sciendo

DOI: 10.2478/auoc-2018-0012

Ovidius University Annals of Chemistry Volume 29, Number 2, pp. 85-91, 2018

Spectrophotometric determination of metoclopramide medicine in bulk form and in pharmaceuticals using orcinol as reagent

Hanaa Khazal Abdulghareeb TAHA, Mohauman Mohammed AL-RUFAIE,* and Zahraa Yosif MOTAWEQ

Faculty of Science, Kufa University, Kufa Street 1, Najaf, Iraq

Abstract. A modern, accurate, simple and sensitive spectrophotometric procedure is tested for the appreciation of metoclopramide medicine as perspicuous form, as well as in various kinds of pharmaceutical dosages. The procedure depends on the interaction of metoclopramide (MCP) medicine and orcinol reagent by utilizing azo coupling reaction. The orcinol in NaOH solution middle to give a latterly ligand which reacts with copper (II) to output the complex with strong yellow color at 50°C. The resulting complex is water soluble, stable and can be determined spectrophotometrically at wavelength 459 nm. The calibration curve absorbance *vs*. concentration was established in the concentration range 0.6-12 ppm, and the curve followed the Beer's law in this range. The procedure precision is given by the average recovery of 99.91% sequentially, as well as by the average relative standard deviation 0.70%, related to the amount of drug. The sensitivity is established at molar absorptivity 1.9044×10^4 $l\cdot cm^{-1}\cdot mol^{-1}$. The Sandell sensitivity is tested as 0.002 $\mu g/cm^2$. The analytical results for the tested procedure agree with the official procedure. The interferences from medicine additives were tested. The established procedure is successfully examined on the appreciation of MCP in diverse kinds of pharmaceuticals.

Keywords: metoclopramide medicine; orcinol; diazotization-coupling reaction; copper (II) complex.

1. Introduction

Metoclopramide, an organic compound containing primary amine group, is one of the amino derivatives of medicinal significance which is used for stomach and esophageal problems.

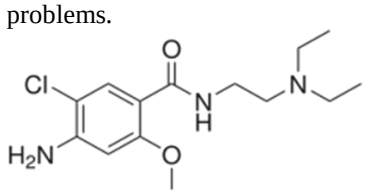

Figure 1. The structural formula of metoclopramide hydrochloride

The molecular formula of the metoclopramide hydrochloride (MCP-HCl) is $C_{14}H_{22}ClN_3O_2\cdot HCl\cdot H_2O$, the molar mass is 354.27 $g\cdot mol^{-1}$, and the structural formula is shown in Fig. 1. The IUPAC name for the medicine MCP-HCl is 4 – amino – 5 – chloro – N - (2 - (diethylamino)ethyl) – 2 – methoxybenzamide hydrochloride, and its melting interval is 182.5 - 184 ˚C. It is a white crystalline powder with high solubility in water; it dissolves freely in alcohol and has a low solubility in methylene chloride. It is medically used as an anti-emetic medicine. This medicine is in the form of pharmaceutical preparations as tablets, oral solutions or injection solutions (ampoules) [1]. Therefore simple as well as delicate procedures are needed for its quantitative appreciation. The British Pharmacopoeia (BP) [2] encouraged the acid–base titration by utilizing non aqueous solutions with potentiometric measurements for the endpoint for the assessment of the pure compound by utilizing the dose forms of tablets samples; injection as well as oral solution recommended as chromatographic procedures. Diversified analytical procedures have been advanced for the appreciation of this medicine. These procedures contain spectrofluorimetric [3, 4], spectrophotometic [5, 6], flow injection analysis [7, 8], electrochemical [9, 10], and chromatographic procedures [11, 12].

This study is established on the reaction of diazo-coupling between diazionium salt and another compound containing electronically donating groups. The pharmaceutical compounds analyzed in this reaction are those containing primary groups such as *p*-amino benzoic acid [13], hydroxy groups or ritodrine HCl [14]. The reactions of diazotization-coupling are those widely used in the production of dyes and in the field of analytical chemistry to estimate some of the varieties [15, 16].

A number of formulations including metoclopramide as ingredient effective were analyzed. These are summarized in Table 1.

Table 1. Pharmaceutical formulations studied for MCP

Pharmaceutical formulations	Declared composition	Company
Eminorm syrup	Per 5 ml syrup 5 mg MCP	Brown India
Parmesan syrup	Per 5 ml syrup 5 mg Metoclopramide	Gulf pharmacutical industries, Ras Al khaimah, U.A.E
Meclodin oral drops	Per 5 ml drop 4 mg MCP	SDI – Iraq
Placilab oral drops	Per 5 ml drop 5 mg MCP	Pharmacuticals India Ltd.

*Corresponding author. *E-mail address*: muhaimin.alrufaie@uokufa.edu.iq or mohaumanmajeed@yahoo.com (Mohauman Mohammed Al-Rufaie)

Pharmaceutical formulations	Declared composition	Company
Metoclopramide injection	Per 2 ml ampoule 10 mg MCP	Kontam Pharmaceuticals (Zhongshan) Co. Ltd. China
Meclodin tablets (10)	Per tablet 5 mg MCP	SDI – Iraq

The target of existent work was to improve a selective, sensitive, and simple spectrophotometric procedure for the appreciation of MCP in a pure form and pharmaceutical doseages, established on diazotization-coupling reaction with the orcinol reagent to get latterly ligand which reacts with copper (II) ions to obtain a strong yellow color complex.

2. Experimental

2.1. *Materials*

The high purity reagents were purchased from BDH chemicals (Germany) (hydrochloric acid, HCl; sodium hydroxde, NaOH; sodium nitrite, $NaNO_2$; copper chloride, $CuCl_2{\cdot}2H_2O$; 3,5-dihydroxytoluene or orcinol monohidrate, $CH_3C_6H_3$-1,3-$(OH)_2{\cdot}H_2O$) and used without further purification. The metoclopramide (MCP) 500 ppm was purchased from SDI Company (Iraq).

2.2. *Methods*

In a sequence of 25 ml volumetric flasks, equal volumes of standard solutions from MCP with concentrations ranges of 0.5 – 18 ppm, sequentially in end volume were added separately, pursued by addition of 1 ml HCl 1M and 1 ml $NaNO_2$ 1%. The solutions have been left for 10 min to accomplish the azo conjugation reaction. After that, 0.25 ml of NaOH 0.5 M has been added to the drug solution, then followed by addition of 2 ml orcinol. The volumes have been completed by deionized water.

The solutions were left for 10 min at room temperature. Then in a 10 ml volumetric flask we placed 1 ml of $CuCl_2$ 0.003 M solution with 3 ml of the prepared medicine and supplemented with deionized water. The computed absorbance was at 459 nm, sequentially versus the blank solution reagent. A calibration curve was drawn, correlating absorbance and concentration [17].

Metoclopramide in pharmaceutical formulations:

1. *Tablets formulations*: The tablets were crushed and finely powdered. An amount of powder equivalent to 0.05 g MCP was precisely weighed and put into a 50 ml beaker. The powder was alleviated in the deionized water and a purified solution was obtained by filtering the alleviate through filter paper Whatmann 41. After filtration, the solution was transferred in the 100 ml volumetric flask and completed to the end volume with deionized water. The medicine solutions were analyzed as in the common procedure [18];
2. *Syrup formulations*. Two containers with MCP syrup from every syrup formulation were tested; each contains 5 mg MCP in 5 mL syrup. From these, two samples of 125 ml solution were obtained such as each included 0.05 g from the medicine. Further, standard solutions were obtained through convenient dilution according to an advised procedure for the appreciation of MCP medicine [19];
3. *Injection formulations*. 2 ml ampoules each containing 0.01 g of MCP were transferred quantitatively into 100 ml volumetric flasks and the volume was completed with deionized water. At that point, the concentration was determined by using the calibration curve [2].

3. Results and discussion

3.1. *Absorption spectrum*

MCP interacts with orcinol to get a latterly ligand that interacts in basic solution with copper (II) to obtain a complex with bright yellow color after the warming for 10 min at 50°C. As seen in Fig. 2, the maximum of absorption for aqueous complex solution is situated at 459 nm.

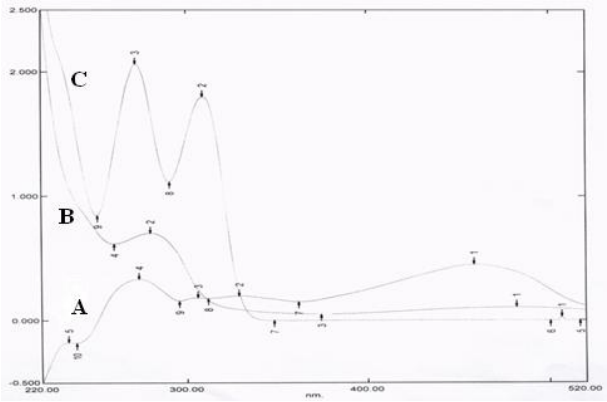

Figure 2. The absorption spectra of copper (II) complex in aqueous solution versus blank solution (A). The absorption spectrum of the blank solution including orcinol, $CuCl_2$ and NaOH versus water as a blank (B); Pure medicine absorption spectra versus water as blank (C).

Various circumstances influencing the absorbance were considered in order to optimize the method.

3.2. *Influence of base*

The reaction medium influence on the absorbance of complex solution was tested. The basic media are preferable for the interaction of reactants. Bases such as ammonia, potassium hydroxide, ammonium hydroxide, sodium carbonate, as well as sodium hydroxide were checked and showed that NaOH strongly influences comparing to other bases used in the tested procedure [18].

In Fig. 3, it appears that by adding 0.25 ml of 0.5 M NaOH in 25 ml samples leads to a robust complexation reaction in forming the colored product. The absorbance at λmax 459 nm proves this. Therefore, this volume of 0.5 M NaOH solution was exercised in all subsequent experiences.

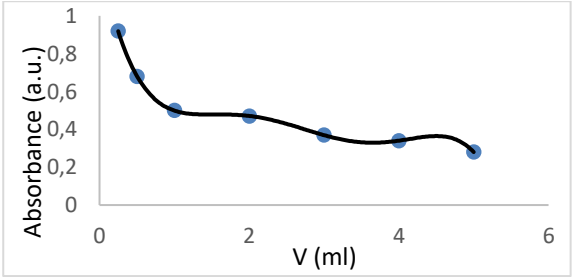

Figure 3. Influence of NaOH 0.5 M solution volume on the absorbance of color product

3.3. *Influence of orcinol solution volume*

Volumes of 1 ml of MCP 500 ppm solution were put into a sequence of 25 ml volumetric flasks. Different volumes of orcinol 500 ppm (from 0.5 to 8 ml) were added and completed to the volumes of 15 ml with ethanolic sulfuric acid solution. The solutions were heated and well-mixed on warm water bath for 50 min, for the synthesis of the azo dye. 1 ml copper (II) chloride 0.003 M solution was added and the volumes of 25 mL were completed with ethanol.

We observed that the optimum volume for the determination of MCP was 2 ml of 500 ppm orcinol solution, which produces the strongest absorption (Fig. 4). This volume was utilized in the next experiences.

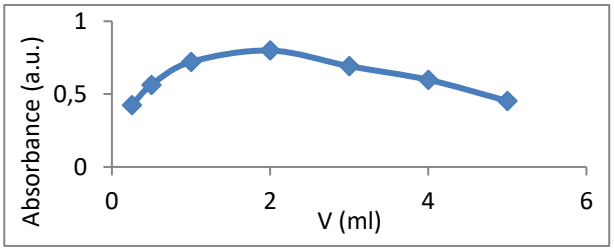

Figure 4. The effect of orcinol 500 ppm solution volume on the absorbance of complex solution

3.4. *Influence of sodium nitrite volume*

Volumes of 1 ml 500 ppm MCP solution were taken into a sequence of volumetric flasks 25 ml. Different volumes of sodium nitrite 1% solution (0.5 – 5 ml) were added and completed to the volumes of 15 ml with ethanolic sulfuric acid solution. The solutions were heated and well-mixed on warm water bath for 50 min, for the synthesis of the azo dye. 1 ml of $CuCl_2$ 0.003 M solution was added and the volumes of 25 mL were completed with ethanol [18].

The results showed that the optimum volume for the determination of MCP was 1 ml of sodium nitrite 1% solution, which produces the strongest absorption (Table 2). This volume was utilized in the next experiences.

Table 2. Influence of sodium nitrite volume on the absorbance of complex solution

Volume of sodium nitrite 1% solution (ml)	Absorbance (a.u.)
0.5	0.833
1	0.881
1.5	0.821
2	0.778
2.5	0.701
3	0.661
3.5	0.611
4	0.542
4.5	0.447
5	0.398

3.5. *Influence of acid*

Three strong acids (HCl, H_2SO_4 and HNO_3) in solutions of 1 M concentration were tested for the determination of MCP [19].

We observed that the highest value for absorbance of complex solution was obtained by using HCl 1 M solution and the optimum volume for the determination of MCP was 1 ml (Table 3). This volume was utilized in the next experiences.

Table 3. Acid influence on the absorbance of complex solution

Acid type	Volume of acid (ml)	Absorbance (a.u.)
HCl	1	0.911
	2	0.889
	3	0.855
	4	0.822
	5	0.776
H_2SO_4	1	0.645
	2	0.626
	3	0.532
	4	0.451
	5	0.333
HNO_3	1	0.522
	2	0.430
	3	0.412
	4	0.355
	5	0.321

3.6. *Influence of copper (II) chloride volume*

The effect of different volumes (0.1 - 5 ml) of copper (II) chloride 0.003 M solution for the complex synthesis was also examined (Fig. 5). An expansion was observed in the absorbance of complex formed up to 1.0 ml, then remained constant at bigger volumes added. Therefore, 1.0 ml of 0.003 M Cu(II) solution was used for the determination of drug, since it gives high sensitivity and minimum reagent blank [19].

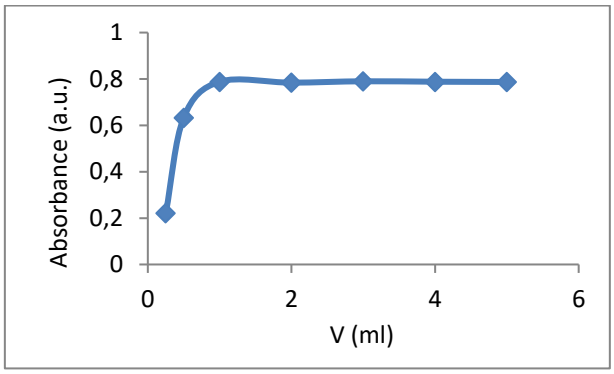

Figure 5. The effect of copper choride 0.003 M solution volume on the absorbance of complex solution

3.7. *Temperature effectiveness*

The effectiveness of temperature was checked in the range of 20 - 80 ºC [20]. It was found that the color intensity expanded with temperature increasing at temperatures higher than 25 ºC. The highest absorbance was at 50 ºC (Fig. 6), so the next experiments were performed by heating on water bath at 50 ºC needed for azo dye synthesis.

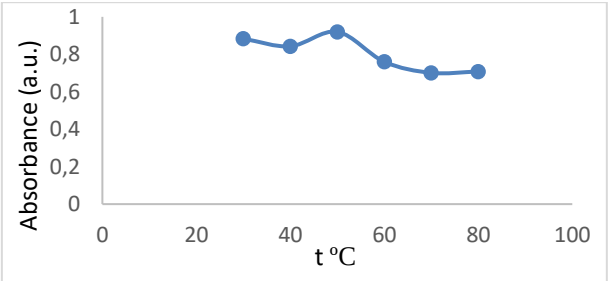

Figure 6. The reaction temperature effect on the absorbance of complex solution

3.8. *Effect of order addition*

Different orders of addition of the reagents had been performed [21]. The results in Table 4 indicate that the following order: drug (MCP), reagent (ORC), sulfuric acid ethanolic solution and Cu(II) solution (denoted No.1) gave the highest absorbance and this was selected in the subsequent experiments.

Table 4. Addition order effect*

No.	Addition order	Absorbance
1	D+A+N+R+M	0.920
2	R+M+D+A+N	0.775
3	M+D+A+R+N	0,810
4	A+R+M+D+N	0.871

*Where: D = Drug; N = $NaNO_2$; R = Reagent; M = Cu(II); A = Acid.

3.9. *Reaction time effect*

The color intensity for the product reached the maximum and stabilized after 10 minutes from the mixing of MCP diazonium salt and Cu(II) solution (Fig. 7). No improvement was observed after this period and the color remained stable over 24 hours [22].

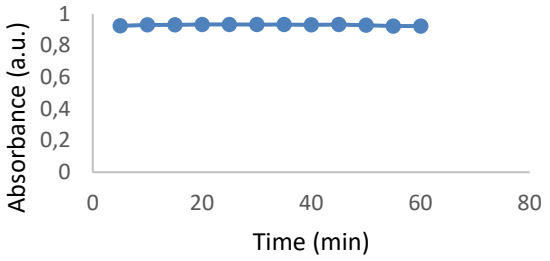

Figure 7. The reaction time effect on the absorbance of complex solution

3.10. *The calibration curve*

The range of concentration appreciated for the absorbance at λmax = 459 nm to follow the law of Beer was 6-12 ppm (Fig. 8). The law of Beer limits, molar absorptivity as well as Sandell's sensitivity, were tested as seen in Table 5, and showed the sensibility for the tested procedure. The linearity appeared very good by the correlation coefficient of regression equation (R^2 = 0.9989). Additionally, LOD and LOQ were determined for the tested procedure. Undoubtedly, the LOQ a modicum portion overruns the lower of the range of Beer's law. However, LOD is additionally lower than the least of the range of Beer's law.

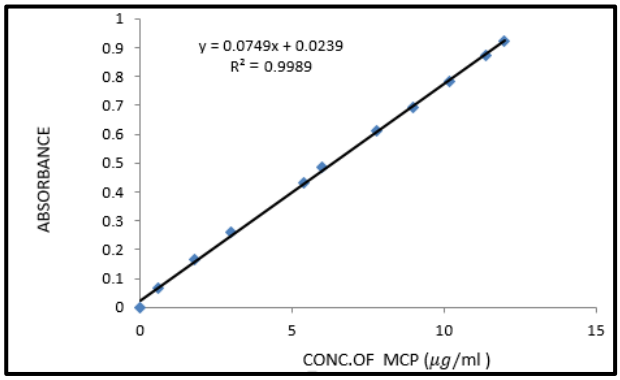

Figure 8. The calibration curve for determination of MCP medicine

Table 5. Analytical data for the spectrophotometric determination of MCP drug

Parameter	Value
λmax, nm	459
Correlation coefficient, R^2	0.9989
Slope (b)	0.0259
The molar absorptivity ($l \cdot mol^{-1} \cdot cm^{-1}$)	1.9044×10^4
The law of Beer limits (ppm)	0.6-12
The sensitivity of Sandell ($\mu g \cdot cm^{-2}$)	0.002
Intercept (a)	0.0749
Limit of detection (LOD) (ppm)	0.134
Limit of quantification (LOQ) (ppm)	0.255

3.11. *Accuracy and precision study*

The accuracy as well as precision for the studied spectrophotometric procedure were investigated at three various concentrations from MCP drug breaking down five repeated tests of every concentration by the proposed method. Percentage relative error (E%) as accuracy and percentage relative standard deviation (RSD%), the precision for the proposed procedure were computed [19].

The results in Table 6 depict good accuracy and precision as illustrated by the low values of RSD% and low values of E%, giving evidence for repeatability as well as reproducibility of the proposed method. All the results were calculated for the five determinations. The average for the relative standard deviation values was 0.70% as well the average for recovery values was 99.91% sequentially.

Table 6. Precision and accuracy of the studied method

MCP conc. present (ppm)	MCP conc. found (ppm)	% E	% Re	%R.S.D
1	0.988	- 1.20	98.80	1.10
6	6.012	+ 0.60	100.60	0.71
10	10.033	+0.33	100.33	0.31

3.12. *Interferences*

Specificity of the suggested spectrophotometric procedure (fixed time procedure) for investigation of the MCP drugs, having in view excipients such as lactose, talc, acacia, sucrose, aspartate, glucose, polyvinylpirrolidone (PVP), magnesium stearate, and starch, was considered. Each of the studied excipients was given independently by ten-times concentrations more than of MCP prepared by the self-approach in the calibration curve. 1 ml of 500 ppm MCP and 1 ml of every excipients were connected for the study of interferences [21]. Dilution to the sign of volumetric flask 25 ml grade of impedance was made. The procedure was believed satisfactory if the error was less than ± 2% in respect to the normal value. The determinations were performed in triplicate and results are shown in Table 7.

Table 7. Excipients effect at 60 ppm on the recovery of MCP drug at 6 ppm for studied method

Interference	% Error	% Recovery
Talc	+ 1.150	101.150
Lactose	- 1.120	98.880
Acacia	+ 0.987	100.987
Starch	- 0.690	99.310
Glucose	- 1.200	98.800
Sucrose	+.0.850	100.850
Magnesium stearate	+ 1.200	100.200
Aspartate	+ 0.710	100.710
PVP	- 0.450	99.550

3.13. *Application of the procedure*

The tested procedure was exercised to analyse six various potion formulations involving MCP to evaluate the analytical benefit of the spectrophotometric method [23, 24]. The tested procedure was applied successfully to the analyses. Reproducibility as well as recovery were established into limitations of three various amounts of every pharmaceutical formulation, as see in Table 6.

Ultimately, *F*-test as well as *t*-test (statistical analysis) show that there is no considerable variation in accuracy between the tested procedure and the common BP procedure.

Table 8. MCP drug in as pure substance and forms of dosage

MCP pharmaceutical preparations	Proposed procedure		Standard procedure		Nominal values *t*, *F**
	Recovery %	RSD%	Recovery %	RSD%	
Pure MCP	99.91	0.70	98.99	0.62	*F* value = 2.311 *t* value = 1.421
Eminorm syrup	99.44	0.92	99.01	0.55	
Parmesan syrup	101.12	1.06	99.62	0.92	
Meclodin oral drops	99.72	0.44	99.12	0.57	
Placilab oral drops	98.86	1.11	98.54	0.64	
Metoclopramide injection	101.41	0.82	99.23	0.60	
Meclodin tablets	99.82	0.63	99.52	0.65	

*The quantity for tabulated *t* at 95% dependability level for 12 degrees of freedom, two appended is 2.18.
The quantity of (tabulated) *F* at 95% dependability level for 6, 6 degrees of freedom, two followed is 5.82 [25].

Wherever the three normal determinations, also, the standard strategy was obtained from British Pharmacopeia, 2009 edition. The outcomes were replicable and the determination procedure of formulations was examined by the standard procedure.

3.14. *Method comparison*

Table 9 shows the advantages of spectrophotometric procedures established through diazotization - coupling interaction utilized at the determination of MCP. We concluded that reagents coupling by amino group are more sensible than hydroxyl group (rapprochement between the phenol group as well as aniline). The strong clear color while matching aniline with our tested orcinol reagent and making new ligand coupling with copper ion is shown in Table 9.

Table 9. A comparison between some characteristics of methods proposed for determination of MCP

Reagent	λmax (nm)	Linear range µg/ml	ε × 10^4	Ref
8-Hydroxyquinoline	528	0.2-12	3.10	[26]
Aniline	410	0.5-12	3.53	[27]
2,4-Dihydroxy acetophenone	450	0.4-12	2.48	[28]
Phenol	463	1-20	2.42	[29]
1-Naphthol	550	0.4-18	3.49	[30]
Benzoyl acetone	411	-	2.97	[31]
Phloroglucinol	424	0.2-16	4.30	[32]
2-Naphthol	553	1-10	2.74	[33]
Imipramine hydrochloride	570	0.5-5	4.50	[34]
Citrazinic acid	465	-	1.92	[35]
Dibenzoyl methane	440	-	2.85	[36]
2,5-Dimethoxyaniline	486	0.1-12	4.55	[19]
Orcinol	459	0.6-12	1.90	current study

** ε = molar absorptivity: l/mol·cm*

4. Conclusion

The present spectrophotometric procedure is a rapid, easy, sensitive as well as precise process, created for the detection of trace amounts of MCP and relevant for the investigation of MCP in tablets and injection. The proposed procedures are free from basic exploratory conditions and muddled systems, for example, extraction step. The reagents utilized as a part of the procedures are common, promptly accessible and the methods don't include any dreary sample preparation. These points of interest empower the utilization of the presented technique in quality routine control investigation of MCP in pharmaceutical preparations.

Conflict of interest

Authors declare no conflict of interest.

References

[1]. J.H. Block and J.M. Beale, Wilson and Gisvolds Text Book of Organic Medicinal and Pharmaceutical Chemistry, Lippincott Williams & Wilkins, USA, pp. 110-114 (2004).

[2]. British Pharmacopoeia, Her Majesty's Stationary Office, London, pp. 3921, 9413, 9414, 9415 (2009).
[3]. M.S. Attia and M.M. Abualy, Highly sensitive and selective spectrofluorimetric determination of metoclopramide hydrochloride in pharmaceutical tablets and serum samples using Eu^{3+} ion doped in sol-gel matrix, Talanta 82 (2010) 78- 84.
[4]. S.M. Sabry, Application of 2-acetylbutyrolactone to spectrofluorimetry: Fluorescence properties of Schiff bases derived from 2-acetylbutyrolactone and spectrofluorimetric determination of primary amine-containing compounds, J. Pharm. Biomed. Anal. 40 (20065) 1057-1067.
[5]. J.C. Liu, H.K. Li, and Y.H. Wang, Spectrophotometric determination of metoclopramide based on the chargetransfer reaction between metoclopramide and purpurin, Fenxi Kexue Xuebao 26 (2010) 361-363.
[6]. S.R. Patel and L.J. Patel, Development and validation of first derivative spectroscopy method for simultaneous determination of ondansetron and metoclopramide in combined dosage form, Int. J. Pharm. Sci. 3 (2011) 85-88.
[7]. J. Fan, A. Wang, S. Feng, and J.J. Wang, Non-equilibrium determination of metoclopramide and tetracaine hydrochloride by sequential injection spectrophotometry, Talanta 66 (2005) 236-243.
[8]. M.R. Herrero, A.M. Romero, and J.M. Calatayud, Flow injection- spectrophotometric determination of metoclopramide hydrochloride, Talanta 47 (1998) 223-228.
[9]. X.X. Li, W.Q. Zhao, L.X. Miao, and Q.R. Liu, Electrochemical determination of metoclopramide hydrochloride and its interaction with bovine serum albumin, Fenxi Ceshi Xuebao 29 (2010) 1126-1131.
[10]. Z.H. Wang, H.Z. Zhang, S.P. Zhou, and W.J. Dong: Determination of trace metoclopramide by anodic stripping voltammetry with nafion modified glassy carbon electrode, Talanta 53 (2001) 1133-1138.
[11]. J. Shi, X.H. Wang, J.W. Wen, J K. Wu, and Q. Zhang, RP-HPLC determination of metoclopramide hydrochloride injection and its related substance, Yaowu Fenxi Zazhi 30 (2010) 117-119.
[12]. M. Cossu, V. Sanna, E. Gavini, G. Rassu, and P. Giunchedi, A new sensitive reversed-phase high-performance liquid chromatography method for the quantitative determination of metoclopramide in canine plasma, Anal. Lett. 41 (2008) 767-778.
[13]. A. Chisvert, J.V. Izquierdo, and A. Salvador, A sequential-injection system for spectrophotometric determination of *p* - amino benzoic acid in sunscreens, Anal. Bioanal. Chem 374 (2002) 963-967.
[14]. H.D. Revanasiddappa and B. Manju, Spectrophotometric methods for the determination of ritodrine hydrochloride and its application to pharmaceutical preparations, Analyst 56 (2001) 615-619.
[15]. A.N. Pankratov, Azo-coupling reactions used in analytical chemistry, The role of reactants, intermediates, and aqueous Medium, Talanta 77 (2004**)** 1561-1573.
[16]. B.S. Fumiss and Vogels, Textbook of practical organic chemistry, 5th Ed., Longman Group, UK, p. 946 (1989).
[17]. R.S. Abdul Satar, Development of new spectrophotometric methods for determination of some organic drug compounds in pharmaceutical preparations, "Ph. D. Thesis", Baghdad University, pp. 72, 88 (2006).
[18]. M. M. Al-Rufaie, New spectrophotometric method for the determination of sulfamethoxazole drug, W. J. of Pharmacy and Pharmaceutical Sciences 5 (2016) 172-180.
[19]. A.A. Jawad and K.H. Kathem, Spectrophotometric determination of metoclopramide hydrochloride in bulk and pharmaceutical preparations by diazotization-coupling reaction, Inter. J. of Pharmacy and Pharmaceutical Sciences 5 (2013) 294-298.
[20]. M.M. Al-Rufaie, A.N. Al-Sharefy, and K.H. Kathem, 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 (2013) 184-189.
[21]. M.M. Al-Rufaie, Modern kinetic spectro-photometric procedure for estimation of furosemide drug as bulk form and in pharmaceuticals preparations, Curr. Issues Pharm. Med. Sci. 29 (2016) 184-189.
[22]. G.V. Raja, C. Sekaran, D.W. Teja, B. Madhuri and B. Jayasree, Simple spectrophotometric methods for the determination of sulfamethaxazole in pharmaceuticals using Folin - Ciocalteau and orcinol as reagents, E-J. Chemistry 6 (2009) 357-362.
[23]. P.P Shirke, V.A.Tamhane, M.K. Ratel, V.B. Tirodkar, and P. D. Sethi, Novel procedure for the quantitive assay of furosemide in pure form, J. Indian Chem. Soc. 73 (1996) 445-449.
[24]. The United States Pharmacopoeia, 23 Ed., p. 298 (1995).
[25]. US Pharmacopoeia XXIIth Rev., US Pharmacopoeia Convention, p. 311 (2007).
[26]. L.A. Sarsam, S.A. Mohammed, and K.M. Al-Abbasi, Spectrophotometric determination of metoclopramide hydrochloride in pharmaceutical preparations using diazotization reaction, Rafidain J. Sci. 22 (2011) 76-88.
[27]. J. Shah, M.R. Jan, M.A. Khan, and S. Amin, Spectrophotometric determination of metoclopramide in pharmaceutical preparations, J. Anal. Chem. 60 (2005) 633-635.
[28]. N.S. Othman, H.S. Mahmood, and N.A. Khaleel, Spectrophotometric and high performance liquid chromatographic methods for determination of metoclopramide in pharmaceutical preparations, Rafidain J. Sci. 22 (2011) 39-56.
[29]. R. Sinan and S.S. Abed, Spectrophotometric determination of metoclopramide hydrochloride in tablets by diazotization and coupling reaction with Phenol, Iraqi. J. Sci. 50 (2009) 136-143.

[30]. R. Sinan, Spectrophotometric determination of metoclopramide hydrochloride in pharmaceutical tablets, by diazotization-coupling method with 1-naphthol as the coupling agent, J. Baghdad Sci. 7 (2010) 704-712.
[31]. A.A. Omran, Individual and simultaneous spectrophotometric determination of dapsone and metoclopramide HCl in pharmaceutical dosage forms and synthetic binary mixtures, Chem. Pharm. Bull. 53 (2005) 1498- 1501.
[32]. S.H. Sultan, Spectrophotometric determination of metoclopramide hydrochloride in pharmaceutical preparations by the diazotization-coupling method with phloroglucinol, Tikrit J. Pure Sci. 14 (2009) 155-160.
[33]. S.A. Patel, C.N. Patel, and M.M. Patel, Visible spectrophotometric methods for the estimation of metoclopramide hydrochloride in tablets, Indian J. Pharma. Sci. 68 (2006) 397-399.
[34]. H.D. Revanasiddappa and M.A. Veena, Sensitive spectrophotometric determination of metoclopramide hydrochloride and dapsone in bulk sample and dosage forms, Sci. Asia 32 (2006) 319-321.
[35]. H.D. Revanasiddappa, M.A. Veena, B. Manju, and T.N.K. Kumar, Assay of some chemotherapeutic agents by visible spectrophotometry, Bulgarian Chem. Commun. 35 (2003) 235- 241.
[36]. H.D. Revanasiddappa and B. Manju, A spectrophotometric method for the determination of metoclopramide HCl and dapsone, J. Pharm. Biomed Anal. 25 **(**2001) 631-637.

Received: 15.06.2018
Received in revised form: 22.09.2018
Accepted: 24.09.2018