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SPECTROPHOTOMETRIC ESTIMATION OF METOCLOPRAMIDE HYDROCHLORIDE IN PHARMACEUTICAL PREPARATIONS

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ABSTRACT

Two spectrophotometric methods were developed for the quantitative determination of metoclopramide hydrochloride and its dosage forms. The first method (method I) is based upon the interaction of the drug with 3-methyl benzothiazolinone-2-hydrazone (MBTH) in the presence of ferric chloride as an oxidizing agent, where a violet colour is formed that measured at λ 555 nm in an aqueous media. The second method (method II) is based upon the interaction of the chloroformic extract of the drug free base, after alkalinization , with 1,3-dinitrobenzene (DNB), where a charge-transfer complex product is formed that measured at λ 381 nm in chloroform. The two proposed methods are accurate, sensitive, reproducible and applicable for the analysis of metoclopramide in the pure form and in its dosage forms (tablets and injections). The results obtained are compared with those of the titrimetric and UV measurement official B.P. 1998 method showing good agreement.

INTRODUCTION

Chemically , metoclopramide HCl is 4-amino-5-chloro-N-(2-diethyl-amino ethyl)-2-methoxybenzamide hydrochloride monohydrate. It is indicated for nausea, vomiting, hiccup and digestive dyskinesias. Several methods were reported for the determination of metoclopramide including: titrimetry[1], fluorimetry [2], spectrophotometry [3-7], ^{1}H-NMR-spectroscopy [8] and high performance liquid chromatography[9-11]. The 3-methylbenzothiazolinone -2-hydrazone reagent (MBTH) was previously utilized for the estimation of salbutamol sulphate and its formulations [12,13]. Also, the 1,3-dinitrobenzene (DNB) acceptor was utilized in the charge transfer complexation reaction for determination of certain aromatic hydrocarbons [14]. The use of chloranil and bromanil acceptors for estimation of metoclopramide was reported [15]. The official pharmacopoeial methods (B.P. 1998 [16] and USP 1995 [17]) for estimation of metoclopramide HCl are titrimetrically, that requires at least 300 mg of the drug for its determination.

In the present study, we introduce two spectrocolorimetric methods for the estimation of metoclopramide HCl in the different pharmaceutical preparations.

EXPERIMENTAL

Apparatus : Shimadzu 260 uv, uv-visible self recording spectrophotometer.

Materials and Reagents:

Metoclopramide HCl: was obtained from laboratories Delagrange-Paris; Standard stock solution is prepared in concentration of 100 mg/100 ml distilled water.

3- Methylbenzothiazolinone - 2 - hydrazone (MBTH): was obtained from Aldrich Chem. Co., U.S.A. ; Standard stock solution, 100 mg/100 ml in distilled water .

Ferric chloride reagent: 1% w/v solution in dist. water, freshly prepared.

1,3-Dinitrobenzene (DNB): was obtained from Fluka AG, Chem. Germany; Standard stock solution 100mg/100 ml chloroform,

Sodium hydroxide solution: 1.25 M. in distilled water.

Hydrochloric acid : 0.1 M. in distilled water.

Chloroform; Prolabo.

Primperan tablets; labelled to contain 10 mg of metoclopramide HCl per tablet.

Primperan injections; labelled to contain 10 mg of metoclopramide HCl per ampoule.

Tablets and injections were obtained from Memphis Co. for Pharm. Chem. Ind., Cairo, Egypt

Procedures:

A) Authentic Powder.

Method I (MBTH-method):

Appropriate volumes of the standard stock solution of the drug ranged from 0.1-1 ml were transferred into series of 25 ml-volumetric flasks. Exactly, 5 mls of ferric chloride solution followed by 3 mls of MBTH reagent were added. The reaction mixture was allowed to stand for 30 minutes, then completed to the volume with distilled water and the absorbance was measured at λ 555 nm against the corresponding reagent blank.

Method II (DNB-method):

To 20 ml of the standard stock solution of the drug, 15 ml of 1.25 M. sodium hydroxide solution was added. The mixture was then extracted with three 30 ml quantities of chloroform, and filtered through sodium sulphate (anhydrous) . The combined extracts were transferred into 100 ml volumetric flask and completed to the volume with chloroform.

An appropriate volumes of the chloroformic extract of the drug ranged from 0.5-2.5 ml were treated with 5 ml of DNB reagent. The mixture was heated on a water bath at 60°C for 15 minutes, then cooled and transferred quantitatively to a 10 ml volumetric flasks. The reaction mixture was then completed to the volume with chloroform and the absorbance was measured at maximum at λ 381 nm against the corresponding reagent blank.

B) Application to pharmaceutical preparations:

1) Primperan tablets:

Twenty tablets were finely powdered and an accurately weighed amount equivalent to 100 mg of drug was added to 50 ml of 0.1 M hydrochloric acid. The mixture was heated on a water bath at 70°C for 15 minutes, then cooled, completed to a 100 ml with distilled water and filtered. An appropriate volumes of the filtrate were subjected to the reaction procedures (method I and II) as described above .

2) Primperan injections:

An accurately measured volume of the injection equivalent to 100 mg of the drug was transferred into a 100 ml volumetric flask. An appropriate volumes of the mixed solution were subjected to the reaction procedures (method I and II) as described above.

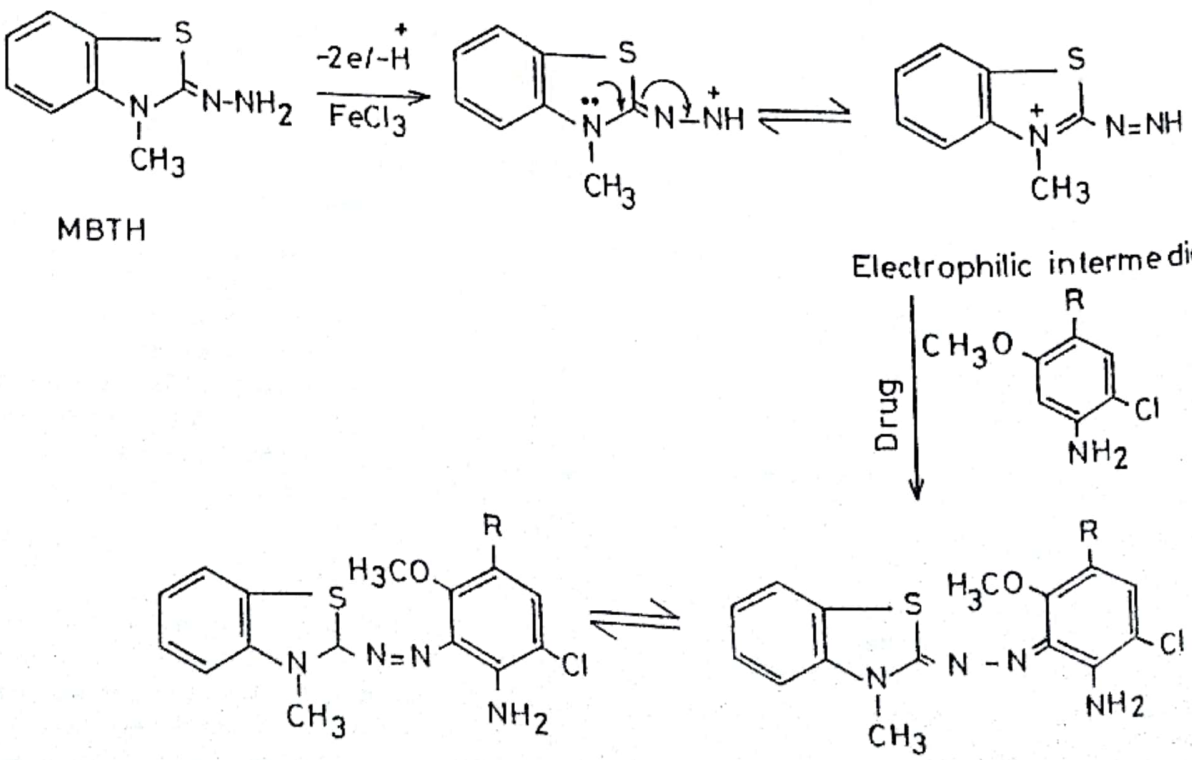
RESULTS AND DISCUSSION

Method (I) MBTH-method:

It has been reported that MBTH loses a proton and two electrons to form the electrophilic intermediate that undergoes electrophilic substitution with phenols in the ortho and para positions to produce coloured product[12,18]. Metoclopramide has only one free ortho position and hence it was readily attackable by the electrophilic intermediate at the position of the highly electron density giving the diazonium derivative according to the following pathway (Scheme 1) :

It was found that 5 ml of 1% ferric chloride solution as an oxidizing agent; 3 ml of 0.1% MBTH reagent and allowing to stand for 30 minutes at room temperature (25°C) are the optimal conditions to obtain maximum constant absorbance readings. Different oxidizing agents were tried in the reaction including $FeCl_3$, $K_2Cr_2O_7$ and $Ce_2(SO_4)_4$, only $FeCl_3$ gave high colour intensity. Higher temperature above 60°C led to decomposition of the resulting product.

The absorption graphs of metoclopramide HCl alone showed λ max at 308 nm and that of MBTH reagent at λ 217 nm, while that of the reaction product showed maximum at λ 555 nm in the aqueous media. Fig. (1, 2). Stoicheiometric relationship of the reactants (drug: MBTH) was found to be 1:1 using the continuous variation method[19] Fig. (3).



Scheme (1) suggested reaction pathway of metoclopramide with MBTH reagent.

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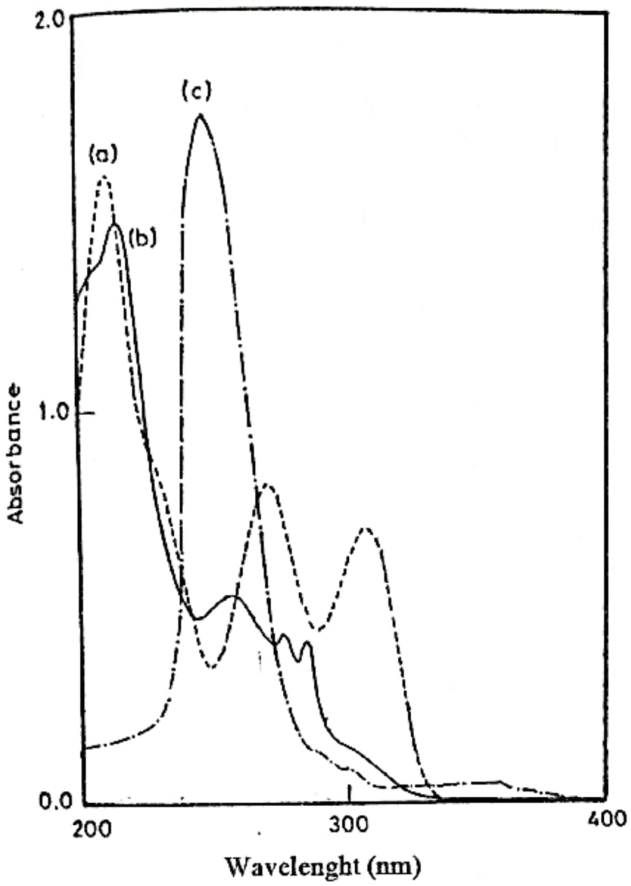


Fig.(1) Absorption spectra of (a) metoclopramide 20 μg ml^{-1} in dist water (b) MBTH 10 μgml^{-1}in dist. water and (c) DNB 20 μgml^{-1} in chloroform.

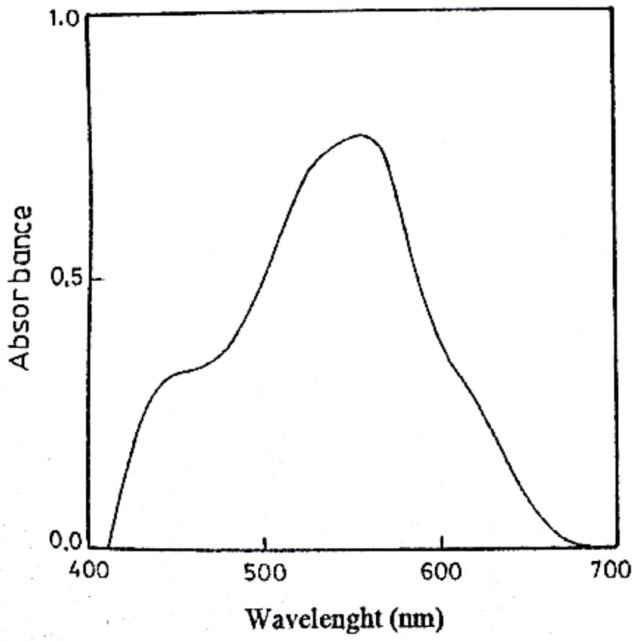


Fig.(2) Absorption spectra of 24 μg/ml-1 metoclorpramide HCL with MBTH.

This was expected hence metoclopramide has only one free ortho position.

Beer's law was obeyed in the concentration range (4-40) μg.ml^{-1} in the final measured solution. The molar absorptivity has been found to be 11072 liter $mole^{-1}.cm^{-1}$, indicating high sensitivity. The calibration graph was described by the regression equation **A = a +bc** obtained by the least-squares method [20]; where :

A is the absorbance,

a = intercept, **b** = slope,

c = concentration in mg% in the final measured solution. The value of **a** was - 0.001 and that of **b** was 0.314.

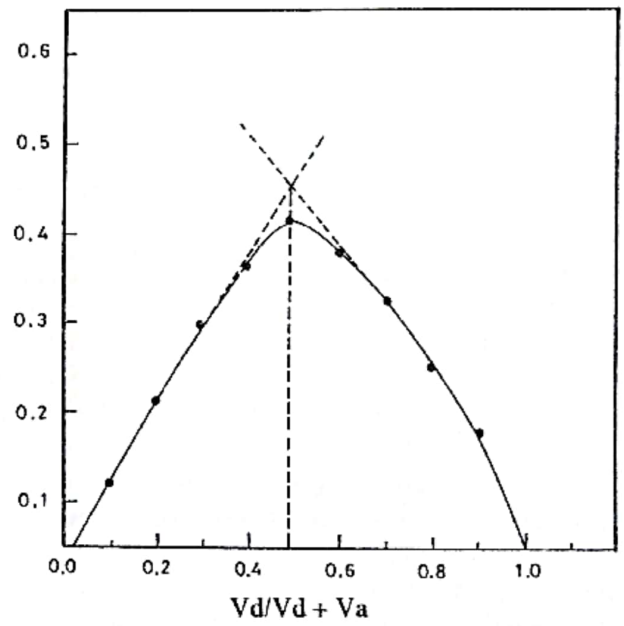
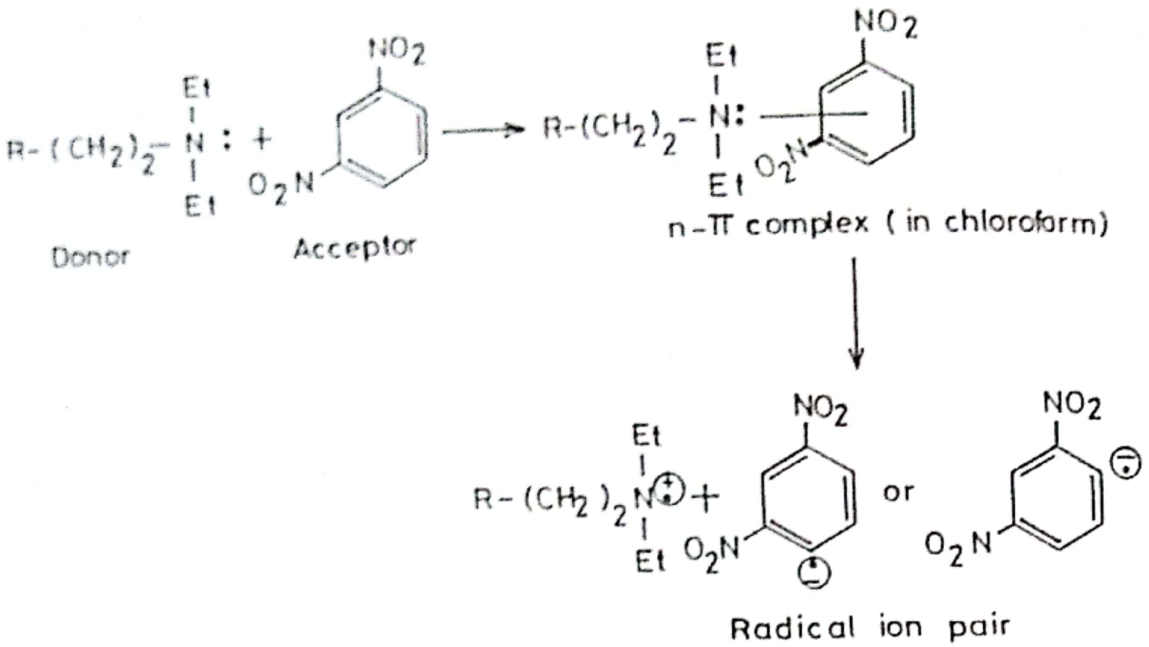


Fig.(3) Job's curve of equimolar solution of metoclopramide. HCL & MBTH (2 x 10^{-3} M) at 555 nm.

Method II (DNB-method):

Alkalinization of metoclopramide HCl with sodium hydroxide, followed by the chloroformic extraction of the free base of drug was essential for the interaction with DNB reagent. The terminal aliphatic amine of drug acting as n-donor and the II-electron acceptor of dinitrobenzene have led to charge-transfer complexation reaction, followed by radical ion formation. Chloroform, the chosen extraction solvent, was also an appropriate medium for charge-transfer complexation, as it has the desired solubilizing, lipotropic characteristic and reasonable degree of polarity. The reaction pathway may be suggested as follows (Scheme 2):

It has been found that 5 mls of DNB reagent was adequate for the complexation reaction. The colour of



Scheme (2): Suggested reaction pathway of metoclopramide with DNB acceptor in chloroform.

the complex reached its maximum intensity and stability on heating in a water bath at 60°C for 15 minutes. Higher temperature over 60°C led to dissociation of the formed complex. The absorption graphs of the drug showed λ max at 305 nm, and that of DNB-acceptor at 247 nm, while that of the complex showed a high absorption band at λ 381 nm in chloroform Fig. (4).

The absorption spectra of DNB complex showed characteristic absorption bands frequently with numerous vibrational maxima. This is essentially a summation of the bands characteristic of neutral DNB and its radical anions. The molar ratio of the reactants (donor: acceptor) was found 1:1 by applying the Job's continuous variation method Fig. (5). This was expected, where the more basic terminal aliphatic amine moiety was only utilized in the complexation reaction, in view of the weak basicity of the aromatic amino group or the amidic nitrogen.

A linear relationship was obtained for the absorbance of the complex when the concentration of the drug was in range 10-50 $\mu g.ml^{-1}$ in the final measured solution. The molar absorptivity has been found to be 10629 $L.mole^{-1}.cm^{-1}$, indicating high sensitivity. The regression $A = a + bc$ describing the calibration graph was $A = -0.009 + 0.313\ c$, where A is the absorbance and C is the concentration in mg% in the final measured solution.

Accuracy and precision of methods (I and II):

The validity of both procedures of the proposed methods for the quantitative determination of metoclopramide HCl and its dosage forms was assessed by applying the methods to commercial preparations and adding known amounts to the tablets or ampoules followed by its estimation using standard addition technique.

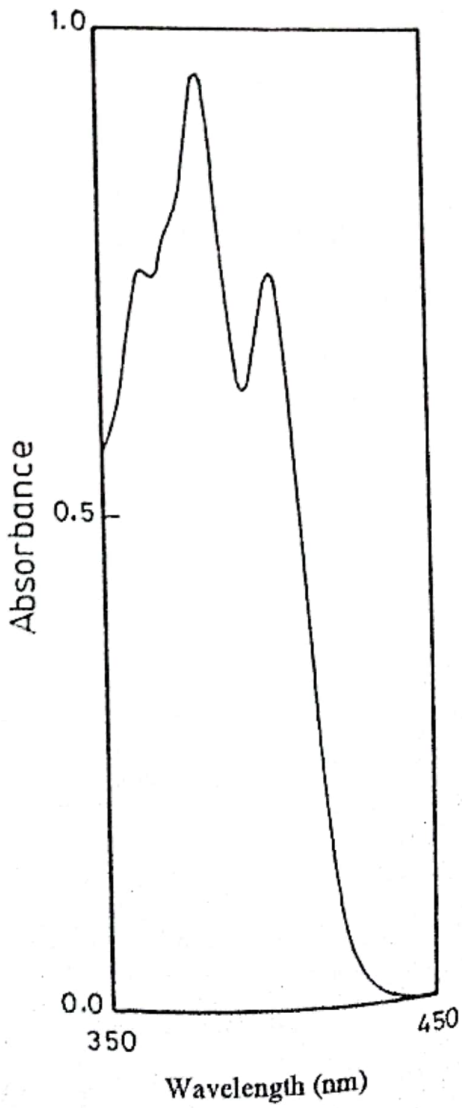


Fig. (4) Absorption spectrum of 30.6 μgml^{-1} metoclopramide with DNB in chloroform.

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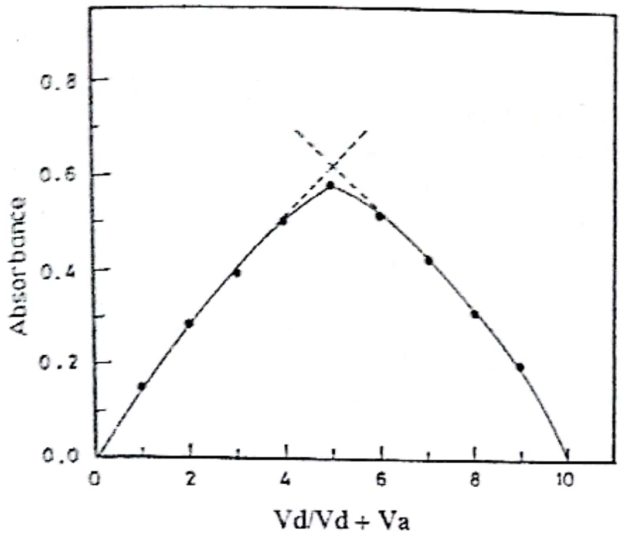

Fig.(5) Job's curve of equimolar solution of metoclopramide and DNB (3 x 10^{-1} M) at 381 nm.

The results obtained were reproducible with low standard deviation and the mean recovery was comparable to that obtained by the official B.P. 1998 method, Tables (1,2,3). No interferences from the tablets excipients were exhibited as the heating of the mixture at 70°C followed by filtration, together with extraction of the drug with chloroform excludes any form of interference.

The official B.P. 1998 method[16] for the assay of metoclopramide HCl is acid-base titrimetrically, that requires 250 mg of the drug for its determination. While the assay method for tablets and injections is a direct UV measurement for the chloroformic extract of the drug at λ max 305 nm. On the other hand, the official U.S.P. 1995 method[17] for the assay of metoclopramide HCl is non aqueous titrimetrically that requires 300 mg of the drug for its estimation and requires standing 3 hours for the assay mixture before the titration. While the assay method for tablets and injections is HPLC technique.

Table (1): Determination of metoclopramide HCl in authentic powder using the proposed methods compared with the titrimetric B.P. 1998 method.

	Proposed method I (MBTH)	Proposed method II (DNB)	B.P. 1998 method
Mean± SD	100.22±0.66	99.46±0.52	99.94±0.581
N	5	5	5
Variance	0.447	0.27	0.338
S.E.	0.299	0.23	0.260
t-test	0.70(2.31)*	1.37(2.31)*	
F-test	1.32(6.39)*	1.25(6.39)*	

Table (2): Determination of metoclopramide HCl in primperan tablets using the proposed methods compared with the spectrophotometric B.P. 1998 method.

	Proposed method I (MBTH)	Proposed method II (DNB)	B.P. 1998 method
Mean± SD	99.96±0.33	100.36±0.47	100.10±0.43
N	5	5	5
Variance	0.113	0.22	0.185
S.E.	0.150	0.21	0.192
t-test	0.58(2.31)*	0.93(2.31)*	
F-test	1.64(6.39)*	1.19(6.39)*	

Table (3): Determination of metoclopramide HCl in primperan ampoules using the proposed methods compared with the spectrophotometric B.P. 1998 method.

	Proposed method I (MBTH)	Proposed method II (DNB)	B.P. 1998 method
Mean± SD	100.06±0.53	100.28±0.33	100.16±0.36
N	5	5	5
Variance	0.283	0.115	0.133
S.E.	0.238	0.152	0.163
t-test	0.35(2.31)*	0.54(2.31)*	
F-test	2.13(6.39)*	1.16(6.39)*	

*Figures in parentheses are the tabulated t and F- values.

The two proposed procedures are easy to follow, require no complicated instrumentation and give accurate & precise results. These features should encourage their application in the quality control of the drug. The methods may be considered to be of potential stability-indicating value as they apply to the intact molecule, which is highly stable.

REFERENCES

1-Badwan, A.A.; Jawan, O.A. and Owais, L.; **Int. J. Pharm.**, 28 (1), 41 (1986).

2-Rao, H.L.; Aroor, A.R. and Rao, P.G.; **Indian Drugs**,, 28 (4): 195 (1991).

3-Emmanuel, J. and Naik, P.N.; **Indian Drugs**, 20 (9), 387 (1983)

4-Sastry, C.S.P.; Kumari, P.L. and Rao, B.G.; **Chem. Anal. (Warsaw)**, 30 (3), 461 (1985).

5-Singh, S., Shukla, S. and Shukla, I.C.; **J. Inst. Chem. (India)**, 62 (3), 126 (1990).

6-Raghuveer, S., Rao, B.E., Srivastava, C.M. and Vatsa, D.K.; **East. Pharm.**, 35 (413), 125 (1992).

7-Abdel-Gawad, F.M. and El-Guindi, N.M.; **Anal. Lett.**, 28 (8), 1437 (1995).

8-Hanna, G.M. and Lau-Cam, C.A.; **Drug Dev. Ind. Pharm.**, 17 (7), 975 (1991).

9-Shields, B.J. and Mackichan, J.J.; **J. Liq. Chromatogr.**, 13 (13) 2643 (1990).

10-Foda, N.H.; **Anal. Lett.**, 27 (3), 549 (1994).

11-Radwan, M.A.; **Anal. Lett.**, 31 (14), 2397 (1998).

12-Geeta, N. and Baggi, T.R.; **Microchem. J.**, 39, 137 (1989).

13-Sastry, C.S.P.; Shankar, D.G., Reddy, M.N. and Singh, N.R., **Indian Drugs**, 25 (3), 130 (1987).

14-Foster, R.; "Organic Charge Transfer Complexes", Academic Press, London, p. 379, (1969).

15-El-Gendy, A.E.; **Spectrosc. Lett.**, 25 (8), 1297 (1992).

16-British Pharmacopoeia, HM. Stationary Office, London, p. 888, (1998).

17-United States Pharmacopoeia XXIII, NF 18, P. 1011, (1995).

18-Sawicki, E.; Stanley, T.W.; Hauser, T.R.; Elbert, W.; and Noe, J.L.; **Anal. Chem.**, 33, 722 (1961).

19-Rose, J.;"Advanced Physico - Chemical Experiments", Pitman, London, p. 54 (1964)

20-Bauer, E.L.; "Statistical Manual For Chemists". Academic Press, London, p. 61, (1971).

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التقدير الطيفي لمركب الميتوكلوبراميد هيدروكلوريد في المستحضرات الصيدلية

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فى هذا البحث تم تطوير طريقتين طيفيتين جديدتين لتعيين مركب الميتوكلوبراميد هيدروكلوريد وتطبيقة على مستحضراته الصيدلية.

تعتمد الطريقة الأولى على تعيين المركب باستخدام ٣ - ميثيل بنزثيازولينون -٢- هيدرازون فى وجود كلوريد الحديديك كعامل أكسدة ، حيث يتكون مشتق الديازونيوم ويتم قياس اللون الناتج عند ٥٥٥ نانوميتر فى محلول مائى.

وتعتمد الطريقة الثانية على تعيين المركب بعد إحداث القلوية واستخلاص القاعدة الحرة للمركب بواسطة الكلوروفورم ثم تفاعلة مع ١، ٣ - ثنائى نيترو البنزين عند درجة حرارة ٦٠ درجة مئوية فى حمام مائى ويتم قياس المعقد الناتج عند ٣٨١ نانوميتر فى الكلوروفورم.

وقد تم تطبيق الطريقتين على أقراص وحقن البرمبران ، وأعطت نتائج جيدة ، ولقد تمت مقارنة النتائج بالطريقة الدستورية الإنجليزية لعام ١٩٩٨ وأعطت نتائج متماثلة فى الدقة ، ولكن الطرق المقترحة كانت تفوقها فى الحساسية.