Spectrophotometric assay of metoclopramide hydrochloride in some pharmaceutical preparations via oxidation coupling reaction

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ABSTRACT

Objectives: A simple and sensitive spectrophotometric method has been developed for the quantitative determination of metoclopramide hydrochloride (MCP) in both pure form and in its pharmaceutical formulations.

Materials and methods: The method is based on oxidative coupling reaction of the determined metoclopramide hydrochloride with promethazine in acidic medium (٠.١ M hydrochloric acid) by N-chlorosuccinamide (NCS) to form red-violet thiazine.

Results: Water-soluble coloured product which showed maximum absorption at ٦١٠ nm with a molar absorptivity of ٢.٠٥×١٠^{٤} L.mol$^{-١}$.cm$^{-١}$. Beer's law was obeyed over the concentration range of ٠.١-١٤ µg/mL. A relative standard deviation of the method was less than ٠.٥% and the recoveries were obtained in the range of ٩٨-١٠١.٥ %.

Conclusion: The method does not require either temperature control or solvent extraction, the composition of the coloured product and common excipients on spectrophotometric properties were studied. The proposed method has successfully applied for the determination of metoclopramide in pure and pharmaceutical formulations. The additives did not interfere in this method.

Keywords: Spectrophotometric assay, metoclopramide hydrochloride.

الخلاصة

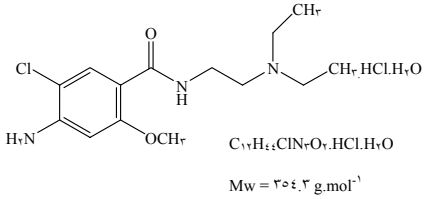
الهدف: يشمل هذا البحث تطوير طريقة طيفية بسيطة وحساسة لتقدير هيدروكلوريد الميتوكلوبراميد في حالته النقية وفي بعض المستحضرات الصيدلانية.

المواد وطريق العمل: تعتمد الطريقة على مفاعلة الميتوكلوبراميد مع الكاشف البروميثازين والعامل المؤكسد ن-كلوروسكسينايمد في وسط حامضي (٠.١ مولاري حامض الهيدروكلوريك) .

النتائج: تكونت صبغة بنفسجية حمراء ذائبة في الماء التي اعطت اعلى امتصاص عند طول موجي مقداره 610 نانوميتر بامتصاصية مولارية ٠.٥×١٠^{٤} لتر.مول$^{-1}$.سم$^{-1}$. تتبع الطريقة قانون بير لمدى من التراكيز تقع بين ٠.١-١٤ مايكروغرام/مللتر. كان الانحراف القياسي النسبي للطريقة اقل من ٠.٥% ومعدل الاسترجاعية تراوح بين ٩٨-١٠١.٥% .

الاستنتاج: الطريقة المقترحة لاتحتاج الى السيطرة على درجات الحرارة او الاستخلاص بالمذيب، تمت دراسة طيفية وتركيب الصبغة والمتداخلات، وطبقت الطريقة المقترحة بنجاح في تقدير الميتوكلوبراميد في حالته النقية وفي بعض مستحضراته الصيدلانية. كما وجد ان لاتاثير للمضافات الدوائية في الطريقة المقترحة.

Metoclopramide hydrochloride (MCP), is the monohydrate ٤-amino-٥-chloro-N-(٢-diethylaminoethyl) -٢-methoxy-benzamide[١]. Metoclopramide is the active ingredient of many pharmaceutical preparations, which accelerates gastric emptying[٢].



$C_{١٧}H_{٢٤}ClN_{٣}O_{٢}.HCl.H_{٢}O$

Mw = ٣٥٤.٣ g.mol$^{-١}$

It was considered as dopamine receptor antagonsit[٣]. It also has an anti-emetic action on the central nervous system[٤].

Many analytical methods have been developed for the determination of MCP, most of them are spectrophotometric based on oxidative coupling reaction[٥,٦], charge-transfer complex formation[٧], redox reaction[٨], or through formation of the Schiff's base with p-dimethylamine cinamaldehyde[٩]. Other methods based on fluorimetric[١٠], or on diazotization and coupling with different coupling agents such as dibenzoyl methan[١١], benzoyl-acetone[١٢], aniline[١٣], β-naphthol[١٤]. Some of methods based on flow injection-chemiluminescent[١٥], on capillary electrophoresis[١٦], voltam-metry[١٧], H^1NMR spectro-scopy[١٨], and chromate-graphic technique[١٩-٢١]. The above methods are time consuming[١١], heat dependent[٩], unselective[١٠], and not suitable for routine analysis. The British pharmacopoeia reported a potentiometric method using perchloric acid solution for the determination of MCP powder and a UV method for tablets and ampoules[١]. The potentiometric method requires about ٢٥٠ mg of drug, where as the UV ethod is liable to interferences from tablets excipients, and requires pre-extraction with chloroform. These difficulties have encourage the researchers to develop a simple, selective, sensitive and inexpensive method for the analysis of the studied drug.

The present work describes the application of N-chlorosuccinamide as an inexpensive new oxidant reagent with promethazine agent for the determination of MCP in both pure form and in pharmaceutical preparations.

Experimental

Apparatus

The absorption spectra were recorded on a double-beam Shimadzu UV-Visible recording spectrophotometer UV-١٦٠ with ١.٠ cm matched silica cells. The absorbance measurements were obtained using double–beam SOHZ ٩٢٠٠ spectrophotometer with ١ cm quartze cells. PH measurements were performed using Philips PW ٩٤٢٠ pH meter.

Reagents

All chemical used were of analytical-reagent grade. MCP (١٠٠ µg / ml) solution. MCP powder was provided from Ninavah drug industry (NDI). It was prepared by dissolving ٠.٠١ g of MCP in distilled water and the volume was completed to ١٠٠ ml with distilled water in a volumetric flask. The solution was then transferred to an opaque bottle and it was stable for at least one month. Working solution of MCP was prepared by appropriate dilution of the stock solution with distilled water. .

Promethazine (٠.١%) solution

It was prepared by dissolving ٠.١ g of promethazine reagent (Hopkins and Williams) in ١٠٠ ml distilled water.

N-Chlorosuccinamide (NCS ٠.١%): This solution was prepared by dissolving ١.٠g of NCS (BDH) in ١٠٠ ml distilled water. Hydrochloric acid (Thomas Baker). Solutions of ١M NaOH is also prepared.

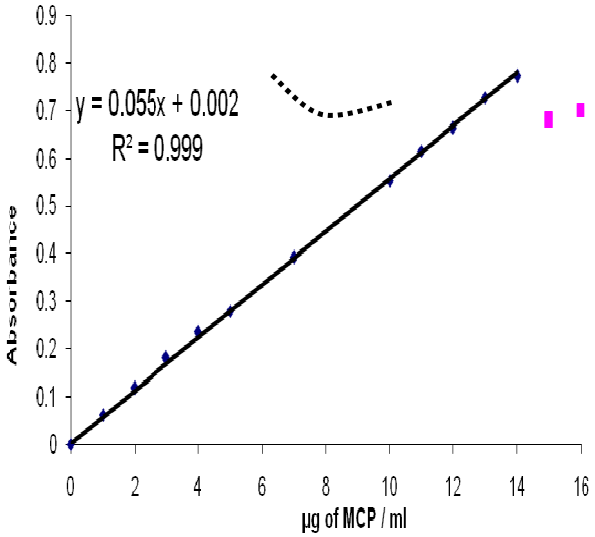


Figure ١. Calibration curve for MCP determination

General procedure

Different volumes of standard solutions (١٠-and ٥٠ µg/mL) were transferred into a series of ١٠ mL volumetric flasks. T٠ each flask, ٠.٥ mL of ٠.١N HCl acid, ٢.٥ mL of ٠.١% promethazine were added. The mixture is diluted to volume with distilled water, and allowed standing for ٥ min. The absorbance is measured at ٦١٠ nm against a reagent blank.

Analysis of pharmaceutical preparations

At least ten tablets (٥ mg MCP-HCl/tablet) were weighed, powdered and mixed well. A portion equivalent to ٠.٠١ g is weighed and dissolved in ٥٠ ml of distilled water, shaken well, filtered and diluted with water to ١٠٠ ml in a volumetric flask. An aliquot of the diluted drug solution is then treated as mentioned in the recommended procedure.

The content of MCP syrup (٥ mg MCP HCl/٥ mL) is mixed well and ٢ ml of the syrup was quantitatively transferred into ١٠٠ ml volumetric flask and completed to the mark with distilled water. An aliquot of the drug (١٠٠٠ ppm) and its diluted (٢٠ ppm) solution are then treated as mention in the recommended procedure.

An accurate volume ٢.٥ ml of MCP drops (٤ mg MCP HCl/ml) is transferred into a ١٠٠ ml volumetric flask and completed to the mark with distilled water, then it is proceeded as the recommended procedure.

Results and discussion

Under the reaction conditions, the formation of the product probably occurs as follows (Scheme ١).

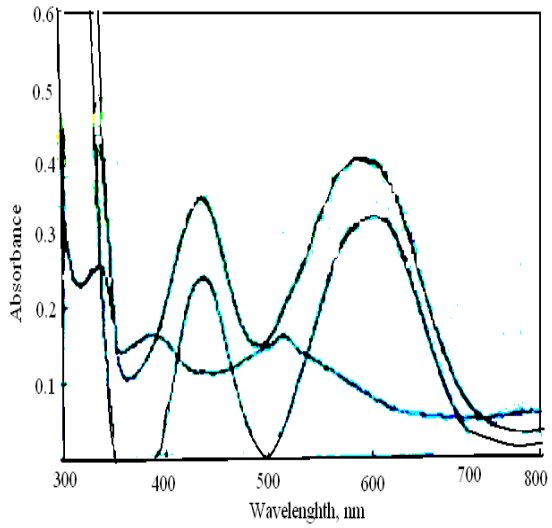
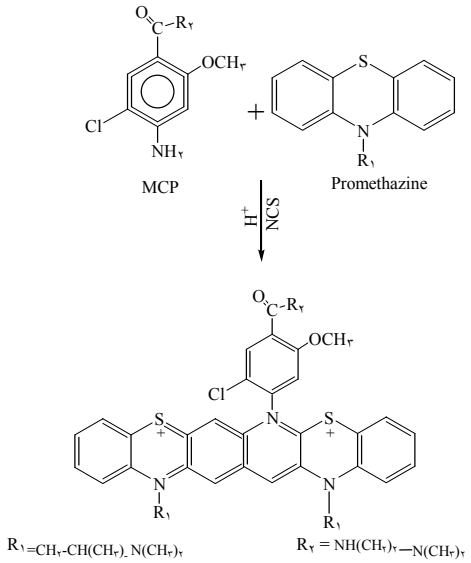


Fig ٢. Absorption spectra of ١٠٠ µg of MCP/١٠ ml measured against (A) blank, (B) distilled water, and (C) blank measured against distilled water.



Scheme.١. Probable product formation pathway

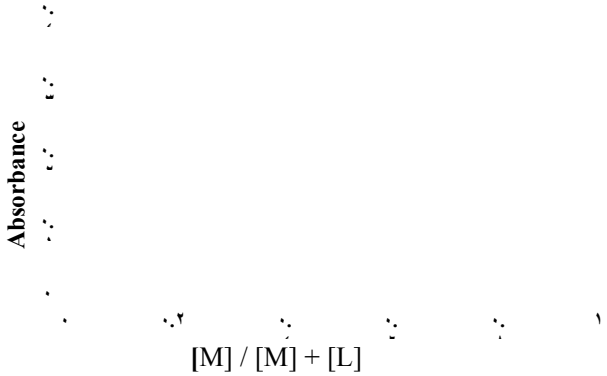


Fig ٣. Job's plot for [MP] / [MCP] + [Promethazine]

The effect of pH on the sensitivity of the product is examined. Only pH ٣.٢ (٠.١ N hydrochloric acid) is found to be optimum. The effect of the amount of ٠.١ N hydrochloric acid is also investigated and ١.٠ ml is found to be the most suitable effect on the intensity with corresponding low reagent blank absorbance. Different amount of various acids such as HCl, CH_3COOH, HNO_3, H_2SO_4 have been tried for the producing intense coloured products and alower blank value to obtain high variance value between the absorbance of sample against blank**.**

The oxidative coupling reaction was carried out in the presence of various oxidizing agents cerium (IV) sulphate, potassium dichromate, potassium iodate, and N-chlorosuccinimide (NCS). The experimental data revealed that NCS was the most suitable oxidizing agent.

The amount of NCS solution (٠.١%) for maximal colour intensity was examined. The maximum colour intensity was reached when (١.٥-٣.٠) ml were used. However ٢.٥ ml of NCS solution was selected because it gives the most suitable effect on the intensity of the coloured product with corresponding low reagent blank absorbance.

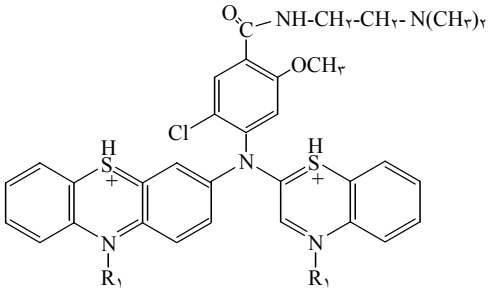
The effect of surfactant addition to the reaction mixture was studied. In this respect sodium dodecyl sulfate (SDS), (anionic surfactant), cetyltrimethyl-ammonium bromide (CTAB), (Cationic surfactant) andtriton x-١٠٠ (non-ionic surfactant) have been introduced. The results indicated that addition of surfactants gave no useful effect, therefore, it was omitted in this study.

The effect of temperature on the intensity of the coloured product was studied. In practice the absorbance was decreased when the coloured is developed at ºC or when the calibrated flask is placed in a water-bath at ٤٠, ٥٠, ٧٠, ٨٠ and ١٠٠ ºC. Therefore, it is recommended to proceed the reaction at room temperature ٢٥ ºC.

To obtain optimum results, the order of addition of reagents should followed as the procedure cited above, otherwise a loss in coloured intensity was observed.

To test the effect of time on the absorbance of the colour product at the wavelength of maximum absorption at ٦١٠ nm, the coloured product has been prepared from different amounts of MCP under the optimal experimental conditions, and the absorbance were measured at different intervals of time up to ٢hr. The experimental results showed that the colour product developed immediately and the absorbance remains maximum and constant for at least ٩٠ minutes.

The stoichiometry of the reaction between MCP and promethazine was investigated using continuous (Job's method). Figure ٣ were indicated that the product was formed in ratio of ١:٢.



Red-violet coloured product

$R_1 = CH_2\text{-}CH(CH_3)\text{-}N(CH_3)_2$

The results indicate that the coloured product was formed as the following structure[٦].

Accuracy and precision

To check the accuracy and precision of the calibration graph, MCP was determined at three different concentrations. The results are shown in Table ١ indicated that the method is satisfactory.

Effect of organic solvents

Different organic solvents are examined to evaluate their effects on the spectrum of the resulting coloured product and the data are shown in Table ٢.

Table ١. Accuracy and precision of the calibration graph

Amount of MCP taken, µg/ml	Recovery % *	Relative standard deviation, % *
٢	١٠١.٥	± ٠.٥٠٤
٥	٩٨.٠	± ٠.٤٤٧
١٠	١٠١.٣	± ٠.٣١٦

*Average of five determinations

Table ٢. Different organic solvents and their effects on the spectrum

Solvent	Colour		λ max, (nm)	ε $l.mol^{-1}.cm^{-1}$
	Sample	Blank		
Acetic acid	Red-violet	Pale pink	٦١٠	٠.١ × ١٠^{٣}
Acetone	Red-violet	Pale pink	٦١٣	٠.١١ × ١٠^{٣}
١,٤-Dioxane	Pale red-violet	Pale pink	٦١٥	٠.٤ × ١٠^{٣}
Ethanol	Pale red-violet	Pale pink	٦١٣	٠.٧ × ١٠^{٣}
Methanol	Red-violet	Pale pink	٦١٣	٠.١ × ١٠^{٤}
n-Butanol	Pale pink	Pale pink	٦١٥	٠.١ × ١٠^{٣}
Water	Red-violet	Pale pink	٦١٠	٢.٠٥ × ١٠^{٤}

Water is still chosen in the subsequent experiment of availability, non-toxicity and cheap as well as being a suitable medium from the sensitivity point of view.

Effect of interferences

In order to test the efficiency and selectivity of the proposed analytical method, application of some foreign substances (e.g. acacia, glucose, starch and lactose), that usually present in dosage forms were studied by adding amounts of foreign substances to ١٠٠ µg MCP/١٠ mL The colour was developed following the procedure described ealier. It was observed that the studied foreign species did not interfere in the present method Table ٣.

Application of the method

The proposed method was successfully applied to the determination of MCP-HCl in its pharmaceutical preparations (tablet, syrup and drop). The results are shown in Table ٤ indicated that a good recovery was obtained.

Table ٣. Effect of additives and excipients on the determination of ١٠٠ µg of MCP

Interferences	Recovery(%) of ١٠٠ µg MCP / µg of interfere of added		
	١٠٠	٥٠٠	١٠٠٠
Acacia	٩٨.٨	٩٧.٢	٩٦.٤
Glucose	٩٥.٧	٩٦.٨	١٠٠.٦
Lactose	٩٤.٥	٩٨.٤	٩٤.٢
Starch	٩٤.٤	٩٥.٨	١٠٠.٦

Table ٤. Analytical applications

MCP amount, µg	Recovery(%) of MCP*		
	MCP-HCl (٥mg/ tablet) NDI-Iraq	MCP-HCl syrup (٥mg/٥ml) NDI-Iraq	MCP-HCl drops (٤mg/ml) NDI-Iraq
١٠	٩٥.٨	١٠٣.٠	١٠٣.٥
٥٠	٩٥.٠	٩٥.٢	٩٧.٠
١٠٠	٩٩.٥	٩٧.٥	٩٩.٧

* Average of five determinations.

The performance of the proposed method was assessed by calculating the student's t-test and F-test compared with the literature method [٦]. The results in Table ٥ show that the calculated value of t and F did not exceed the theoretical values at the ٩٥% confidence level for five degrees of freedom indicating that there is no significant difference between the proposed method and the literature method.

Comparison of the method

Table ٦ shows the comparison between some analytical variables for the present method with these of recent spectrophotometric methods.

Table ٥. Determination of metoclopramide in pharmaceutical preparations

Drug	Pharmaceutical preparation amount	Recovery * %	
		Present method	Literature method[٦]
MCP HCl (٥mg/ tablet) SDI, Iraq	Tablet	٩٩.٥ ± ٠.٥ t = ٢.٣ F = ٠.٢٠	٩٨.٠ ± ٢.٠
MCP-HCl (٥mg/٥ml) SDI, Iraq	Syrup	١٠٠.٧ ± ٠.٧ t = ١.٤ F = ٠.٧٧	١٠١.٢ ± ١.٢
MCP-HCl (٤mg/ml) NDI, Iraq	Drop	١٠٣.١ ± ٣.١ t = ١.٥٩ F = ٠.٠١٨	١٠٢.٥ ± ٢.٥

* Average of five determinations.

Table ٦. Comparison of the methods

Analytical parameters	Present method	Literature method [٥]
Coupling condition	Acidic medium	Acidic medium
λ max (nm)	٦١٠	٦١٢
Reagent	Promethazine	Phenothiazine
Type of method	Oxidative coupling	Oxidative coupling
Oxidizing reagent	N-chlorsuccinimide	Sodiummetaperiodate
Beer's law range, ppm	٠.١ - ١٤	٠.١-١٦
Molar absorptivity , $l.mol^{-1}.cm^{-1}$	٠.٥×١٠^{٤}	١.٦٥×١٠^{٤}
Application of the method	Tablets, syrup and drops	Tablets
Error %	-٢ -٠	+١.٩٥

Conclusion

The developed spectrophotometric method for the assay of MCP is simple, sensitive, selective, inexpensive and exhibits a fair degree of precision and accuracy. The method does not involve any critical reaction conditions and can be compared favorably with other existing methods. The proposed method does not require neither temperature control nor solvent extraction step and it can be applied successfully for the determination of drug in tablets, syrup and drop.

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