Spectrophotometric Determination of Metoclopramide Hydrochloride in Pharmaceutical Preparations Via Oxidative Coupling Reaction

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(**Received:** 1 / 11 / 2009 ---- **Accepted:** 18 / 1 / 2010)

Abstract

A simple and rapid spectropotometric method for the determination of metoclopramide-HCl(MCP) was described. The method is based on the oxidative coupling reaction of pyrocatecol (PC) with MCP using ammonium ceric sulphate (ACS) as oxidizing agent in acidic medium to form a water soluble product, that is stable and has a maximum absorption at 500 nm. Beer's law is obeyed in a concentration range of 5-35 μg.ml^{-1} MCP with a molar absorptivity of 3.01×10^3 l.mol^{-1}.cm^{-1}, a relative error of –0.22 to -0.90 % and a relative standard deviation of ± 0.09 to ± 1.90 % depending on the concentration of MCP. The proposed method has been successfully applied to the determination of MCP in various pharmaceutical preparations.

Introduction

Metoclopramide, 4-amino-5-chloro-2-methoxy-N-(2-diethyl-ami-no-ethyl) benzamide is a dopamine-receptor antagonist,an antiemetic and a stimulant of upper gastroin-testinal motility. It is used for the management of gastrointestinal mo-tility disorders and gastrointestinal reflux and for the prevention of cancer chemotherapy-induced emes-is at much higher doses (1).

Most of the methods used in the determination of metoclo-pramide in pure or dosage forms are chromatographic methods including liquid chromatography (2), gas chromatography (3), gas chromato-graphy-MS (4), high performance liquid chromatography (5-7) and reverse phase high performance liquid chromatogramphy (8).

The spectrophotometric methods are the most analytical methods used for metoclopramide determination using different reagent including: orcinol (9), dibenzoylmethane (10), acetyl acetone (11), aniline (12), benzoyl acetone (13) α -naphthol (14), diazotized p-nitroaniline (15), phenothiazine in presence of sodium metaperiodate (16), promethazine in presence of hypocloride (17), flouranil (18), 2,3-di chloro 5,6- dicyano p-benzoquinone (19), 4-dimethylaminobenzaldehyde (20), phenothiazine in presence of ferric nitrate (21), 1,10-phenathraline or bipyridyle in the presence of Fe(III) or Ce(IV) ions (22),2,4-dinitro-1-flourobenzene (23),4-dimethylamine cinnamaldehyde (24).

Other reported methods include titrimetry (25-26), voltametry (27), flameless atomic absorption spectro-photometry (28) and flow injection method (29,30).

Reviewing the literature revealed that up to the present time, nothing has been published concerning the using of pyrocatecol as coupling reagent in the presence of cerium(IV) ion in oxidative coupling reaction for determination of metaclopramide, so that it is used in the development of a simple spectrophotometric method for the determination of metaclopramide. The method has been satisfactorily applied to the determination of metaclopramide hydrochloride in dosage forms.

Experimental

Apparatus

All spectral and absorbance measurements were performed on Shimadzu UV-Visible-160 double beam recording spectrophotometer using 1 cm silica cell. pH meter type Philips PW 9420 was used for pH reading.

Reagents

All chemicals used in this study were of analytical reagent grade, and MCP material was provided from general establishment for medical appliance and drugs / SDI – Samaraa / Iraq.

Standard Solutions

Metoclopramide-HCl*(MCP) solution, 100 μg.ml^{-1}*. This solution was prepared by dissolving 0.01 g of MCP in 100 ml distilled water in a volumetric flask.

Pyrocatecol(PC)solution, 1.5×10^{-2} M. This solution was prepared by dissolving 0.082 g of PC in 100 ml of distilled water.

Ammonium ceric sulphate (ACS) solution, 4×10^{-3}M. This solution was prepared by dissolving 0.00632 g of ammonium ceric sulphate dihydrate (BDH) in 250 ml of distilled water in a volumetric flask, this solution was freshly prepared daily.

Procedure and calibration graph

To a series of 10 ml calibrated flasks, transfer 0.5 ml of PC reagent (1.5×10^{-2}M), an increasing volumes (0.5-3.5 ml) of MCP (100μg.ml^{-1}) are added, shaked , followed by addition of 3 ml of ACS solution (4×10^{-3}M) and the volumes are completed to the mark with distilled water, then the absorbances are read at 500 nm against reagent blank. The calibration graph is linear over the range 5-35 μg.ml^{-1} (Fig. 1). The apparent molar absorptivity referred to MCP, has been found to be 3.01×10^3l.mol^{-1}.cm^{-1}.

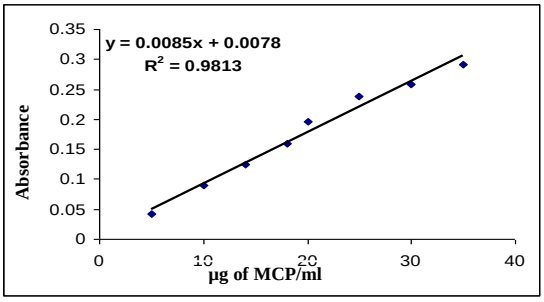


Fig. 1: The calibration graph for MCP determination applying the proposed method.

Results and discussion

The effect of various variables on the colour development was tested to establish the optimum conditions.

Choice of coupling agent

Several aromatic coupling agents have been tested for optimum conditions. The results in Table 1 show that pyrocatecol give a sensitive reaction ($\varepsilon = 3.72\times10^{3}$ l.mol^{-1} .cm^{-1}) in acidic medium and the highest value of colour contrast. Therefore, it used in the subsequent experiments.

Table 1.Choice of the coupling agent

Reagent* (0.015M)	Vairable	Absorbance	λ_{max}, nm	$\Delta\lambda_{max}$**, nm	ε l.mol^{-1}.cm^{-1}
p-Aminophenol***	S	0.354	304	25	6.27×10^{3}
	B	0.921	279		
Trifluoperazine.2HCl (TFP)	*S*	0.060	400	97	1.06×10^{3}
	B	2.139	303		
Pyrocatechol	S	0.210	500	137	3.72×10^{3}
	B	0.891	363		

* A 0.4 ml of reagent added

** $\Delta\lambda = \lambda_{maxS}-\lambda_{maxB}$ S= Sample B=Blank

***Unstable product

Choice of oxidizing agent

Different types of oxidizing agents have been tested for optimum conditions. Although The results in Table 2 show that using N-bromosuccinimide as oxidizing agent gives high intensity of colour but cerric ammonium sulphate has been selected for subsequent experiments according to the high value of colour contrast and the good intensity.

Table 2.Choice of the oxidizing agent

Oxidizing agent* (4×10^{-3}M)	*Absorbance*	λ_{max}, nm		$\Delta\lambda_{max}$**,nm
		Sample	Blank	
N-Bromosuccinimde	0.397	300	273	27
Ammonium ceric sulphate	0.196	498	272	226
KIO_3	0.689	303	273	30
K_2CrO_4	No colour contrast			
KIO_4	0.504	303	279	24
N-Chlorosuccinimide	0.688	303	271	32

* A 4 ml of oxidizing agents was used

** $\Delta\lambda_{max,} = \lambda_{max}S - \lambda_{max}B$, when S=Sample , B=Blank.

The effect of different volumes (2-6 ml) of ACS solution (4×10^{-3}M) on the colour intensity has been studied, it was observed that 5 ml of ACS is the most suitable amount, since it gives the highest intensity of the formed product (Table 3).

Table 3. The effect of ACS amount on absorbance

ml of Ce^{+4} Solution (4×10^{-3} M)	Absorbance / µg MCP in 10ml					r^2
	50	100	150	200	300	
2	0.051	0.097	0.104	0.109	0.104	0.465818
3	0.050	0.090	0.121	0.131	0.143	0.833674
4	0.050	0.089	0.142	0.191	0.198	0.874584
5	0.054	0.083	0.132	0.193	0.254	0.994158
6	0.034	0.061	0.113	0.164	0.230	0.989483

Effect of PC concentration

Various volumes of PC (1.5×10^{-2} M) were tested, the results indicated that using 0.5 ml of PC solution give maximum absorbance of the coloured product (Table 4).

Table 4. Effect of reagent amount

Ml of Pyrocatechol (0.015M)	Absorbance / µg MCP in 10ml					r^2
	50	100	150	200	300	
0.25	0.034	0.021	0.017	0.081	0.148	0.927168
0.5	0.028	0.076	0.110	0.195	0.242	0.961845
0.75	0.010	0.064	0.098	0.135	0.170	0.949954
1	0.005	0.060	0.098	0.132	0.166	0.941513

Effect of pH

The effect of pH on the intensity of the coloured product was studied using different amounts of hydrochloric acid and sodium hydroxide solutions(Table5).

Table 5. Effect of pH on absorbance

ml of HCL (0.05N)	Absorbance	pH	ml of NaOH (0.05N)	Absorbance	pH
0	0.197	2.23	0	0.197	2.23
0.1	0.175	2.22	0.1	0.098	2.27
0.3	0.172	2.14	0.3	0.07	2.27
0.5	0.167	2.11	0.5	0.068	2. 31
0.7	0.162	2.11	0.7	0.068	2. 37
1	0.159	2.08	1	0.068	2. 38
1.5	0.149	2.03	1.5	0.068	2.62

The results shown in Table 5 indicate that the pH of 2.23 is considered optimum, it is selected for subsequent investigation because of good sensitivity.

Effect of temperature and time on absorbance

The effect of temperature on the colour intensity of the resulting product was investigated. In practical the high value of absorbance was obtained when the colour was developed at room temperature (21±1°C),but when the calibrated flasks were placed in an ice-bath at(10°C) or in water-bath at(35°C)a loss in colour intensity and stability were observed ,it is therefore recommended that the colour reaction should be carried out at room temperature.

Table 6. Effect of temperature and time on absorbance

Temperature °C	Absorbance / minute standing						
	0	5	10	15	20	25	30
10	0.190	0.184	0.182	0.178	0.171	0.166	0.161
R.T.*	0.200	0.198	0.195	0.193	0.191	0.191	0.189
35	0.186	0.183	0.181	0.180	0.176	0.175	0.173

* R.T. = Room temperature = 21±1°C

Order of addition of reagents

The order of additions of reagents was examined. The results (Table 7) indicate that the order (I) of addition of reagents was the optimum order it gives the highest intensity of the product.

Table 7. The effect of order of addition

Order of addition	Order number	Absorbance
Pyrocatechol(R)+MCP+O	I	0.193
MCP + O + R	II	0.136
R + O + MCP	III	0.181
MCP + R + O	IV	0.187

Effect of reaction time

The effect of time on the development and stability period of the coloured product was investigated under the optimum conditions of the reaction. The maximum colour intensity was reached immediately after mixing the components of reaction, and the absorbance of the coloured product remained constant for at least 60 minutes for low concentrations of MCP (≤ 100 g) and at least 30 minutes for concentration above 100 to 300 g MCP (Table 8).

Table 8. Effect of time on absorbance

g of MCP present/10ml	Absorbance / minute standing							
	0	5	10	20	30	40	50	60
100	0.111	0.112	0.112	0.112	0.111	0.109	0.108	0.106
300	0.279	0.279	0.278	0.270	0.266	0.256	0.252	0.249

* Average of five determinations

Absorption spectrum

Absorption spectra of the coloured product formed from the reaction between metoclopramide with pyrocatecol in presence of ACS in acidic medium against its corresponding reagent blank show maximum absorption at 500 nm contrast to the reagent blank solution (Fig. 2).

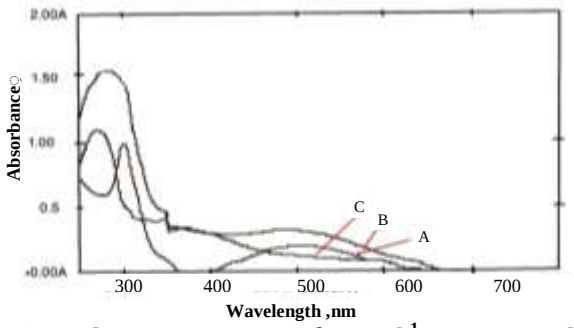


Fig.2:Absorption spectra of 20g.ml^{-1} MCP treated according to the recommended procedure and measured against (A) blank, (B) distilled water and (C) blank measured against distilled water.

Accuracy and precision

To estimate the accuracy and precision of the method, MCP was determined at three different concentrations. The results indicated the high precision and accuracy of the proposed method(Table9).

Table 9. Accuracy and precision of the proposed method

MCP (µg/10ml)	Relative Error, %*	Relative standard deviation, %*
100	-0.90	±0.90
200	-0.50	±0.09
300	-0.22	±1.90

The nature of the reaction product:

Job's (Fig. 3) and mole-ratio (Fig. 4) methods indicate that the coloured product has a composition of 1:1 MCP to PC reagent at 500 nm.

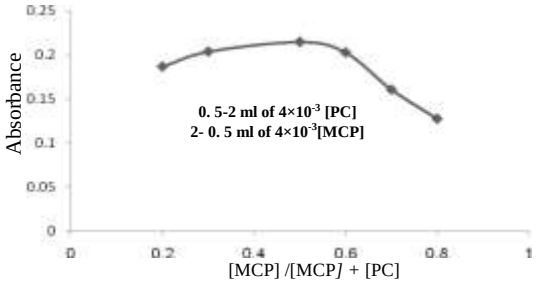


Fig. 3 : Job's plot for MCP – PC coloured product

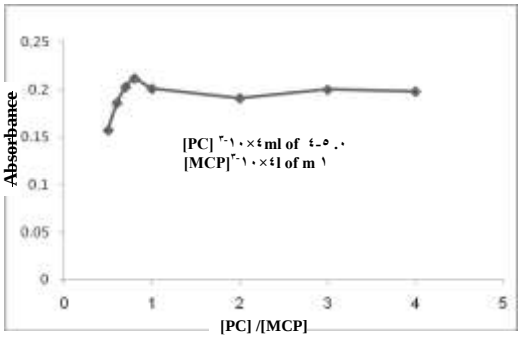
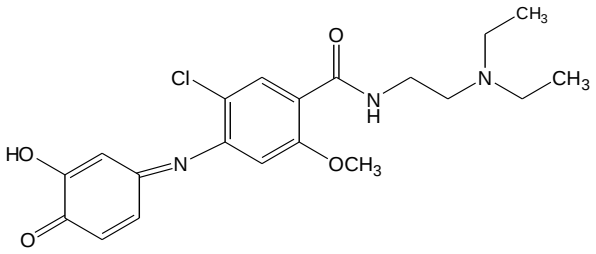


Fig. 4: Mole ratio's plot for MCP - PC coloured product

Therefore, the structure of the formed dye may be written as follows :



Orange product

Application

The proposed method was applied to determine of MCP in different pharmaceutical preparations (Table 10).

Table 10. Application of the proposed method for the determination of MCP in pharmaceutical preparations

Drug	µg MCP present in 10ml	µg MCP measured in 10ml	Recovery (%)
Metoclopramide (500mg/Tablet) Alpharma, Barnstaple, England	50	51.2	102.40
	100	100.5	100.50
	150	150	100.00
	200	192	96.00
Metoclopramide Syrup (5mg/5ml) SDI-Iraq	50	47.5	95.00
	100	95.29	95.29
	150	150	100.00
	200	194.02	97.01
Metoclopramide Injection (10mg /2ml) Ltd.Sult.Jordan	50	49.37	98.74
	100	101.7	101.70
	150	154..9	103.26
	200	205..9	102.95

*Average of three determinations

The results illustrated in Table 10 indicated that a good recoveries of MCP were obtained.

Comparison of the methods and t-test

A comparison between the present method and an a new literature method (14) for the determination of MCP in the three drugs ,is based on the t-test to show the ability of using the present method in the determination of investigated drugs (Table 11).

Table 11. Comparison of the methods and experimental t-test values

Drug	Pharmaceutical preparation	Recovery*%		t.exp
		Present method	Literature method[14]	
Metoclopramide-Alpharma,Barnstaple, (500mg/Tablet)	Tablet	96.10	100.4	0.374
MetoclopramideSyrup (5mg/5ml)SDI-Iraq	Syrup	97.02	99.8	0.892
Metoclopramide Injection Ltd.Sult.Jordan (10mg/2ml)	Injection	96.04	100.2	0.477

* Average of five determinations

The results in Table 11 indicate that the calculated experimental t-values are less than their values in the statistic table at confidence level (95%) and for nine degrees of freedom. These results indicated that there is no significant difference between the present method and the literature method.

Table 12 shows the comparison between some of analytical variables obtained from the present method with that of a recent spectrophotometric method.

Table 12.Comparision of the methods

Analytical parameters	Present method	Literature method[14]	Literature method[17]
pH	2.23	Alkaline	.....
Temperature (°C)	At room temperature	At room temperature	At room temperature
λ_{max} (nm)	500	549	٥٩٦
Medium of reaction	Aqueous	Aqueous	Aqueous
Reagent	Pyrocatechol	α - Naphthol	Bromethazine
Beer's law range (ppm)	5-35	0.5 –8	٣-٣0
Molar absorptivity ($l.mol^{-1}.cm^{-1}$)	3.01×10^3	3.85×10^4	1.10×10^4
RSD (%)	$\leq \pm 1.9$	$\leq \pm 2.17$	<1.2
Stability of the colour (minutes)	60	60	.....
Colour of the dye	Orange	Violet	Blue
Application of the method	Has been applied to the assay of MCP in pharmaceutical preparations	Has been applied to the assay of MCP in pharmaceutical preparations	Has been applied to the assay of MCP in pharmaceutical preparations

Conclusion

A simple and rapid method has been proposed for the determination of metaclopramide-HCl in pure form and in its pharmaceutical preparations. The method is based on the oxidative coupling reaction of metaclopramide-HCl with pyroc-atecol in presence of ACS in acidic medium. The method provides accurate and precise results.

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التقدير الطيفي لهيدروكلوريد الميتاكلوبرامايد في مستحضراته الصيدلانية باستخدام تفاعل الأكسدة والاقتران

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(تاريخ الاستلام: ١ / ١١ / ٢٠٠٩ ---- **تاريخ القبول:** ١٨ / ١ / ٢٠١٠ **)**

الملخص :

يتضمن البحث تطوير طريقة طيفية بسيطة و سريعة لتقدير هيدروكلوريد الميتاكلوبرامايد تعتمد الطريقة على السيريوم الأمونياكية في وسط حامضي. إذ يتكون ناتج مستقر وذائب في الماء يعطي أعلى شده امتصاص عند تفاعل الاقتران التأكسدي للكاشف بايروكاتيكول مع هيدروكلوريد الميتاكلوبرامايد باستخدام العامل المؤكسد كبريتات الطول الموجي 500 نانوميتر خضع لقانون بير ضمن مدى التركيز من 5 إلى 35 مايكروغرام.مل$^{-1}$ هيدروكلوريد الميتاكلوبرامايد وكانت قيمة معامل الامتصاص المولاري 3.01×10^3 لتر.مول$^{-1}$.سم$^{-1}$ وتراوح الخطأ النسبي بين 0.22− و 0.90− % والانحراف القياسي النسبي بين ±0.09 و1.90±% اعتماداً على مستوى التركيز المراد تقديره. وتم تطبيق الطريقة بنجاح في تقدير هيدروكلوريد الميتاكلوبرامايد في محاليل مستحضراته الصيدلانيه.