A., Sarsam, L. A. 2011. Spectrophotometric Determination of Metoclopramide Hydrochloride in Pharmaceutical Preparations UsingDiazotization Reaction. Rafidain journal of science, 22(3E):76–88.

Al-Rufaie, M. M. 2016a. Modern kinetic spectrophotometric procedure for estimation of furosemide drug as bulk form and in pharmaceuticals preparations. Current Issues in Pharmacy and Medical Sciences, 29(4):184–189.

Al-Rufaie, M. M. 2016b. New spectrophotometric method for the determination of Sulfamethoxazole drug. WJ of pharmacy and pharmaceutical sciences, 5(3):172–180.

Al-Rufaie, M. M., Al-Sharefy, A. N., Kathem, K. H. 2013. New spectrophotometric method for the determination chlorpromazine hydrochloride in pharmaceutical preparations by using oxidative coupling reaction. Inter. J. of Uni. Pharmacy and Bio Sciences, 2(4):184–189.

Al-Salman, H. N. K. 2018a. Analytical methods for diagnosis a mixture of narcotic substances in seized materials. International Journal of Green Pharmacy (IJGP), (03):216–226.

Al-Salman, H. N. K. 2018b. Quantitative Analysis of Cephradine using the Modern High-performance Liquid Chromatographic Method. Asian Journal of Pharmaceutics, (03):228–234. Asian J Pharm.

Al-Salman, H. N. K. 2019. Optimization of a micro-high-performance liquid chromatography method for determination of metronidazole benzoate in their standard powder and in dosage pharmaceuticals. International Journal of Green Pharmacy (IJGP), (01):48–59.

Aljarah, R. N., Obedagha, A. N. 2014. Development of Spectrophotometric Method for the Determination of Metoclopramide. HCl in a Pharmaceutical Preparations. Rafidain journal of science, 25(2E):10–21.

Alshirifi, A. N., Abbas, M. H. 2015. New spectrophotometric method for the determination of metoclopramide hydrochloride in pharmaceutical preparations based on coupling with doxycycline hyclate. International Journal of Chemical Sciences, 13:1093–1108.

Annapurna, V., Jyothi, G., Rambabu, C., Sailaja, B. B. V. 2009. Spectrophotometric Determination of Ceftiofur Hydrochloride Using N -Bromosuccinimide and p -Dimethylaminobenzaldehyde. E-Journal of Chemistry, 6(3):763–769.

Deokate, U. A., Gorde, A. M. 2014. A stability indicating UV specrophotometric method for determi-

nation of metoclopramide hyrdrochloride. Int J Pharm Pharm Sci, 6(9):394–397.

Devi, O. Z., Basavaiah, K., Vinay, K. B., Revanasiddappa, H. D. 2016. Sensitive spectrophotometric determination of metoclopramide hydrochloride in dosage forms and spiked human urine using vanillin. Arabian Journal of Chemistry, pages 1–7.

Dusane, A. R., Gaikwad, P. D., Bankar, V. H., Pawar, S. P. 2011. A Review on Sustain release technology. International journal research in ayurvedic and pharmacy, 2(6):1701–1708.

Elmansi, H., Abass, A. E., Mohamed, S., Fathy, M. E. 2016. Simultaneous determination of metoclopramide and aspirin by spectrofluorimetric technique: application to pharmaceutical formulations and human plasma. Analytical Methods, 8(6):1281–1292.

Gulsu, A., Ayhan, H., Ayhan, F. 2012. Preparation and characterization of ketoprofen loaded albumin microspheres. Turkish Journal of Biochemistry, 37(2):120–128.

Hemalatha, K., Lathaeswari, R., Suganeswari, M., Kumar, S. V., Shering, A. M. 2011. Formulation and evaluation of metoclopramide hydrochloride microbeads by ionotropic gelation method. Int J Pharma Biol Arch, 2:921–925.

Jawad, A. A., Kadhim, K. H. 2013. Spectrophotometric determination of metoclopramide hydrochloride in bulk and pharmaceutical preparations by diazotization-coupling reaction. J. of Pharmacy and Pharmaceutical Sciences, 5:294–298.

Jia, B., Li, Y., Liu, C., Li, K., Qi, Y. 2010. Flow injection determination of metoclopramide based on KMnO4-HCHO chemiluminescence in a micellar medium. Journal of Luminescence, 130(11):2188–2191.

Khaleel, N. A., Mahmood, H. S., Othman, N. S. 2011a. Spectrophotometric and High Performance Liquid Chromatographic Methods for Determination of Metoclopramide inPharmaceutical Preparations. Rafidain journal of science, 22(3E):39–56.

Khaleel, N. A., Mahmood, H. S., Othman, N. S. 2011b. Spectrophotometric and High Performance Liquid Chromatographic Methods for Determination of Metoclopramide inPharmaceutical Preparations. Rafidain journal of science, 22(3E):39–56.

Malih, I. K., Abdulla, N. I., Haideri, A. M. A. 2012. Polymeric membrane sensors for the selective determination of metoclopramide hydrochloride and their applications to pharmaceutical analysis. Iraqi Journal of Pharmaceutical Sciences, 21(1):70–77.

Menaka, M., Pandey, V. P. 2013. Nasal drug delivery system as a potential for nasal solution of metoclopramide hydrochloride - in vitro and in vivo properties. Research Journal of Pharmaceutical, Biological and Chemical Sciences, pages 967–975.

Naggar, A. H., Elnasr, T., Sayed, A. A., Kotb, A., El, Sayed, A. Y. 2009. Determination of Metoclopramide Hydrochloride in Pharmaceutical Formulations Using Three Different Spectrophotometric Methods. Pharmaceutica Analytica Acta, (02):8–8.

Nancy, K., Jasmina, K. A., Kahali, N., Khanam, J. 2018. A Novel HPLC Method Validation Based on Analytical Techniques of Metoclopramide Benzamide Derivative (Metoclopramide Base) and its Determination from Solid Dispersion by Solvent Evaporation Method. Journal of Applied Pharmaceutical Science, 8(02):18–026.

Neha, S., Singh, N., Yasir, M. 2015. Sustained release solid dispersion of Metoclopramide HCL: formulation, evaluation and pharmacokinetic studies. Journal of Applied Pharmaceutical Science, 5:55–065.

Okram, D., Kanakapura, B., Kanakapura, V., Hosakere 2012. Determination of metoclopramide hydrochloride in pharmaceuticals and spiked human urine through diazotization reaction. Journal of Food and Drug Analysis, 20(2):454–463.

Patil, S. M., Nandibewoor, S. T. 2015. Electrochemical behavior of antiemetic drug metoclopramide at electrochemically pre-treated pencil graphite electrode. Analytical and Bioanalytical Electrochemistry, 7:387–400.

Poddar, S. S. S., Nigade, S. U., Dinesh, K. K. S. 2011. Designing of ritonavir solid dispersion through spray drying. Der Pharmacia Lettre, 3(5):213–223.

Rashmika, B., Veena, V., Kachhwaha, S., Bhikshapathi, D. V. R. N. 2013. Formulation development and in vivo evaluation of Fexofenadine HCL solid dispersions by spray drying technique. Der Pharmacia Lettre, 5(6):73–82.

Satyanary, K., Nagesara, P. 2012. Simple and selective s spectrophotometric methods for the determination of mosapride citrate by diazo coupling reaction in pharmaceutical formulations. International Journal of Pharmacy and Pharmaceutical Sciences, 4(2):363–368.

Sawale, R. T., Kalyankar, T. M., George, R., Deosarkar, S. D. 2016. Molar Refraction and Polarizability of Antiemetic drug 4-amino-5-chloro-N-(2-(diethylamino) ethyl)-2 methoxybenzamide hydrochloride monohydrate in {Aqueous-Sodium or Lithium Chloride} Solutions at 30oC. Journal of

Applied Pharmaceutical Science, 6(03):120–124.

Shakeel, F., Shazly, G. A., Haq, N. 2014. Solubility of Metoclopramide Hydrochloride in Six Green Solvents at (298.15 to 338.15) K. Journal of Chemical & Engineering Data, 59(5):1700–1703.

Suresh, S., Pai, R., Pandit, V., Devi, K. 2012. In vitro-in vivo evaluation of fast-dissolving tablets containing solid dispersion of pioglitazone hydrochloride. Journal of Advanced Pharmaceutical Technology & Research, 3(3):160–170.

Tyagi, R., Dhillon, V. 2012. Enhancement of solubility and dissoultion rate of domperidone using cogrinding and kneading technique. Journal of Drug Delivery and Therapeutics, 2(4):152–158.

Vandenplas, Y., Hauser, B. 2015. An updated review on gastro-esophageal reflux in pediatrics. Expert review of gastroenterology & hepatology, 9(12):1511–1521.

Wan, S., Sun, Y., Qi, X., Tan, F. 2012. Improved Bioavailability of Poorly Water-Soluble Drug Curcumin in Cellulose Acetate Solid Dispersion. AAPS PharmSciTech, 13(1):159–166.

Yadav, A. S., Kumar, A. P., Vinod, R., Rao, S. B., Kulkarni, S. V. 2010. Design and evaluation of guar gum based controlled release matrix tablets of Zidovudine. Journal of Pharmaceutical Science and Technology, 2(3):156–162.

Yuvaraja, K., Khanam, J. 2014. Enhancement of carvedilol solubility by solid dispersion technique using cyclodextrins, water soluble polymers and hydroxyl acid. Journal of Pharmaceutical and Biomedical Analysis, 96:10–20.

Zhai, X., Li, C., Lenon, G. B., Xue, C. C. L., Li, W. 2017. Preparation and characterisation of solid dispersions of tanshinone IIA, cryptotanshinone and total tanshinones. Asian Journal of Pharmaceutical Sciences, 12(1):85–97.