

Spectrophotometric Determination of Metoclopramide Hydrochloride in Pharmaceutical Preparations by Charge Transfer Reaction with Metol

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Abstract

A simple, rapid and sensitive spectrophotometric method was developed for the determination of metoclopramide hydrochloride (MPH) in pharmaceutical preparations. The method was based on the charge transfer reaction of MPH with metol in the presence of ferric sulfate to form red water soluble product with maximum absorbance at 505 nm. The reaction conditions were studied and optimized. The linear range for the determination of MPH, and the detection limit were $2 - 50 \mu\text{g mL}^{-1}$ and $0.635 \mu\text{g mL}^{-1}$, respectively. The effect of the substrates commonly employed as excipients with MPH have been studied. The proposed method has been applied successfully for the determination of MPH in pharmaceutical preparations. A statistical comparison of these results with those obtained by the British pharmacopoeia procedure using the Student t-test and variance ratio F-test shows a good agreement and indicates no significant difference in accuracy and precision at the 95% confidence.

Keywords: Metoclopramide hydrochloride; Spectrophotometric; Metol; Pharmaceutical preparations.

Introduction

Metoclopramide hydrochloride (MPH) is benzamide, 4-amino - 5 - chloro - N - [2 - (diethylamino) ethyl] - 2 - methoxy-, monohydrochloride, monohydrate, $\text{C}_{14}\text{H}_{22}\text{ClN}_3\text{O}_2 \cdot \text{HCl} \cdot \text{H}_2\text{O}^{[1]}$. It is used as anti-emetic in the treatment of some forms of nausea and vomiting and to increase gastrointestinal motility. It is of little benefit in the prevention or treatment of motion sickness or in the treatment of nausea and vertigo due to Meniere disease or other labyrinth disturbance^[2].

Various analytical methods have been reported for analysis of MPH in pharmaceutical preparations, most of them are based on biamprometric titration^[3], amperometric

titration^[4], potentiometric titration^[4], ion-selective electrode potentiometric^[5], voltammetric^[6], liquid chromatography-tandem mass spectrometric^[7], reverse phase-high performance liquid chromatographic^[8-11], spectrofluorimetric^[12,13], flow injection-chemiluminescence^[14, 15], flameless-atomic absorption spectrophotometric^[16], spectrophotometric^[3], flow injection spectrophotometric^[17] and stopped-flow and continuous-flow sequential injection spectrophotometric^[18].

Many colorimetric methods for determination of MPH in pharmaceutical preparations are described in Table (1)

Table (1): Colorimetric methods for determination of metoclopramide hydrochloride in pharmaceutical preparations

Reagents	Colored species	$\lambda_{\text{max.}}$, nm	Linear range, $\mu\text{g mL}^{-1}$	Ref.
Citric acid – acetic anhydride in non-aqueous medium	Ion-pair complex	600	$(2 - 14) 10^3$	19
N-(1-naphthyl)ethylenediamine dihydrochloride	Diazotization and coupling	525	0.4 – 11	20
Terbutaline sulfate	Diazotization	440	0.5 – 10	21
1-naphthylamine	and coupling	510	0.1 – 11	
Thymol and NaOH	Diazotization and coupling	495	1 – 11	22
Resorcinol	Diazotization and coupling	415	1 – 6	23
2-Aminophenol and KIO_3 at pH 1.7 ± 0.3	Oxidative coupling	520	----	24
Na_2HPO_4 – citric acid buffer of pH 5.6, bromothymol blue and CHCl_3 for extraction	Ion-pair complex	----	1 – 10	25
4-Dimethylaminocinnaldehyde and methanol for dilution	Schiff base	548	5 – 30	26
Dibenzoyl methane and NaOH in methanol for dilution	Diazotization and coupling	440	1 – 12	27
Phenothiazine and $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$	Oxidative coupling	600	2 – 40	28

The British Pharmacopoeia (BP) method^[29] was based on the extraction of the MPH from the alkaline aqueous solution by CHCl_3 ; the aliquots from the organic layer were spectrophotometrically tested at 305 nm.

This search describes the development of simple and rapid spectrophotometric method for the quantitative determination of MPH in pharmaceutical preparations. The proposed method was based on charge transfer

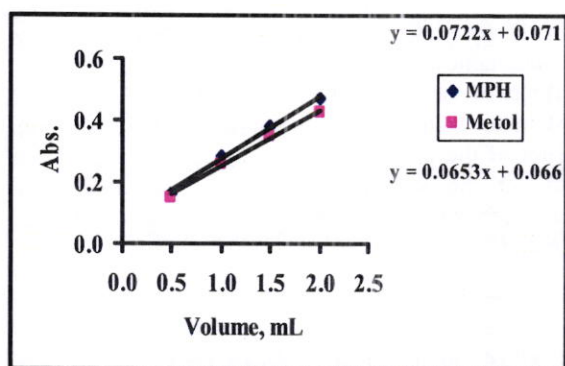


Fig. (5): slope ratio plot

The red charge transfer complex may be presumed to arise by electron transfer from the highest π molecular orbital of MPH to the lowest empty orbital (π^*) of two adjacent p-N-methylbenzoquinoneimine molecules (formed in situ on treating metol with ferric sulfate). The two p-N-methyl-benzoquinoneimine molecules are being probably brought closer by primary arylamine through hydrogen bonding thus facilitating the simultaneous overlap of the π molecular orbital of MPH with the π^* orbitals of the two p-N-methylbenzoquinoneimine molecules^[30], as shown in Fig. (6).

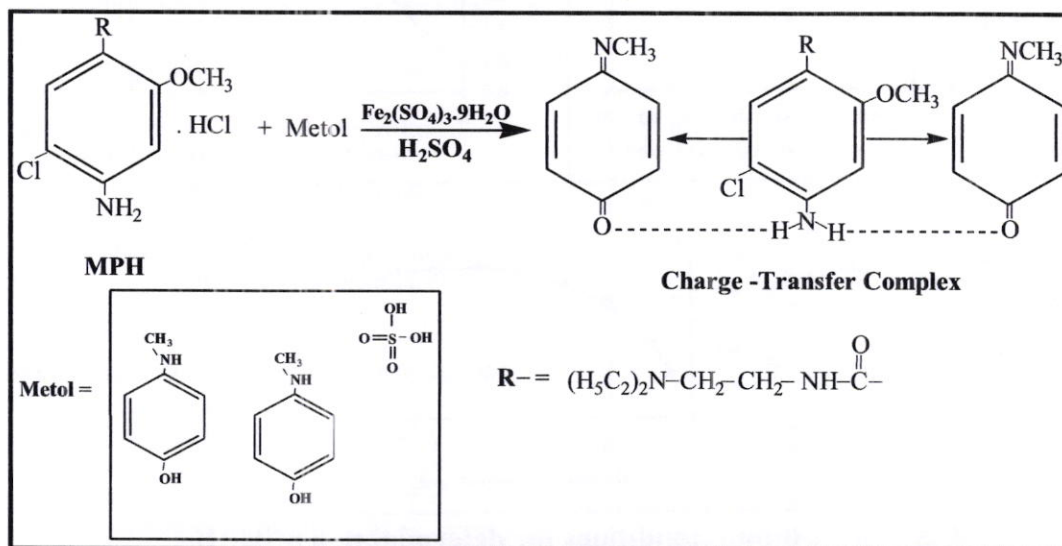


Fig. (6): Reaction scheme

Stability constant of the product

The product formed was soluble in water. The apparent stability constant was calculated by comparing the absorbance of a solution containing stoichiometric amount of MPH and metol (concentration of both MPH and metol are 2.822 mM) that of a solution containing a five-fold excess of pyrocatechol reagent. The stability constant of the product in water under the described experimental conditions was $1.88 \times 10^4 \text{ L mol}^{-1}$.

Optical characteristics

Employing the conditions described under the analytical procedure, a calibration graph for MPH was studied. The linearity of calibration graph, molar absorptivity, Sandell's sensitivity, limit of detection, and limit of quantitative are summarized in Table (2). The slope, the intercept, the standard deviations for residuals, slope and intercept and the correlation coefficient were evaluated by a least-squares regression analysis^[31], and are also included in the same Table. The obtained correlation coefficient value is highly significant.

Table (2): Analytical values of statistical treatments for the calibration graph

Parameter	Value
Correlation coefficient, r	0.9999
Regression equation $y = b x + a$; y = absorbance, x = concentration ($\mu\text{g mL}^{-1}$)	$y = 0.011486 x + 0.014010$
Standard deviation of the residuals, $S_{y/x}$	2.430513×10^{-3}
Standard deviation of the slope, S_b	5.424343×10^{-5}
Standard deviation of the intercept, S_a	1.524478×10^{-3}
Linearity range ($\mu\text{g mL}^{-1}$)	2 – 50
Molar absorptivity, ϵ ($\text{L mol}^{-1} \text{ cm}^{-1}$)	4.069536×10^3
Sandell's sensitivity, S ($\mu\text{g cm}^{-2}$) per 0.001 absorbance unit	0.0871
Limit of detection, LOD ($\mu\text{g mL}^{-1}$)	0.6348
Limit of quantification, LOQ ($\mu\text{g mL}^{-1}$)	2.116042

Accuracy and precision

The accuracy and precision of the determination of MPH was studied depending upon the value percentage of the relative error (E%), recovery (Rec.%), and relative standard deviation (RSD%), respectively. For five replicates of each concentration of MPH containing 10, 20, and 30 $\mu\text{g mL}^{-1}$. The results in Table (3) show a good accuracy and precision.

Table (3): Accuracy and precision of the proposed method

Concn., $\mu\text{g mL}^{-1}$		E%	Rec.%	RSD%
Present	Found			
10.000	9.992	-0.080	99.920	1.096
20.000	20.025	+0.125	100.125	0.743
30.000	30.075	+0.250	100.250	0.556

Effect of interferences

To evaluate the selectivity of the proposed method for the analysis of pharmaceutical preparations containing MPH, the interfering effect of excipients were examined by determining MPH in the presence of the interference applying the recommended procedure.

The excipients studied were: lactose, talc, starch, magnesium stearate, and PVP. For this study, solution

was containing MPH and each one of the excipients was taken separately in concentrations ten-times greater than that of MPH were analyzed. Under the reaction conditions used all of them do no interfere as shown in Table (4).

Table (4): Effect of excipients on the recovery of MPH ($40 \mu\text{g mL}^{-1}$)

Excipient ($400 \mu\text{g mL}^{-1}$)	Concn. of MPH, $\mu\text{g mL}^{-1}$ Found	E%*	Rec.%*
Lactose	39.780	-0.550	99.450
Talc	39.848	-0.380	99.620
Starch	39.797	-0.508	99.492
Mg stearate	39.814	-0.465	99.535
PVP	39.763	-0.593	99.407

• Average of five determinations.

Pharmaceutical applications

The proposed method was applied for the determination of MPH in three different types of tablets by the analysis of three different concentrations of each sample using the analytical procedure. The results obtained are summarized in Table (5).

Table (5): Application of the proposed method for determination of MPH in pharmaceutical preparations

Pharmaceutical preparation	Concn. of MPH, $\mu\text{g mL}^{-1}$		E%*	Rec.%*	RSD%*
	Present	Found			
Meclodin-5 Tablets	10.000	9.938	-0.620	99.380	1.395
	20.000	20.098	+0.490	99.443	0.892
	30.000	29.833	-0.557	99.443	0.559
Meclodin-10 Tablets	10.000	9.984	-0.160	99.840	1.276
	20.000	20.016	+0.080	99.777	0.797
	30.000	29.933	-0.223	99.777	0.604
Metoclopramide Tablets	10.000	9.907	-0.930	99.070	1.160
	20.000	20.049	+0.245	99.390	0.862
	30.000	29.817	-0.610	99.390	0.606

• Average of five determinations.

Evaluation of the proposed method

For evaluating the competence and the success of the proposed method, the results obtained were compared with those obtained by standard BP method^[29].

The same pharmaceutical preparations for MPH were analyzed by standard BP method. The results obtained by the two different methods (Table (6)) were statistically

compared, using the Student t-test and variance ratio F-test at 95% confidence level^[31]. In all cases, the calculated t- and F-values (Table (6)) did not exceed the theoretical values, which indicate that there is no significant difference between either methods in accuracy and precision in the determination of MPH in pharmaceutical preparations.

Table (6): The comparison of the proposed method with standard BP method using t- and F-statistical tests

Pharmaceutical preparation	Proposed method		BP method		s	Value t (theor.)	F (theor.)
	Rec.%* (x_1) ₁	($x_i - \bar{X}$) ₁ ²	Rec.%* (x_1) ₂	($x_i - \bar{X}$) ₂ ²			
MPH pure	100.000	0.0361	100.000	0.2970	0.346	1.451 (2.447)	5.881 (9.277)
Meclodin-5 Tablets	99.771	0.0015	98.900	0.3080			
Meclodin-10 Tablets	99.899	0.0079	99.400	0.0030			
Metoclopramide Tablets	99.568	0.0586	99.520	0.0042			
	$\bar{X}_1 =$ 99.810	$\Sigma =$ 0.1041	$\bar{X}_2 =$ 99.455	$\Sigma =$ 0.6122	(n ₁ + n ₂ - 2) = 6		(n ₁ - 1) = 3 (n ₂ - 1) = 3

* Average of five determinations.

Conclusions

The proposed method offers clear advantages for the fast determination of MPH in pharmaceutical preparations. The method was found to be simple, rapid, low cost, and fairly selective than some of the reported colorimetric methods (Table (1)). It has the advantage of being accurate, did not require the removal of excipients, any chemical sample pretreatment, temperature control, pH control, solvent extraction step, and expensive reagents and solvents.

Many analytical methods have been developed for the determination of MPH. The spectrofluorimetric method has a higher sensitivity, but solvent extraction is needed and the procedure is laborious. The colorimetric methods are chiefly based on the diazotization and coupling reactions, so that they are time-consuming. The chromatographic method needs a long time of extraction and expensive instrument, so that it is difficult to popularize. The BP method is prone to interfere from

References

1. C. A. Fleeger, "USAN and the USP Dictionary of Drug Names", (1992), United States Pharmacopeial Convention, Inc., USA, 407.
2. Martindale, "The Extra Pharmacopoeia", 46th Ed., (2000), The Pharmaceutical Press, London, 1200.
3. S. Groszkowski, Z. Ochocki and G. Krzemieniewska, *Farm. Pol.*: 40, (1984), 6, 341; through *Anal. Abstr.*, 47, (1985), 10E67.
4. A. A. Badwan, O. A. Jawan and L. Owais, *Int. J. Pharm.*: 28, (1986), 1, 41; through *Anal. Abstr.*, 48, (1986), 11E73.
5. A. A. Al-Sultani, "M. Sc. Thesis", Baghdad University, (2005), Baghdad, Iraq.
6. S. A. Ozkan, B. Uslu and Z. Senturk, *Electroanalysis*: 16, (2004), 3, 231.
7. M. E. Abdel-Hamid and D. Sharma, *J. Liq. Chromatogr. Relat. Technol.*: 27, (2004), 4, 641.
8. N. H. Foda, *Anal. Lett.*: 27 (1994), 3, 549.
9. T. G. Venkateshwaran, D. T. King and J. T. Stewart, *J. Liq. Chromatogr.*: 18 (1995), 1, 117.
10. W. V. Caufield and J. T. Stewart, *Chromatographia*: 51, (2000), 5-6, 308.
11. A. El-Gindy, *J. Pharm. Biomed. Anal.*: 32, (2003), 2, 277.
12. W. Baeyens and P. De Moerloose, *Analyst*: 103, (1978), 1225, 359.
13. M. Buna, J. J. Aaron, P. Prognon and G. Mahuzier, *Analyst*: 121, (1996), 11, 1551.
14. S. L. Fan, Z. H. Wu, L. Zhang and C. Lv, *Anal. Lett.*: 35, (2002), 9, 1479.
15. N. A. Al-Arfaj, *Talanta*: 62, (2004), 2, 255.
16. M. K. Park, B. R. Lim, K. S. Yu and K. H. Yong, *Yakhak Hoe Chi*: 22, (1978), 1, 27; through *Anal. Abstr.*: 38, (1980), 4E81.
17. M. R. Herrero, A. M. Romero and J. M. Calatayud, *Talanta*: 47, (1998), 1, 223.
18. J. Fan, A. Wang, S. Feng and J. Wang, *Talanta*: 66, (2005), 1, 236.
19. J. Emmanuel and T. V. Yegyanaranan, *Talanta*: 24, (1981), 285, 133; through *Anal. Abstr.*: 43, (1982), 3E82.
20. D. M. Shingbal and K. V. Sawant, *Indian Drugs*: 19, (1982), 6, 239; through *Anal. Abstr.*: 43, (1982), 3E83.
21. O. S. Kamalapurkar and S. R. S. Priolkar, *Indian Drugs*: 20, (1982), 3, 108; through *Anal. Abstr.*: 44, (1983), 6E40.
22. O. S. Kamalapurkar and J. J. Chudasama, *Indian Drugs*: 20 (1983), 7, 298; through *Anal. Abstr.*: 45, (1983), 4E80.
23. D. M. Shingbal and S. V. Joshi, *Indian Drugs*: 21, (1984), 11, 517; through *Anal. Abstr.*: 47, (1985), 10E69.
24. C. S. P. Sastry, P. L. Kumari and B. G. Rao, *Chem. Anal.*: 30, (1985), 3, 461; through *Anal. Abstr.*: 48, (1986), 4E63.
25. D. M. Shingbal and V. S. Velingkar, *Chem. Anal.*: 25, (1988), 12, 529; through *Anal. Abstr.*: 51, (1989), 1E56.
26. B. A. Moussa, *J. Pharm. Biomed. Anal.*: 23, (2000), 6, 1045.
27. H. D. Revanasiddappa, and B. Manju, *J. Pharm. Biomed. Anal.*: 25 (2001), 3-4, 631.
28. M. Q. Al-Abachi and H. S. Al-Ward, *National J. Chem.*: 7, (2002), 363.
29. "British Pharmacopoeia on CD-ROM", Version 5, 3rd Ed., Vol. 1, (2001), Copyright by System Simulation Ltd, The Stationery Office Ltd., London.
30. C. S. P. Sastry, B. G. Rao, B. S. Reddy and S. S. N. Murthy, *J. Indian Chem. Soc.*: 58 (1981), 7, 655.
31. J.N. Miller and J.C. Miller, "Statistics and Chemometrics for Analytical Chemistry", 4th Ed., (2000), Pearson Education Limited, London.

tablets excipients and requires pre-extraction of MPH with CHCl_3 .

The proposed method advantage over the standard BP method is more specific and less prone to interfere, which is normally encountered in single wavelength UV measurements.

Literature survey indicated that colorimetric determination of MPH by formation charge transfer complex has not been reported. Therefore, the proposed method is considered to be the first charge transfer reaction was used for the determination of MPH in pure and pharmaceutical preparations.

The wider linear range for the proposed method makes it suitable for sample analysis of different targets. The proposed method was applied to analysis of MPH in various tablets solutions, suggesting that they used as a reliable and advantageous alternative to the other previously reported methods for routine analysis of MPH in these samples.

التقدير الطيفي لهيدروكلوريد الميتوكلوبراميد في المستحضرات الصيدلانية بواسطة تفاعل انتقال الشحنة مع الميتول

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الملخص

يتضمن البحث تطوير طريقة طيفية بسيطة و سريعة وحساسة لتقدير هيدروكلوريد الميتوكلوبراميد في المستحضرات الصيدلانية. تعتمد الطريقة على تفاعل انتقال الشحنة لهيدروكلوريد الميتوكلوبراميد مع الميتول بوجود كبريتات الحديدك، إذ يتكون ناتج أحمر ذائب في الماء أظهر أقصى امتصاصية عند طول موجي 505 نانومتراً. تم دراسة و تثبيت ظروف التفاعل الفضلى. كان مدى الخطية لتقدير هيدروكلوريد الميتوكلوبراميد بين 2 – 50 مايكروغرام مل⁻¹ وبحد كشف 0.635 مايكروغرام مل⁻¹. تم دراسة تأثير المواد الشائع استعمالها كمضافات في المستحضرات الصيدلانية لهيدروكلوريد الميتوكلوبراميد. طبقت الطريقة بنجاح في تقدير هيدروكلوريد الميتوكلوبراميد في المستحضرات الصيدلانية، وتم مقارنة نتائجها إحصائياً باستعمال اختباري t و F مع نتائج طريقة دستور الأدوية البريطاني، و وجد أنه لا يوجد فرق معنوي في دقة و مصداقية الطريقة المقترحة مع طريقة دستور الأدوية البريطاني عند مستوى ثقة 95%.

الكلمات المفتاح: هيدروكلوريد الميتوكلوبراميد، التقدير الطيفي، ميتول، المستحضرات الصيدلانية