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Spectrophotometric and High Performance Liquid Chromatographic Methods for Determination of Metoclopramide in Pharmaceutical Preparations

Nabeel S. Othman
Department of Chemistry
College of Science
Mosul University

Hana S. Mahmood **Nada A. Khaleel**
Department of Pharmaceutical Sciences
College of Pharmacy
Mosul University

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ABSTRACT

A rapid, simple, and sensitive spectrophotometric and high performance liquid chromatographic methods have been developed for the quantitative determination of metoclopramide hydrochloride (MCP) in both pure and dosage forms. The spectrophotometric method is based on diazotization of (MCP) and then coupling with 2,4-dihydroxyacetophenone in alkaline medium. The resulting azodye exhibits maximum absorption at 450 nm with a molar absorptivity of 2.48 X 10^4 $l.mol^{-1}.cm^{-1}$. Beer's law is obeyed over the range 10-300µg/25 ml, i.e., 0.4-12 ppm with a relative standard deviation (RSD)of better than±1.092% and relative error better than -1.1%.

HPLC method has been developed for the measurement of (MCP), the analysis was achieved on a C_8 column using acetonitrile, water, and methanol in the ratio of 40:50:10 (V:V:V) (in the presence of 1% of sodium acetate) as a mobile phase by isocratic elution at 1 ml/min. flow rate, and detection was done spectrophotometrically at 308 nm. A linear relationship is obeyed over the range 0.18-0.8 ppm with a relative standard deviation (RSD) of better than ±3.7% and relative error better than -1.6%.

Both methods were applied successfully to the assay of (MCP) in pharmaceutical preparations in the form of syrup, injection, and tablet.

Keywords: Metoclopramide, spectrophotometry, diazometry, HPLC, dosage form.

تقدير هيدروكلوريد الميتوكلوبراميد بالطريقة الطيفية و كروماتوكرافيا السائل عالي الأداء-تطبيقات في مستحضرات صيدلانية

الملخص

تم تقدير الميتوكلوبراميد في مستحضراته الصيدلانية باستخدام طريقتين مختلفتين إذ اعتمدت الأولى على ازوتة (MCP) ثم إقرانه مع 4,2- ثنائي هيدروكسي اسيتوفينون في محيط قاعدي لتكوين ناتج ملون يقاس طيفيا عند طول موجي 450 نانومتر بامتصاصية مولارية 2.48 X 10^4 لتر .مول$^{-1}$.سم$^{-1}$. تتبع

الطريقة قانون بيير لحدود تقديرية 10-300مايكروغرام لكل 25 مل (0.4-12)جزء لكل مليون وكان الانحراف القياسي النسبي أحسن من 1. 092 %والخطأ النسبي أفضل من -1.1%.

في حين تتضمن الطريقة الثانية حقن الميتوكلوبرامايد إلى عمود HPLC نوع C_8 باستخدام اسيتونتريل-ماء-ميثانول بنسب 40:50:10 (V:V:V) بوصفه طوراً متحركاً والمحتوي على 1% من خلات الصوديوم وأزيح النموذج بطريقة ايزوكراتية بمعدل سرعة جريان مللتر للدقيقة الواحدة ثم الكشف عن النموذج بطريقة طيفية عند طول موجي 308 نانومتر. تتبع الطريقة حدود تقديرية من0.8 الى 0.18 جزء لكل مليون. كان الانحراف القياسي النسبي أفضل من 3.7+ % والخطأ النسبي أفضل من 1.6-%.

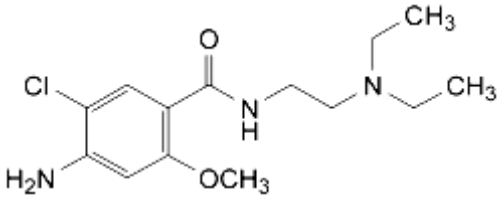
تم تطبيق الطريقتين بنجاح لتقدير الميتوكلوبرامايد في مستحضراته الصيدلانية بشكل شراب وحقن وأقراص.

الكلمات الدالة: ميتوكلوبرامايد، الطرق الطيفية، مبدأ الدايازونيوم، تقنية كروماتوغرافيا السائل عالي الأداء، تطبيقات على مستحضرات صيدلانية.

INTRODUCTION

Metoclopramide (MCP) is a white or almost white, odorless, crystalline powder (m.p. about 185°C) very soluble in water, alcohol freely, partially insoluble in ether. (British Pharmacopoeia, 2008).

Chemically (MCP) is: 4-amino-5-chloro-N-(2-diethylaminoethyl)-2-methoxybenzamide monohydrochloride monohydrate (Sweetman *et al.*, 2005).



$HCl.H_2O$

- **$C_{14}H_{22}ClN_3O_2.HCl.H_2O$ MW= 354.3g.mol^{-1}**

(MCP) has got central antidopaminergic effect (Clarke, 2005) and is used mainly as antiemetic and antinauseant (Roth, 2007). Its metabolic enzymology and drug interactions are poorly understood (Desta, 2002). Various spectrophotometric methods for the determination of metoclopramide have been reported among these, the spectrophotometric determination of (MCP) by coupling of (MCP) with the oxidized promethazine in acetic acid medium to form a blue product with maximum absorption at 596 nm (Ahmad and Ali, 2006).

Aslo, visible spectrophotometric method for the estimation of metoclopramide has been developed by the reaction of (MCP) with 4-dimethylaminobenzaldehyde (Ehrlich reagent) to produce a yellow dye with maximum absorption at 438 nm (Patel *et al.*, 2006).

Interaction between (MCP) and 2,4-dinitro-1-flourobenzene reagent is used for the

assay of (MCP) in alkaline media (Al-Sabha and Al-Hamody, 2006). Other spectrophotometric methods based on diazonium reaction have been reported (Mahmood *et al.,* 2007), (Al-Abbasi, 1999), (Omran, 2005).

Metoclopramide has been also determined by the reaction of (MCP) with chloranil (Mahmood, 2000), DDQ (Al-Ghabsha *et al.,* 2004), and flouranil (Al-Ghabsha *et al.,* 2004) based on charge –transfer principle.

High performance liquid chromatography (HPLC) is one of the most powerful and versatile tool for the quantitative determination of many individual components in mixture in one single procedure. It has wide application in drug analysis field (El-Bagary, 2008).

Metoclopramide has been determined using HPLC after extraction step with chloroform and concentrated aqueous NH_3 solution, 2-propylaminoethyl analogue of (MCP) has been used as internal standard, 25 µl of the sample was submitted to a column (15 cm x 0.5 mm) packed with silica gel N 131 and operated at ambient temperature with methanol chloroform and NH_3 solution (60:140:1) as a mobile phase with 2 ml/min as a flow rate and uv detection at 280 nm. The mean recovery 93.3% and RSD 5.9% , the method has been applied to determination of MCP in human urine after separation by T.L.C. conjugated by six solvent systems for extraction (Robins, 1977).

A simple reliable high HPLC technique for the measurements of (MCP) in serum has been developed, the method has been used for monitoring high dose (MCP) therapy in individual patients with neoplastic disease (Bryson *et al*., 2008).

Acetonitrile, tetramethylammonium hydroxide in methanol (1 in 5) in the presence of sodium acetate has been used as a mobile phase (after adjustment of pH to 6.5 using glacial acetic acid) for elution of (MCP) through a 4.6 mm x 25 cm column packing L1,and detecting at 215 nm (Parkway and Ville, 1995).

The aim of this work is to suggest a method for determination of metoclopramide and make a comparison with the major recent method.

EXPERIMENTAL

Apparatus

A Shimadzu 160A uv-visible recording spectrophotometer with quartz 1-cm cells have been used for spectrophotometric measurements. pH measurements have been done by Philips PW 9420 pH-meter. Sartorius –BL-2105 balance has been used for weight measurements.

A Shimadzu LC-2010 HPLC system with C_8 stainless steel column (25 cm x 4.6 mm) was used in the analysis. Pump pressure 4.5-5.1 MPa and 20 µL is auto injected.

Cary, uv-visible spectrophotometer VARIAN double-beam has been used for prediction of the maximum band of MCP with quartz cell of 1-cm thickness.

The column was conditioned by flushing firstly with acetonitrile for 15 min at 1 ml/min., then with the mobile phase for 15 min. at 1ml/min., also. The peak area of metoclopramide chromatogram was followed and plotted against concentration of the pure metoclopramide for standard curve.

Reagents

All chemicals used were of analytical grade.

Chemicals for HPLC were of analytical HPLC grades, metoclopramide standard powder material was provided from the state company for drug industries and medical

appliances (SDI), Sammara -Iraq.
Acetonitrile (HPLC grade)
Methanol (HPLC grade)
Water used was distilled and filtered

Procedure and calibration graph

Spectrophotometric method:

To increasing volumes (0.1-3) ml of 100µg.ml^{-1} of standard MCP solution ,the following reagents has been added in the following order: 2ml. of HCl (1N),1ml of (1%) $NaNO_2$, 0.3ml. (3%) sulphamic acid, 3 ml. of (1%) of 2,4-dihydroxyacetophenone, and 4 ml of Na_2CO_3(2N) has been finally added, the volume completed to25 ml. in a volumetric flask with distilled water, the absorbance has been measured at 450 nm against blank.

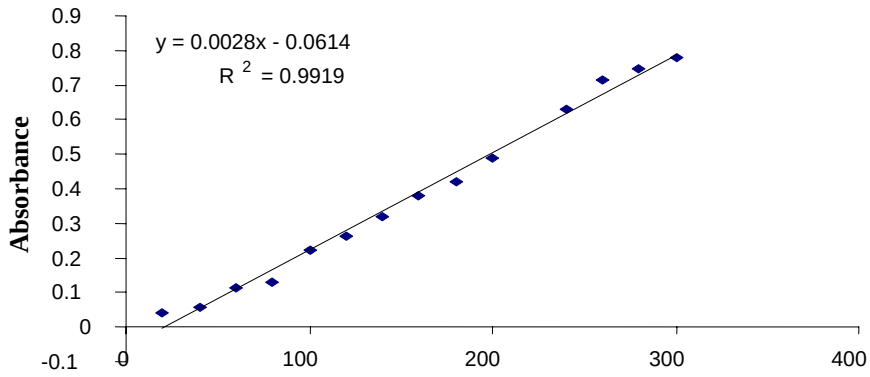


Fig. 1: calibration graph of spectrophotometric method

A linear calibration graph is obtained over the range 10-300 µg of MCP in 25 ml (0.4-12ppm) with a molar absorptivity 2.48x10^4 l.mol.$^{-1}$cm.$^{-1}$and Sandell sensitivity index 0.0142 µg.cm^2.

HPLC method

MCP standard solutions prepared in the concentration between 0.18-0.8 µg/ml in mobile phase. The mobile phase consists of acetonitrile: water: methanol (40:50:10)(v:v:v) isocratically eluted.

Twenty µl of each standard solution was injected to C_8 column at 1ml/min, the peak area of MCP was plotted as a function of MCP concentration at ambient temperature. The peak of metoclopramide was followed at 6.2 min.

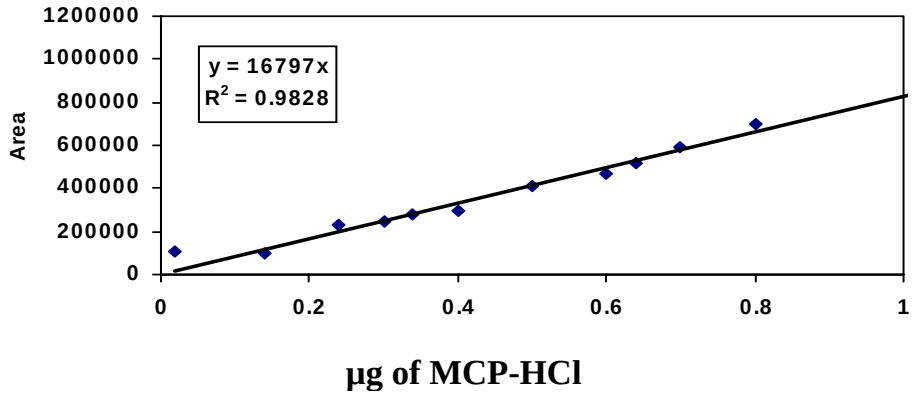


Fig. 2: Calibration graph of HPLC method

A linear calibration graph is obtained between the area under the curve and concentration over the range 0.18-0.8 ppm of MCP**.**

RESULTS AND DISCUSSION

Optimisation of Reaction

Spectrophotometric Method

Selection of coupling agent

Effect of different coupling agents on the absorption intensity and color contrast has been investigated for better analytical results. The reagents tested are: 2,6-dihydroxy-benzoic acid, tyrosine, phenylphrine, histidine, 2,4-dihydroxyacetophenone, 4-thylcatechol, and methylacetoacetate. Only 2,6-dihydroxybenzoic acid, phenylphrine, and 2,4 - dihydroxyacetophenone give useful results. 2,4 - dihydroxy acetophenone gives the maximum absorption intensity with a good color contrast ($\Delta\lambda$ =147nm.), therefore it is selected for subsequent investigations.

Selection of acid and its amount

Effect of different amounts (0.5,1, 1.5, 2,and 3 ml of 1N) of many acids (HCl, HNO_3, H_2SO_4, CH_3COOH) on absorption intensity has been studied. The results in Table1 indicate that 2 ml of HCl gives the maximum absorption intensity of the colored product which is used for the following experiments.

Table 1: Selection of acid and its amount**.**

Acid solution used (1N)	**Absorbance / ml acid used**				
	0.5	1	1.5	2	3
HCl	0.245	0.249	0.255	0.262	0.066
HNO_3	0.250	0.245	0.260	0.261	0.090
H_2SO_4	0.225	0.222	0.215	0.246	0.038
CH_3COOH	0.242	0.227	0.252	0.236	0.223

Effect of nitrite amount with time

Different amount (0.25,0.5,1,2,and 3 ml) of 1% $NaNO_2$ at different period of time (0,1,2,4, and 5 min) have been added, and the absorbance of the solution has been followed. 1ml of 1% $NaNO_2$ has been selected with one minute as a reaction time.

Effect of sulphamic acid amount with time

Between 0-0.4 ml of 3% sulphamic acid solution was added, and absorbance of the solutions was measured at different standing times (0,1,2,4, and 5 min). 0.3 ml of 3% sulphamic acid solution was selected with standing time two minutes.

Effect of coupling agent amount

Effect of (2-4) ml of 1% coupling agent has been studied against 20-140 µg of MCP and the determination coefficient of measured absorbencies has been evaluated. Table (2) shows that 3ml of 1% of the coupling agent solution gives the best results.

Table 2: Effect of coupling agent amount .

ml of 2,4-Dihydroxy acetophenone (1%) solution	**Absorbance / µg of MCP-HCl**						**r^2 (n=6)**
	20	40	80	100	120	140	
2	0.051	0.069	0.150	0.202	0.214	0.306	0.963660
3	0.087	0.145	0.220	0.259	0.320	0.359	0.994950
4	0.051	0.082	0.168	0.247	0.290	0.324	0.988220

Selection of base and its amount:

Four types of bases or basic salts at different volumes (1-5)ml of each have been tested for their effect on the absorption intensity of the dye formed. The results are listed in Table (3).

Table 3: Selection of base and its amount.

ml of base used						
Base used(2N)	**Variable**	**1**	**2**	**3**	**4**	**5**
NaOH	A	0.079	0.207	0.236	0.248	0.234
	Δλ*	84	148	146	128	133
	pH	1.57	11.99	12.79	12.95	12.96
KOH	A	0.100	0.251	0.244	0.245	0.216
	Δλ	128	128	145	130	125
	pH	1.55	3.38	12.70	12.91	12.97
Na_2CO_3	A	0.145	0.276	0.300	0.304	0.300
	Δλ	132	141	142	140	139
	pH	5.96	8.59	9.71	10.03	10.11
$NaHCO_3$	A	0.103	0.118	0.225	0.176	0.198
	Δλ	77	132	132	132	130
	pH	1.65	5.68	6.25	6.80	6.68

*$\Delta\lambda = \lambda^{S}_{max} - \lambda^{B}_{max}$,
Where S=The dye, B=Blank

From Table (3), 4 ml of sodium carbonate (2N) has been selected.

Effect of Surfactants:

In order to study the effect of surfactants on absorption intensity, 3ml of anionic sodium dodecyl sulphate (SDS)] ,cationic [cetylpyridinium chloride (CPC)], and neutral [iso-Octylphenoxy-poly ethoxy ethanol (Triton X-100)] were used.

Surfactants with different order of additions (I. Metoclopramide hydochloride (MCP) + Surfactant (S) + HCl (H) + $NaNO_2$ (N) + Sulphamic acid (F) +2, 4-Dihydroxyaceto phenone (R) +Soduim carbonate (B) II. MCP + H + S + N + F + R+B , III. MCP + H + N + S + F + R+B , IV. MCP + H + N + F + S + R+B, V. MCP + H + N + F + R + S+B , and VI. MCP + H + N + F + R + B + S) were followed. The addition of CPC in order IV and V produces turbid solutions and the addition of SDS decreases the absorption intensity while the addition of Triton X-100 does not exhibit any change on absorption intensity , therefore the use of surfactant was excluded.

Stability of Reaction :

The stability of the colored product against time has been followed using 50 and 100 $\mu g.ml^{-1}$.

Table 4: stability of the colored product.

Times, minutes	**Absorbance/ µg of metoclopramide-HCl**	
	50	**100**
0	0.130	0.286
5	0.130	0.286
10	0.132	0.289
15	0.131	0.290
20	0.134	0.288
25	0.136	0.286
30	0.138	0.286
35	0.137	0.284
40	0.137	0.285
45	0.138	0.285
50	0.140	0.285
55	0.140	0.285
60	0.141	0.285

Table (4) indicate that the colored product is stable for at least one hour.

Absorption Spectrum

Under the optimum reaction conditions studied as above, the absorption spectrum of the colored product against blank (Fig. 1) shows that wavelength of maximum absorption intensity is 450 nm. This wavelength has been used in subsequent investigations.

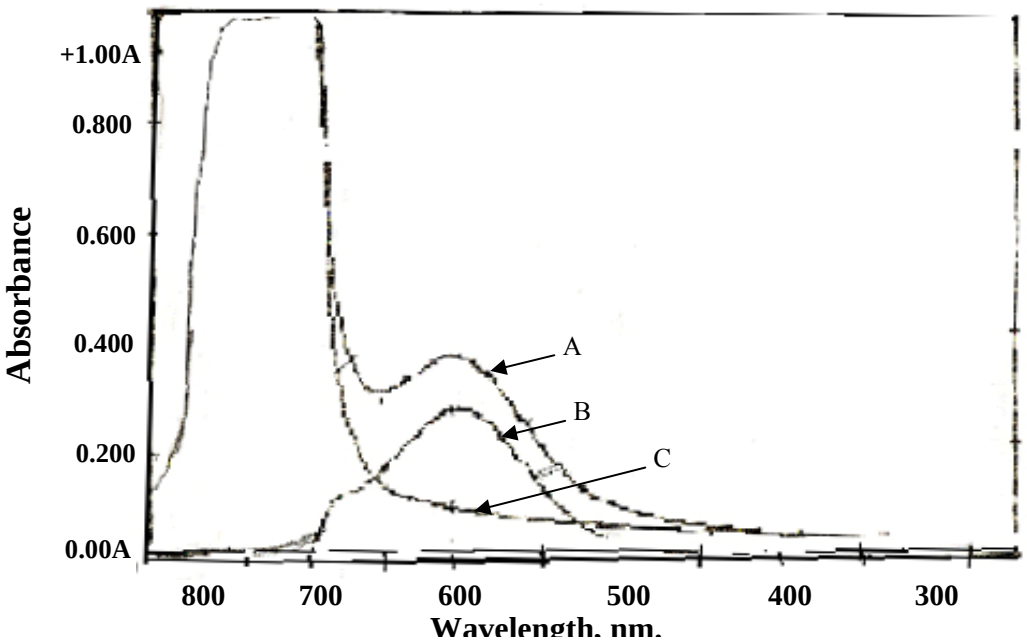


Fig. 3: Absorption spectum of spectrophotometric method.

A: sample against distilled water.
B: sample against blank.
C: Blank against distilled water**.**

Accuracy and Precision:

To check the accuracy and precision of the calibration graph, metoclopramide is determined at three different concentrations and the results are shown in Table(5),which indicate good accuracy and precision.

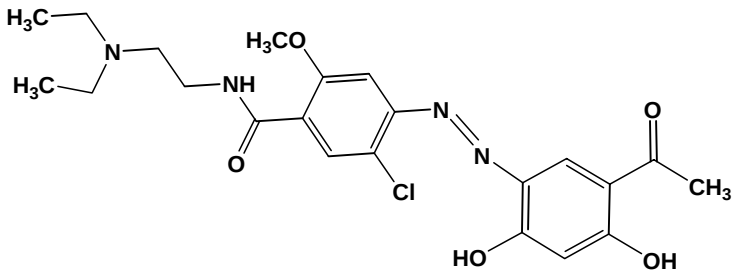
Table 5: Accuracy and Precision.

Amount of metoclopramide-HCl taken µg/25ml	Relative error, %*	Relative standard deviation, %*
50	-1.1	±1.092
120	-0.32	±0.638
240	-0.32	±0.250

* Average of five determinations.

Nature of the Dye:

The composition of the intense yellow azo dye has been established using Job's method and mole –ratio methods. The results show that both methods confirm the presence of 1:1 azo dye of probably the following structure:



The conditional stability constant of the formed azo dye in aqueous solution is estimated and found to be 2.8x 10^5 .

Effect of Organic Solvents:

The spectrophotometric characteristics of the colored product are more detectable using ethanol and water ; water is still being the choice.

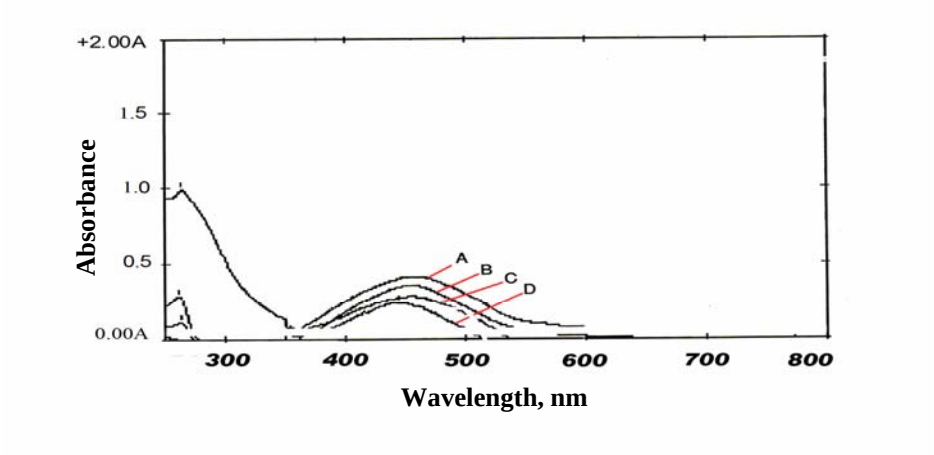


Fig. 4:effect of organic solvent.
A: water B: ethanol C: propanol D: formic acid

Study of Interferences:

In order to realize the analytical application of this method, effect of some excipients has been studied by carrying out the determination of 100 µg of MCP in the presence of 100, 500 and 1000 µg of foreign compound using the recommended procedure. The results are shown in Table (6).

Table 6: Effect of interferences.

Foreign compound	Recovery (%) of 100 µg MCP-HCl /µg foreign compound added		
	100	500	1000
Glucose	104.7	104.4	102.2
Gum Arabic	106.3	102.7	100.9
Lactose	103.3	103.1	103.3
Starch	104.6	103.1	102.5

Application of the Method

To test the applicability of the present method , it has been applied to the determination of MCP in pharmaceutical preparations. The results are listed in Table (7) indicating a good applicability of the method.

Table 7: Application of the method.

Pharmaceutical preparation	µg metoclopramide-HCl present/25ml	µg metoclopramide-HCl measured/25ml	Recovery, * %
Metoclopramide-HCl/Tablet (10mg), Alpharma, UK, England	50	49.36	98.72
	100	96.88	96.88
	150	148.16	98.77
	200	200.74	100.37
Metoclopramide-HCl Injection (10mg/2ml), Ltd. Sult. Jordan	50	51.16	102.32
	100	102.38	102.38
	150	153.31	102.2
	200	205.38	102.69
Metoclopramide-HCl/Syrup (5mg/5ml) SDI-Iraq	50	51.93	103.87
	100	102.38	102.38
	150	152.48	101.6
	200	190.89	95.44

Comparison of the Methods:

Table (8) shows the comparison between some of analytical variables obtained from the present method with that of the recent spectrophotometric method.

Table 8: Comparison of the methods.

Analytical parameters	**Present method**	**Literature method (Mahmood *et al.*, 2007)**
pH	10.03	Alkaline
Temperature (°C)	Room temperature	Room temperature
λ_{max} (nm)	450	549
Medium of reaction	Aqueous	Aqueous
Reagent	2,4- Dihydroxy-acetophenone	α-Naphthol
Beer's law range (ppm)	0.4-12	0.5-8
Molar absorptivity ($l.mol^{-1}.cm^{-1}$)	2.48×10^4	3.85×10^4
RSD (%)	≤±1.092	≤±2.17
Stability of the colour (minute)	60	60
Colour of the product	Orange	Violet
K ($Molar^{-1}$)	2.8×10^5	9×10^4
Nature of the dye	1:1	1:1
Application of the method	Has been applied to the assay of metoclopramide hydrochloride in pharmaceutical preparations (tablets, injection and syrup)	Has been applied to the assay of metoclopramide hydrochloride in pharmaceutical preparations (syrup,mouth drop and injection)

t-test:

Both the present method and the literature method (Mahmood *et al.*, 2007)has been applied at the same time to t-test calculation and the value compared with the statistical tables for eight degrees of freedom at 95% validation level. The results in Table (9) show that there is no a real difference between the two methods.

Table 9: The results of t-test analysis.

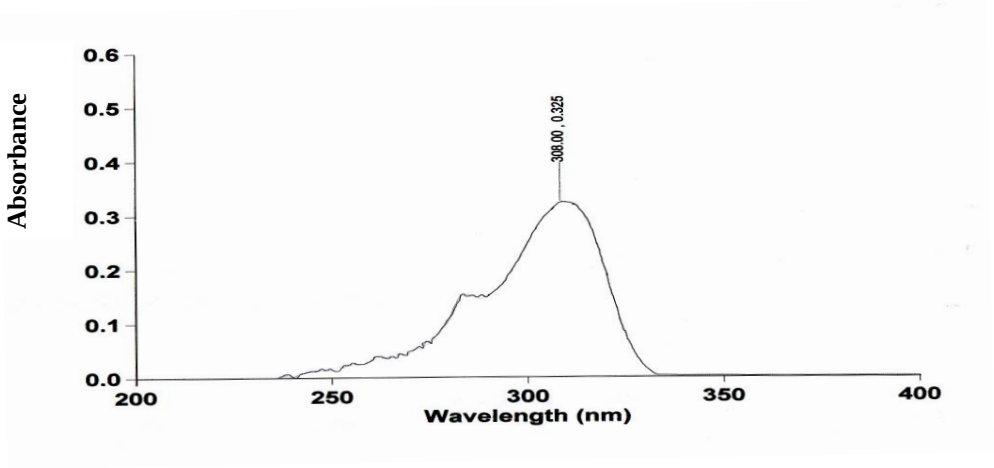
Drug	**Pharmaceutical preparation**	***Recovery*%**		**t. exp**
		Present method	**Literature method (Mahmood *et al.*, 2007)**	
Metoclopramide-HCl/Tablet(10mg), Alpharma, UK,England	Tablet	97.78	100.4	0.235
Metoclopramide-HCl/Syrup (5mg/5ml) SDI-Iraq	Syrup	105.18	99.8	0.562
Metoclopramide-HCl Injection (10mg/2ml), Ltd. Sult. Jordan	Injection	103.6	100.2	0.388

* Average of five determinations

-HPLC method

Selection of wave length:

The absorption spectrum of 100 μ g.ml^{-1} of MCP prepared in 50:50 (v:v) acetonitrile: water has been taken. Fig.(5) shows that the maximum absorbance of MCP is 308 nm. Therefore, 308nm has been used for uv-detection.



Wavelength, nm

Fig. 5: Selection of wavelength.

Selection of mobile phase:

Effect of different polar solvents with different compositions (used as a mobile phase) on the shape of chromatogram has been studied. The retention time and retention factor have been followed (Table 10).

Table 10: Selection of the mobile phase**.**

Mobile phase composition	**Retention time, min**	**Capacity factor (K)**
Acetonitrile-water (50:50)	6.92	2.317
Acetonitrile -Water-Ethanol (40:50:10)	6.99	1.766
Acetonitrile-Water-Methanol) (40:50:10)	6.17	1.538
Acetonitrile-Water-Methanol* (30:50:20)	6.40	0.750
* Does not give clear chromatogram		

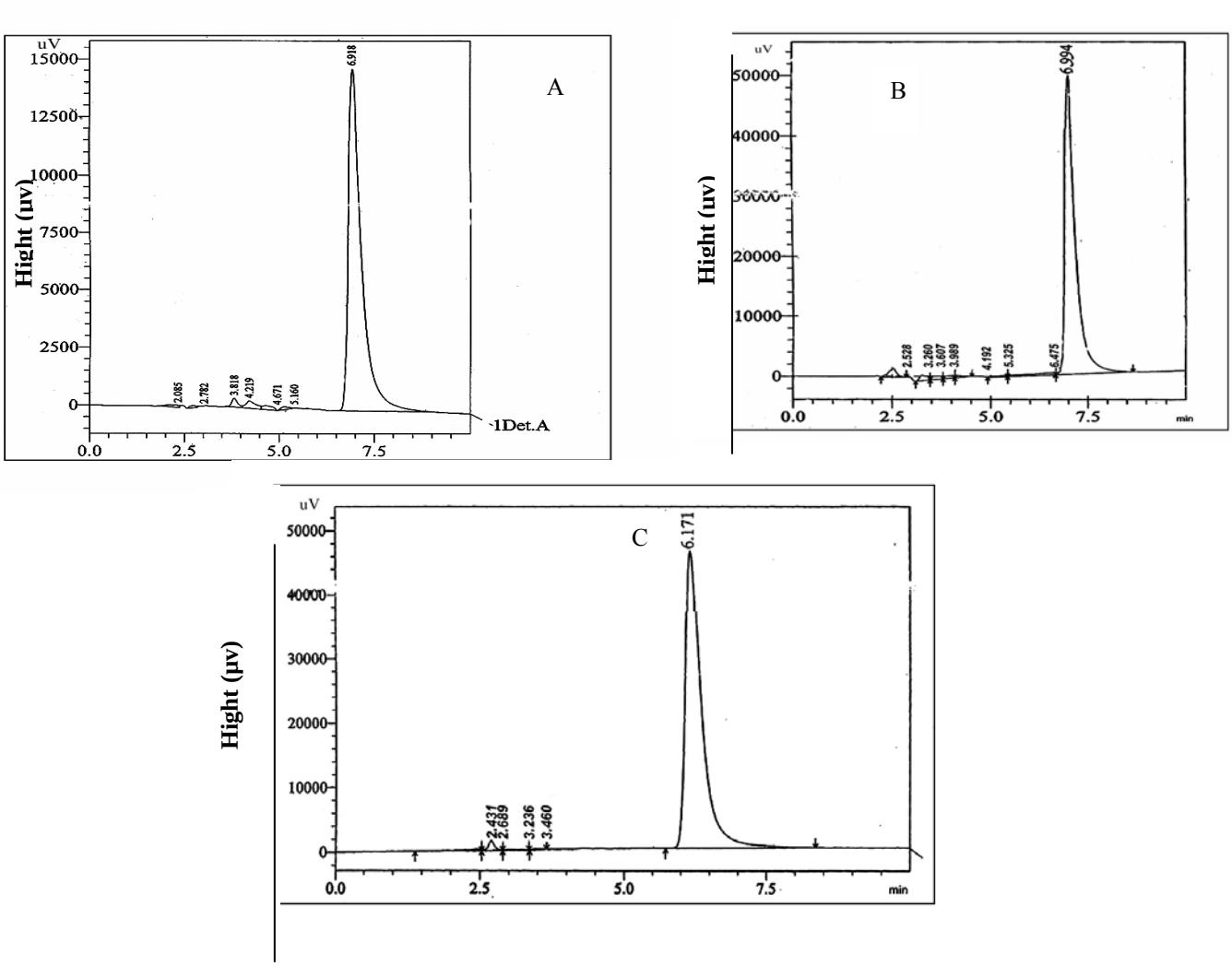


Fig. 6: selection of mobile phase**.**
A: Acetonitrile-Water (50:50)
B: Acetonitrile -Water- Ethanol (40:50:10)
C: Acetonitrile-Water-Methanol (40:50:10)

Fig. 6 Shows that case C is more useful because the resolution is better and is associated with higher sensitivity. Therefore, conditions reported in Fig.6C is recommended.

Selection of Flow Rate:

Effect of (0.8- 2) ml min^{-1} as a flow rate has been studied, 1ml.$min.^{-1}$gives the optimum capacity factor (Table 11)with clear chromatogram and good sharpness (Fig.7)

Table 11**:** Selection of flow rate.

No.	Flow rate (ml/min)	Retention time (min)	Capacity factor (K)
I	0.8	8.5	0.56
II	1.0	6.17	1.53
III	1.2	4.1	1.12
IV	1.5	3.3	1.0
V	1.8	2.7	1.12
VI	2.0	2.2	1.12

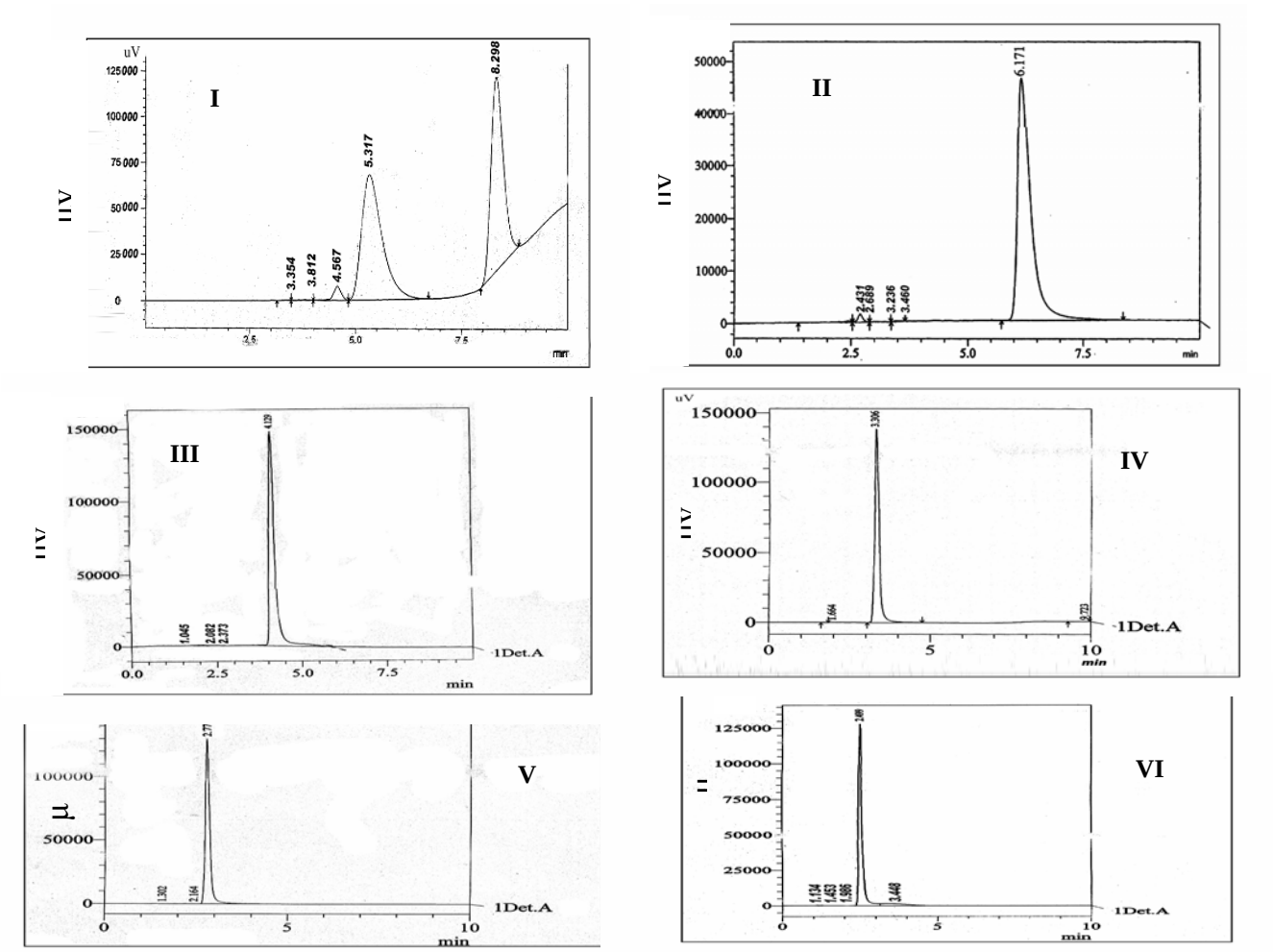


Fig. 7: selection of flow rate.

Selection of Analysis Medium:

Effect of the nature of medium has been studied by the use of sodium acetate once and ammonium acetate in other, the later acetate gives unclear chromatogram, therefore effect of the presence of 0.5-2% of sodium acetate with the mobile phase on retention factor, and retention time has been studied .The results are listed in Table (12).

Table 12**:** Selection of analysis medium.

No.	Sodium acetate solution (%)	Retention Time (min)	Capacity factor (K)
I	0.5	6.63	1.33
II	1	6.17	1.52
III	1.5	5.33	1.31
IV	2	4.93	1.11

From Table (12) the, retention factor of all percent of sodium acetate are within the ideal range. 0.5 and 1% give well defined chromatogram with good resolution from other peaks, therefore 1% has been selected.

Effect of Temperature:

Effect of 20, R.T., 35, and 45^0 C on the chromatogram , capacity factor and on retention time has been studied. Table (13)shows that the capacity factor at all temperatures are ideal. Room temperature has been selected for the following experiments.

Table 13 : Effect of temperature.

Temperature (ºc)	Retention time (min)	Capacity factor (K)
20	8.00	1.23
28*	6.22	1.52
35	5.01	1.15
45	4.94	1.12

* Room temperature

Accuracy and Precision:

To check the accuracy and precision of the calibration graph, metoclopramide is determined at three different concentrations and the results are shown in Table (14), which indicate good accuracy and precision**.**

Table 14: Accuracy and precision.

Amount of MCP µg , taken	Relative error, %*	Relative standard deviation, %*
25	-1.09	1.54
35	-0.012	±0.29
40	-1.6	±3.78

*Average of five determinations

t-test:

Both the present method and the literature method (Mahmood *et al*., 2007) has been verified at the same time for t-test calculation and compared with the value of the statistical tables for eight degrees of freedom at 95% validation level. The results in Table (15) show that there is no real difference between the two methods.

Table 15 : The results of t-test analysis.

Drug	Recovery%*		t-exp
	Present method	literature method (Mahmood *et al*., 2007)	
Metoclopramide-HCl/ Syrup (5mg/5ml) SDI-Iraq	97.38	99.84	0.77
Metoclopramide-HCl Injection (10mg/2ml), Ltd. Sult. Jordan	97.92	100.4	o.64
Metoclopramide-HCl/Tablet (10mg), UK, Alpharma, Barnstaple England	97.54	100.2	0.76

*****Average of five determinations

CONCLUSION

The suggested methods for the determination of MCP are sensitive, pH, and temperature independent, applicable with out resorting to an extraction step.

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