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Spectrophotometric Assay of Metoclopramide Hydrochloride in Pharmaceutical Preparations via Arsenazo III-Cerium (III) Reaction

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ABSTRACT

A simple, rapid, accurate and precise spectrophotometric method is proposed for determining metoclopramide – hydrochloride (MCPH) in pure form and in pharmaceutical preparations .The method is based on oxidation - reduction reaction between metoclopramide - hydrochloride and cerium (IV) ion, then the subsequent reaction of cerium (III) and arsenazo III reagent in acidic medium to produce a blue-violet complex which is stable, water-soluble and has a maximum absorption at 654nm with a molar absorptivity of $9.36x10^4$ $l.mol^{-1}.cm^{-1}$ and Sandell's sensitivity of 0.0038 $\mu g.cm^{-2}$. Beer's law is obeyed in concentration range from 1-30 µg metoclopramide - hydrochloride in final volume of 25 ml, (0.04-1.2) ppm with a relative standard deviation (RSD) (±1.80% - ±3.98%) and the limit of detection (LOD) is 0.0095 µg/ml and the limit of quantitation (LOQ) is 0.0317 µg/ml . The method is suitable for the determination of metoclopramide - hydrochloride in the presence of other ingredients that are usually present in dosage forms and the recoveries are obtained in the range of 97.6-101.0 % . The proposed method has been applied successfully to the determination of the intended compound in its pharmaceutical preparations (tablet and injection).

Keywords: Metoclopramide hydrochloride, spectrophotometry, arsenazo III.

التقدير الطيفي للميتوكلوبراميد هيدروكلوريد في المستحضرات الصيدلانية اعتمادا على تفاعل الكاشف أرسين ازوIII مع أيون السيريوم الثلاثي

الملخص

تم اقتراح طريقة طيفية بسيطة و سريعة و دقيقة ومتوافقة لتقدير الميتوكلوبراميد هيدروكلوريد بـشكله الحر وفي مستحضراته الصيدلانية. اعتمدت الطريقة على تفاعل الأكسدة والاختزال بـين الميتوكلوبراميـد هيدروكلوريد وايون السيريوم الرباعي يتبعها تفاعل ناتج التفاعل أيون السيريوم الثلاثي مع الكاشف أرسـين ازو III في وسط حامضي ليعطي معقدا ذا لون أزرق-بنفسجي مستقر وذائب بالماء وأعطى اعلى امتصاص

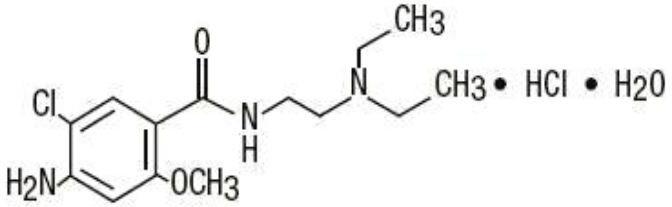
عند الطول الموجي 654 نانوميتر وكانت قيمة الامتصاصية المولارية هي $10x9.36^4$ لتر.مـول$^{-1}$.سـم$^{-1}$ واظهر منحني الامتصاص خطا مستقيما يتبع قانون بير في مدى التركيز من 1 الى 30 مـايكروغرام مـن الميتوكلوبراميد هيدروكلوريد في حجم نهائي 25 مللتر (0.04 - 1.2 جزء بالمليون) وكان الانحراف القياسي النسبي بين % 3.98 ± و % 1.80 ± ودلالة ساندل للحساسية 0.0038 مايكروغرام.سـم$^{-2}$ وحـد الكـشف (LOD) 0.0095 مايكروغرام.مللتر$^{-1}$ وتحديد كمي(LOQ) 0.0317 مايكروغرام.مللتر$^{-1}$. تم تطبيق الطريقة المقترحة بنجاح في تقدير الميتوكلوبراميد هيدروكلوريد في نماذج مختلفـة مـن المستحـضرات الدوائيـة (الاقراص والحقن).

الكلمات الدالة : الميتوكلوبراميد هيدروكلوريد، الطيفية، ارسين ازو III.

INTRODUCTION

Metoclopramide-hydrochloride (MCPH) is a white or almost white, odorless, crystalline powder (m.p. about 185 Cº), very soluble in water, alcohol and partially insoluble in ether .

Chemically (MCPH) is: 4-amino-5-chloro-N-(2-diethylaminoethyl)-2-methoxybenzamide monohydrochloride monohydrate (British Pharmacopoeia, 2008).



$C_{14}H_{22}ClN_3O_2.HCl.H_2O$ MWt.=354.3 g/mole

Metoclopramide was used as a treatment of nausea and vomiting in association with migraine and severe headache. In this setting, the combination of metoclopramide with an analgesic proved to be very efficacious with a short delay of action. The drug was used for the control of sickness due to radiation therapy and chemotherapy, and for the prevention and treatment of postoperative nausea and vomiting (PONV). Metoclopramide also has a gastrointestinal prokinetic effect through cholinergic stimulation.This effect consists of an increased tension in the lower esophageal sphincter and the gastric fundus, an increase in gastric and small intestinal motility, and a relaxation of the pylorus and duodenum during contraction of the stomach. The gastro-kinetic effect is mediated by an antagonism at the D_2 and 5-HT_3 receptors and by activation of the 5-HT_4 receptor (Donnerer, 2003).

Many analytical methods have been employed for the determination of MCPH, such as: fluorimetry (Attia and Aboaly, 2010), chromatography (Avula *et al*., 2011), capillary electrophoresis (Chang *et al*., 2000), liquid chromatography –mass spectroscopy (LC-MS) (Maquille and Jiwan 2009), potentiometry (Faridbod *et al*., 2009), voltammetry (Wang *et al*., 2001), fast stripping continuous cyclic voltammetry (Norouzi *et al*., 2005),

square wave anodic stripping voltammetry (Farghaly *et al*., 2005) and H^1NMR spectroscopy (Hanna and Lau-Cam, 1991).

The chromatographic methods are a lot cost, they are consuming of time and limiting of application and also the flow-injection chemiluminescent are often typically less sensitive and have their own intrinsic disadvantages such as technical complexity or require an expensive instrumentation (Al-Arfaj, 2004).

Spectrophotometry is the technique of choice even today due to its inherent simplicity. In the literature, many spectrophotometric procedures have been applied for the determination of MCPH using different reagents including o-phenanthroline or bipyridyl in the presence of Fe III as an oxidizing agent (Amin and Ragab, 2003); other spectrophotometric methods based on diazotization and coupling with different reagent such as: dibenzoylmethane (Revanasiddappa and Manju, 2001), benzoylacetone (Omran, 2005), aniline (Shah *et al*., 2005), β-naphthol (Patel *et al*., 2006), impramine hydrochloride (Revanasiddappa and Veena, 2006) and 2,4-dihydroxy acetophenone (Khalil, 2010).

Other spectrophotometric methods have been reported such as: ion association complex formation (Abdel-Gawad and El-Guindi, 1995), charge-transfer complex formation (Al-Gabsha *et al*., 2004), or through the formation of the Schiff's base with p-dimethylamino-cinnamaldehyde (Moussa, 2000).

The aim of the present work is to develop a simple, sensitive, specific spectrophotometric method for the determination of MCPH in bulk as well as pharmaceutical formulation.

EXPERIMENTAL

Apparatus

All spectral and absorbance measurements were performed on double-beam Shimadzu UV-Visible-160 recording spectrophotometer with 1.0 cm matched glass cells. pH measurements were preformed using HANNA 301 pH meter.

Reagents

All chemicals used were of analytical grade reagents.

Standard solution of MCPH (100 µg / ml). It was prepared by dissolving 0.0100 g of MCPH (N.D.I) in distilled water and the volume was completed to 100 ml with distilled water in a volumetric flask. The solution was then transferred to a dark bottle and is stable for at least one month.

Working solution of MCPH (25µg/ ml). It was prepared by the appropriate dilution of the stock solution with distilled water.

Ammonium ceric sulphate dihydrate [cerium(IV)ion solution],($4x10^{-4}$M). This solution has been prepared by dissolving 0.0253g of ammonium ceric sulphate dihydrate in sulphuric acid (0.05N) and the volume was completed to 100 ml with sulphuric acid (0.05N) in a volumetric flask.

Arsenazo III reagent solution, ($6x10^{-4}$M). It was prepared by dissolving 0.0535 g of Arsenazo III.$4H_2O$ (HIMEDIA) in 100 ml distilled water in a volumetric flask.

Sulphuric acid solution,(0.05N). This solution is prepared by dilution of 1.4 ml of the concentrated sulphuric acid (35.5 N) solution to 1000 ml with distilled water in a volumetric flask.

Sodium hydroxide solution (1M). This solution is prepared by appropriate dilution of the concentrated volumetric (Fluka) solution with distilled water to 1000 ml in a volumetric flask and then transferred to a plastic bottle.

Sodium hydroxide solution (0.01M). This solution is prepared by dilution of 1.0 ml of the concentrated NaOH (1M) solution to 100 ml with distilled water in a volumetric flask.

Recommended procedure and calibration curve

An aliquot of standard solution (1-50) µg of MCPH was transferred into a series of 25-ml volumetric flasks. To each flask, 2.5 ml of sodium hydroxide (0.01M) solution and 0.5 ml ammonium ceric sulphate dihydrate solution were added. The reaction mixture was allowed to stand for 20 min after mixing thoroughly. A 0.7 ml of arsenazo III was added and the contents were diluted to the mark with distilled water and mixed well. The absorbance of the formed coloure (blue-violet) was measured at 654 nm against the corresponding reagent blank. A linear calibration graph was obtained over the concentration range of (1-30) µg of MCPH /25ml,(0.04-1.2) ppm. Higher concentrations show a negative deviation from Beer's law (Fig.1). The apparent molar absorptivity has been found to be 9.36×10^4 $l.mol^{-1}.cm^{-1}$ and Sandell's sensitivity is 0.0038 $\mu g.cm^{-2}$ and the limit of detection (LOD) is 0.0095 µg/ml and the limit of quantitation (LOQ) is 0.0317 µg/ml.

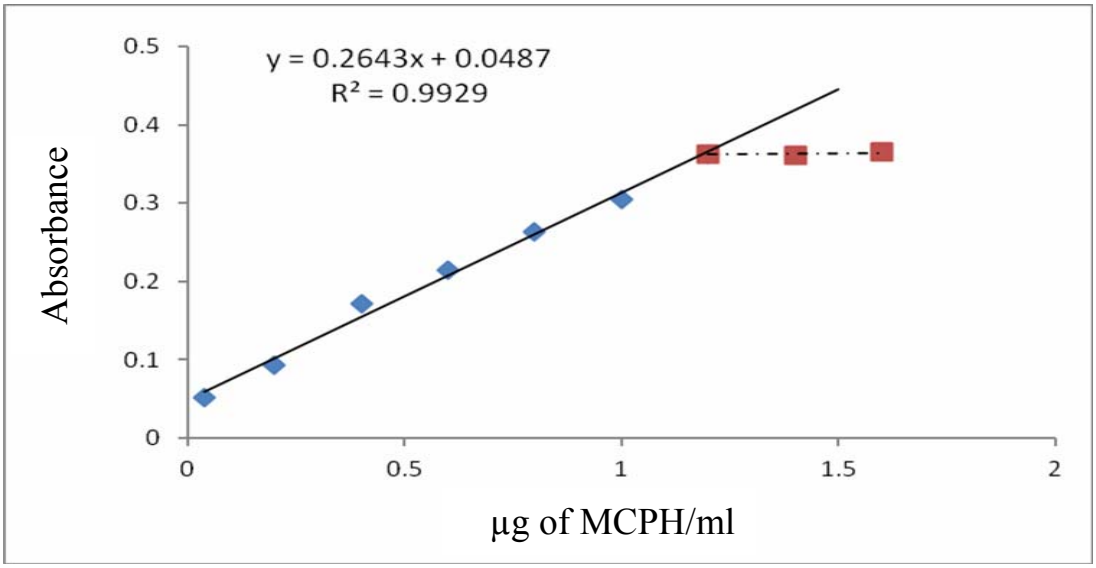


Fig 1: Calibration graph for MCPH determination

Procedure for dosage forms

For tablets: at least ten tablets (5 mg MCPH /tablet) of the drug were weighed, powdered and mixed well. A portion equivalent to 0.01 g of MCPH was weighed and dissolved in 100 ml of distilled water, shaken well, filtered and diluted with water to 100 ml in a volumetric flask. An aliquot of the diluted drug solution was then treated as done in a recommended procedure.

For injection*:* the content of the container of MCPH injection (10 mg MCPH /2 ml) was mixed well and transferred into 100 ml volumetric flask and completed to the mark with distilled water. An aliquot of the diluted drug solution was then treated as done in recommended procedure.

RESULTS AND DISCUSSION

The Principle of colour reaction

Under the reaction conditions, metoclopramide hydrochloride (MCPH) was treated with ammonium ceric sulphate dihydrate in acidic medium, which undergoes oxidation – reduction reaction to give Ce (III) ions. The cerium III formed was quantitatively and rapidly converted into the stable arsenazo III – Ce (III) coulered complex which exhibited absorption maxima at 654 nm against reagent blank solution. The intensity of the formed complex has been found to be proportional to the amount of MCPH originally present in solution.

Optimization of variables

The effect of various parameters on the absorption intensity of the coloured complex is studied and the reaction conditions have been optimized. The preliminary investigation showed that the complex formed have a maximum absorption at 654 nm against reagent blank.

Effect of pH

The effect of pH on the intensity of the coloured complex is examined. Different volumes (0.5-3.5 ml) of 0.01M sodium hydroxide are added to an aliquot of solution containing 25 µg MCPH/25 ml. The absorbances are read against the reagent blank. The results are shown in Table 1

Table 1: Effect of pH on absorbance.

ml of 0.01 M NaOH	Absorbance	Final pH
0	0.065	2.91
0.5	0.192	2.96
1.0	0.273	3.03
1.5	0.284	3.13
2.0	0.298	3.23
2.5	0.310	3.36
3.0	0.288	3.58
3.5	0.278	4.07

The results shown in Table 1 indicate that the pH of 3.36 (pH≈3.4) is considered optimum. A pH 3.4 is selected for subsequent investigation as it gives maximum absorbance for the coloured product. Four buffer solutions of pH 3.4 with different compositions have: tartaric acid-NaOH (B_1), citric acid-NaOH (B_2), KH Phthalate-HCl (B_3), and glycine-HCl (B_4) (Perrin and Dempsey, 1974).The results indicate that all types of buffer solutions decrease the intensity and stability of absorption of the coloured complex, so the use of buffer solutions is not recommended. A 2.5 ml of 0.01M NaOH solution has been recommended for subsequent experiments.

Effect of oxidizing agent [cerium(IV) ion] amount

Different amounts of cerium(IV) ion solution are added to 2.5-30 µg of MCPH/25ml and the optimum amount which gives higher intensity of coloured complex and higher value of correlation coefficient (Table 2) has been selected

Table 2: Effect of ceric ion amount on absorbance.

ml of $4x10^{-4}$ M cerium(IV) ion solution	Absorbance/µg MCPH in 25 ml						ml of NaOH (0.01M)*	R^2
	2.5	5.0	10.0	20	25	30		
0.2	0.063	0.096	0.123	0.135	0.123	0.137	1.0	0.7251
0.5	0.082	0.010	0.150	0.267	0.322	0.363	2.5	0.9976
0.7	0.08	0.111	0.140	0.287	0.339	0.404	3.5	0.9927
1.0	0.101	0.106	0.164	0.300	0.356	0.427	5	0.9941
1.5	0.102	0.135	0.208	0.334	0.379	0.449	7.5	0.9975

* Used for pH adjustment to 3.4

The results shown in Table 2 indicate that the volume of 0.5 ml of $4x10^{-4}$ M cerium (IV) ion solution gives good correlation coefficient and the lower blank value(0.106) compared with 1.5 ml of the oxidant gives (0.289) absorbance value.

Effect of reaction time

The effect of time needed for the complete reduction of cerium (IV) to cerium (III) ion is studied by standing of the solutions after adding cerium (IV) ion solutions for different times, then the reagent is added and the absorbance are measured against the reagent blank and the results indicate that a complete reduction of cerium (IV) ion occurred after 20 minutes. Therefore, the time (20 minutes) is recommended for the subsequent experiments.

Effect of arsenazo III reagent amount

The effect of the amount of arsenazo III reagent on the maximum formation of the coloured complex is investigated for 2.5-30 µg of MCPH/25ml. The results are shown in Table 3.

Table 3: Effect of arsenazo III reagent amount on absorbance.

ml of $6x10^{-4}$ M arseazoIII reagent	Absorbance/µg MCPH in 25ml						Blank	R^2
	2.5	5	10	20	25	30		
0.5	0.07	0.089	0.138	0.245	0.299	0.308	0.085	0.9846
0.7	0.08	0.09	0.160	0.265	0.316	0.363	0.105	0.9969
1.0	0.07	0.085	0.150	0.256	0.302	0.339	0.116	0.9953
1.5	0.054	0.080	0.138	0.236	0.281	0.318	0.122	0.9967
2.0	0.050	0.076	0.120	0.221	0.256	0.292	0.140	0.9962

The results shown in Table 3 indicate that 0.7 ml of arsenazo III reagent solution gives the good sensitivity and good value of correlation coefficient, therefore it has been selected for subsequent experiments.

Effect of surfactant

The effect of surfactant was studied by the addition of 3 ml of various types of surfactant (positive, negative and neutral charged) to the medium of reaction with different orders of addition. The results are shown in Table 4.

Table 4: Effect of surfactants and the order of additions.

Surfactant solution*	Absorbance**/order***of addition			
	I	II	III	IV
CTAB $1x10^{-3}$ M	turbid	turbid	turbid	turbid
SDS $1x10^{-3}$ M	0.294	0.263	0.263	0.226
Triton X-100 1% v/v	0.312	0.292	0.230	0.277

* CTAB :Cetyltrimethylamoniumbromide (positively charged)
SDS :Sodium dodecyl sulphate (negatively charged)
TritonX-100: Iso-Octylphenoxypolyethoxyethanol (neutral)

** Absorbance without surfactant=0.326

*** I. MCPH+ Ce^{+4}+NaOH + Reagent (AzIII)+ Surfactant (S)
II. MCPH+Ce^{+4}+NaOH+S+AzIII
III. MCPH+ Ce^{+4}+S+ NaOH+ AzIII
IV. MCPH+S+ Ce^{+4}+ NaOH+ AzIII

The results in Table 4 indicate that all types of surfactants solutions decrease the intensity of absorption of the coloured complex, so that the use of surfactants solutions is not recommended.

Effect of time

The effect of time on the development and stability of coloured complex for different amounts of MCPH is investigated under the optimum experimental conditions established. Complete colour formation occurs immediately after all reaction mixtures are added and the absorbance of the complex remains constant for at least 60 minutes (Table 5)

Table 5: Effect of time on the absorbance of complex.

µg of MCPH	Absorbance* / min									
	0	5	10	15	20	25	30	40	50	60
5	0.071	0.073	0.073	0.074	0.073	0.072	0.073	0.072	0.071	0.071
25	0.326	0.325	0.323	0.321	0.320	0.319	0.315	0.311	0.308	0.308

* After 20 minutes reaction time of MCPH with Ce^{+4} ion before addition of reagent

The results shown in Table 5 indicate that the stability period is sufficient to allow several measurements to be performed sequentially.

Absorption spectra

Absorption spectra of the coloured complex formed from the reaction between cerium III ion with arsenazo III reagent in acidic medium against its corresponding reagent blank show maximum absorption at 654 nm in contrast to the arsenazo III reagent blank which shows a weak absorption at the same wavelength (Fig.2).

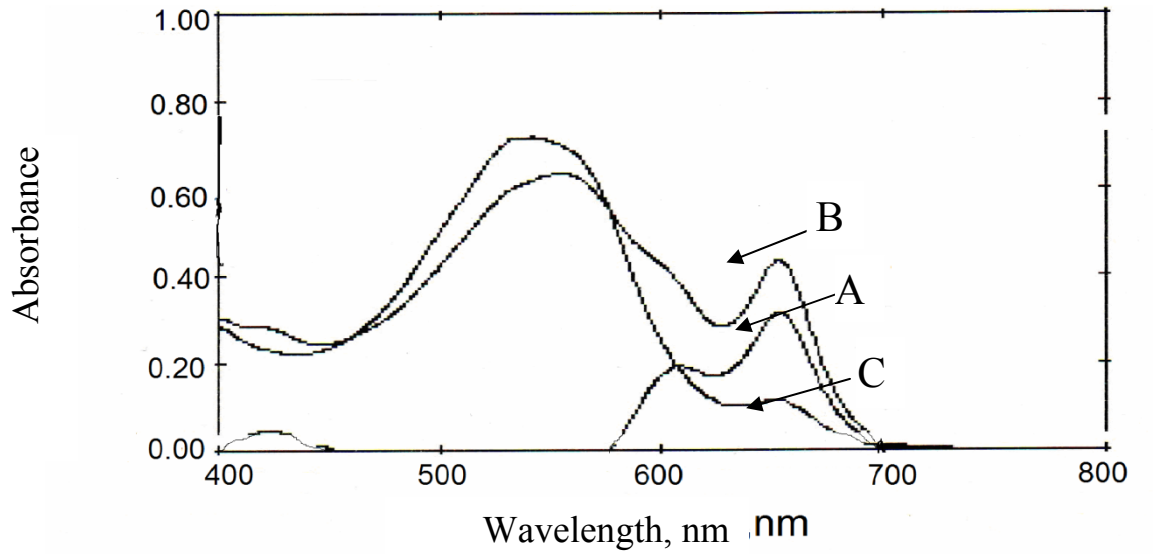


Fig. 2: Absorption spectra of 25 µg MCPH /25 ml treated according to the optimum conditions and measured against (A) blank ,(B) distilled water and (C) blank measured against distilled water.

Accuracy and precision

To check the accuracy and precision, MCPH was determined at three different concentrations. The results are shown in Table 6 indicate that the method is satisfactory.

Table 6: Accuracy and precision of the proposed method.

Amount of MCPH taken, µg.	Recovery % *	Relative standard deviation, % *
5	99.8	± 3.98
10	98.6	± 2.38
25	100.5	± 1.80

*Average of five determinations.

Nature of the reaction between MCPH and cerium IV ion

Job's method has been used in the determination of the reaction ratio of MCPH with cerium(IV) ion. The obtained results in (Fig.3) showed that a1:1 MCPH to cerium IV ion ratio is obtained.

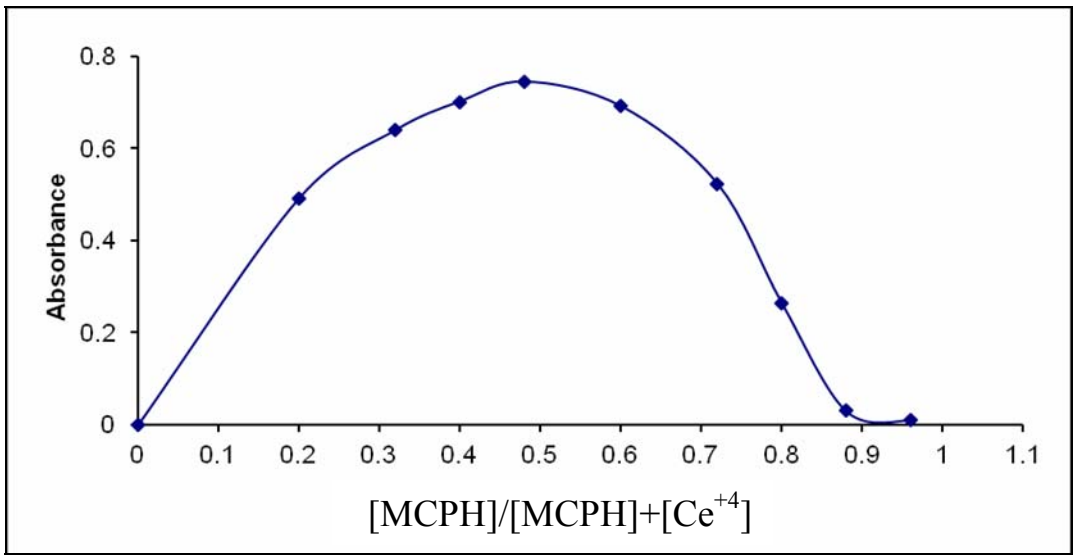
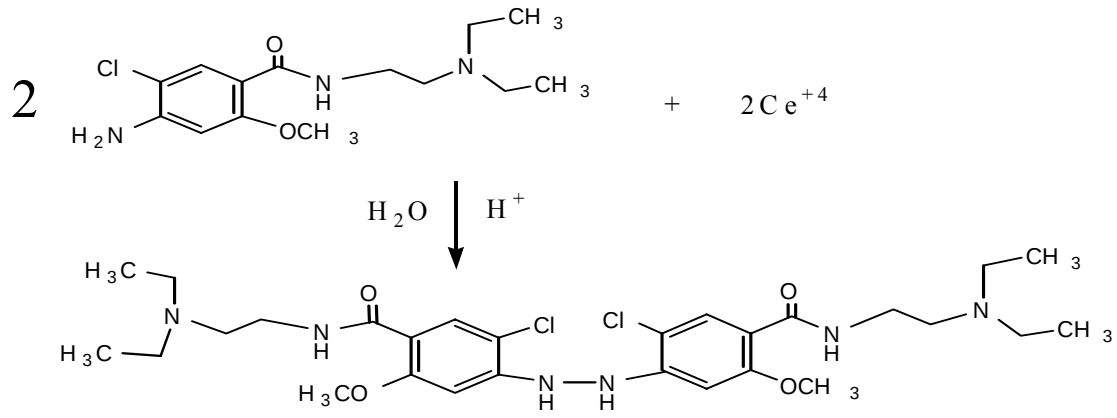


Fig. 3 : Job's plot for MCPH-Cerium(IV) ion

The probable mechanism of the reaction may be according to the following :

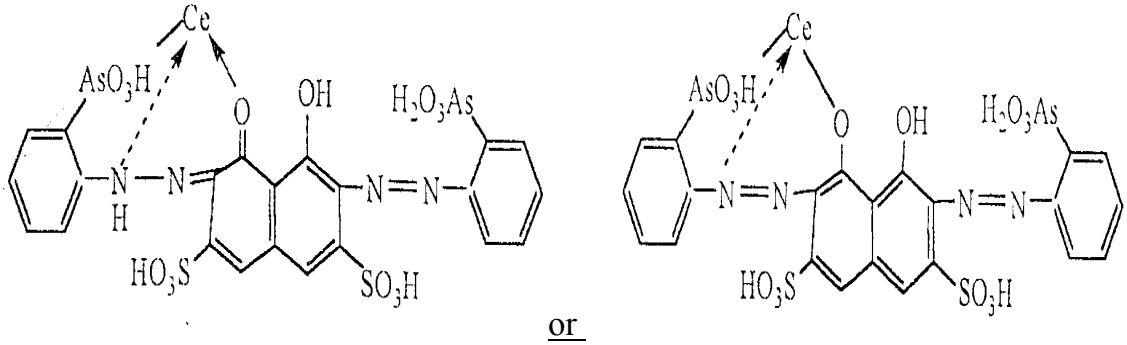


Nature of arsenazo III-cerium (III) ion complex

The stoichiometry of the reaction is investigated using the Job's and mole ratio methods (Delevie,1997) under the optimized conditions. The obtained results showed that a

1:1 arsenazo III to cerium (III) ion ratio is obtained, this result is identical with that in the literature (Sandell and Onishi, 1978)

The probable mechanism of the reaction might be as the following:



or

Effect of interferences

In order to test the efficiency and selectivity of the proposed method , the effect of some foreign substances (e.g., acacia, glucose, lactose, sorbitol, and starch) that usually present in dosage forms were studied by adding different amounts of foreign substances to 25 µg MCPH / 25 ml. It was observed that the studied foreign species did not interfere in the present method (Table 7).

Table 7: Effect of additives and excipients on the determination of 25 µg of MCPH /25ml.

Interferences	Recovery(%) of MCPH / ppm of interfere added		
	100	**500**	**1000**
Acacia	99.3	96.0	95.0
Glucose	101.3	99.3	101.6
Lactose	103.2	102.1	99.3
Sorbitol	102.8	96.7	96.0
Starch	101.9	101.6	103.2

Application of the method

The proposed method was successfully applied to the determination of MCPH in its pharmaceutical preparations (tablet and injection). The results which are shown in Table 8 indicate that good recoveries were obtained.

Table 8: Analytical applications.

MCPH Amount µg/25 ml	Recovery(%) of MCPH*			
	Meclodin (5mg MCPH / tablet) NDI-Iraq	Meclodin (5mg MCPH / tablet) SDI-Iraq	MCPH injection (10 mg/1ml) Germany	MCPH injection (10 mg/1ml) China
10	98.8	101.0	100.0	98.8
15	100.0	99.5	98.3	100.0
25	98.4	97.6	100.0	100.56

*Average of three determinations.

The performance of the proposed method was a ssessed by calculating the student's t-test and F-test (Christian, 2004) compared with the literature method (Khalil, 2010). The results in Table 9 show that the calculated values of t-test and F-test did not exceed the theoretical values at the 95% confidence indicating that there is no significant difference between the proposed method and the literature method.

Table 9: Determination of MCPH in pharmaceutical preparations.

Drug	MCPH amount, µg	Recovery * %			
		Present method	Literature method (Khalil, 2010)	t-exp	F-exp
Meclodin (5mg MCPH / tablet) NDI-Iraq	25	99.06	97.56	0.9	11.31
Meclodin (5mg MCPH / tablet) SDI-Iraq	25	99.36	97.96	0.6	5.59
MCPH injection (10 mg/1ml) Germany	25	99.43	99.20	0.2	3.12

* Average of three determinations.

Comparison of the methods

Table 10, shows the comparison between some of the analytical variables for the present method with that of other literature spectrophotometric methods.

Table 10: Comparison of the methods.

Analytical parameters	Present method	Literature method (Amin and Ragab, 2003)	Literature method (Khalil, 2010)	Literature method (Al-Talib and Mohammed, 1996)
Reaction medium	Acidic	Acidic	Acidic	Acidic medium
λmax (nm)	654	510,522	500	612
Reagent	Arsenazo III	o-phenanthroline ,bipyridyl	Pyrocatechol	Phenothiazine
Type of method	Oxidation-reduction	Oxidation-reduction	Oxidative coupling	Oxidative coupling
Beer's law range, ppm	0.04 -1.2	0.25-5.0, 0.2-5.8	5 - 35	0.1-16
Molar absorptivity , $l.mol^{-1}.cm^{-1}$	$9.36x10^4$	$4.25x10^4$, $3.53x10^4$	3.01×10^3	1.65×10^4
Application of the method	tablets and injection	tablets and injection	tablets , syrup and drops	tablets

The results indicate that the proposed method has a good sensitivity and has a wide application part in determination of the drug under investigation in its pharmaceutical preparations.

CONCLUSION

The proposed method for the spectrophotometric determination of metoclopramide-hydrochloride in pharmaceutical preparations is simple, sensitive, rapid, accurate and precise. The method is based on oxidation – reduction reaction between metoclopramide hydrochloride and cerium (IV) ion (ceric ion), then the subsequent reaction of cerium (III) with arsenazo III reagent in acidic medium to produce blue-violet complex which is stable, water soluble and has a maximum absorption at 654nm. the proposed method has been applied successfully to the determination of the intended compound in its pharmaceutical preparations (tablet and injection).

REFERENCES

Abdel–Gawad, F.M. ; El-Gunidi, N.M. (1995). Spectrophotometric determination of metoclopramide and oxybuprocaine through ion pair formation with thiocyanate and molybdenum (V) or cobalt (II), *Anal. Lett.*, **28**, 1437-1447.

Al-Arfaj, N. A. (2004). Flow-injection chemiluminescent determination of metoclopramide hydrochloride in pharmaceutical formulations and biological fluids using the $[Ru(dipy)_3]^{2+}$ – permanganate system, *Talanta*, **62**, 255.

Al-Talib, S. M. ; Mohammed, S. A. (1996). Spectrophotometric assay of metoclopramide via oxidative coupling with phenothiazine and sodium metaperiodate, *J. Edu. Sci*., **18**(4), 16-22.

Al-Ghabsha, T. S. ; Ahmed, R. A. ; Mahmood, H. Sh. (2004). Spectrophotometric study of some drugs using 2,3-dichloro-5-6-dicyano-p-benzoquinon (DDQ), *J. Edu. Sci.* , **16**(4), 42-53.

Amin, A. S. ; Ragab, G. H. (2003). Spectrophotometric methods for the determination of anti-emetic drugs in bulk and in pharmaceutical preparations, *Anal. Sci.*, **19**, 747-751.

Attia, M. S. ; Aboaly, M. M. (2010). Highly sensitive and selective spectrophotometric determination of metoclopramide hydrochloride in pharmaceutical tablets and serum samples using Eu^{3+} ion doped in sol-gel matrix, *Talanta*, **82**(1), 78-84.

Avula, S. ; Babu, K. N. (2011). Development and validation of LC method for the analysis of metoclopramide in pharmaceutical dosage form and plasma, *Intern. J. Res. Rev. Pharm. Appl. Sci.*, **1** (3),104-117.

British Pharmacopoeia, Her Majesy's Stationary Office (2008). Cambridge, London, CD-ROM

Chang, Y. S. ; Ku, Y. R. ; Wen, K. C. ; Ho, L. K. (2000). Analysis of synthetic gastrointestinal drugs in adulterated traditional chines medicines by HPCE, *J. Liq. Chromatogr. Relat. Technol.* **23**(13), 2009-2019.

Christian, G. D. (2004) ."Analytical Chemistry", 6th ed., John Wiley and Sons, Inc., New York, 90p.

Delevie, R. (1997). "Principles of Quantitative Chemical Analysis", Mcgraw-Hill, International Edition, Singapore, 498p.

Donnerer, J. (2003). "Antiemetic Therapy" , Basel , Karger, pp. 161-162.

Farghaly, O. A. ; Taher, M. A.; Naggar, A. H. ; El-Sayed, A. Y. (2005). Square wave anodic stripping voltammetric determination of metoclopramide in tablet and urine at carbon paste electrode, *J. Pharm. Biomed. Anal.* **38** (1), 14-20.

Faridbod, F. ; Ganjali, M. R. ; Labbafi, S. ; Dinarvand, R. ; Riahi, S. ; Norouzi, P. (2009). A New metoclopramide potentiometric membrane sensor for analysis in pharmaceutical formulation and urine, *Int. J. Electrochem. Sci.*, **4** ,772 – 786.

Hanna, G. M. ; Lau-Cam, C. A. (1991). H^1-NMR Spectroscopic assay method for metoclopramide hydrochloride in tablets and injections, *Drug Dev. Ind. Pharm*, **17 (7)**, 975-984.

Khalil, N. A. (2010). Determination of metoclopramide hydrochloride by spectrophotometric and HPLC methods – applications to pharmaceutical preparations, M.Sc. Thesis, University of Mosul, Iraq, pp. 33 - 54.

Maquille, A. ; Jiwan, J. H. (2009). LC–MS characterization of metoclopramide photolysis products, *J. Photochem. and Photobio.* A: Chemistry **205** , 197–202.

Moussa, B. A. (2000). Determination of some aminobenzoic acid derivatives glafenine and metoclopramide , *J. Pharm. Biomed. Anal.* , **23**(6), 1045-1055.

Norouzi, P. ; Ganjali, M. R. ; Matloobi, P. (2005). Sub-second adsorption for sub-nanomolar monitoring of metoclopramide by fast stripping continuous cyclic voltammetry, *Electrochem. Commun.* **7(4)**, 333-338.

Omran, A. A. (2005). Individual and simultaneous spectrophotometric determination of dapsone and metoclopramide - HCl in pharmaceutical dosage forms and synthetic binary mixtures, *Chem. Pharm. Bull(Tokyo)* , **53**(11), 1498-1501.

Patel, S. A. ; Patel, C. N. ; Patel, M. M. (2006). Visible spectrophotometric methods for the estimation of metoclopramide - HCl in tablets, *Indian J. Pharm. Sci.*, **68**(3), 397-399.

Perrin, D. D. ; Dempsey, B. (1974) ." Buffer for pH and Metal Ion Control", Champman and Hall Ltd., London, pp. 131-135.

Revanasiddappa, H. D. ; Manju, B. (2001). A spectrophotometric method for the determination of metoclopramide hydrochloride and dapsone, *J. Pharm. Biomed. Anal.* , **25**(3-4), 631-637.

Revanasiddappa, H. D. ; Veena, M. A. (2006). Sensitive spectrophotometric determination of metoclopramide hydrochloride and dapsone in bulk sample and dosage forms, *Sci. Asia* , **32**, 319-321.

Sandell, E. B. ; Onishi, H. (1978). "Photometric Determination of Traces of Metals-Part 1" , 4th ed., John Wiley and Sons , New York , pp. 458-459,463-465.

Shah, J. ; Rasul, J. M. ; Azam, K. M. ; Amin, S. (2005). Spectrophotometric determination of metoclopramide in pharmaceutical preparations, *Anal. Chem.* , **60**(7), 633-635.

Wang, Z. H. ; Zhang, H. Z. ; Zhou, S. P. ; Dong, W. J. (2001). Determination of trace metoclopramide by anodic stripping voltammetry with nafion modified glassy carbon electrode, *Talanta*, **53 (6)**, 1133-1138.