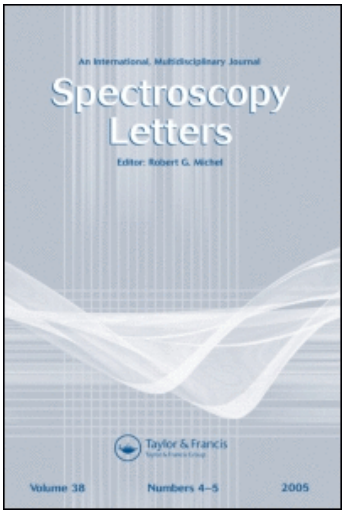

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Spectrophotometric Determination of Metoclopramide VIA Charge-Transfer Complexes

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SPECTROPHOTOMETRIC DETERMINATION OF METOCLOPRAMIDE VIA CHARGE-TRANSFER COMPLEXES

KEY WORDS: Metoclopramide, Spectrophotometry, Charge-transfer complexes, Chloranil, Bromanil.

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ABSTRACT

Simple and sensitive spectrophotometric method for the determination of metoclopramide is described, based on the formation of charge-transfer complexes using chloranil and bromanil as π acceptors. These complexes exhibit intense absorption bands in the electronic spectrum. The molecular ratios of the reactants in the complexes were established and the experimental conditions leading to maximum charge-tranfer bands were also studied. The proposed procedure has been applied successfully to pure samples and drug formulations with good accuracy. The validity of the proposed method was checked by applying the standard addition technique in addition to a comparative study between its results and those obtained by the pharmacopoeial method.

INTRODUCTION

Metoclopramide, 4-amino-5-chloro-2-methoxy-N-(2-diethyl- aminoethyl) benzamide, an antiemetic procaine derivative[1], is currently used in GI diagnostic[2] and in the treatment of various GI disorders[3].

Metoclopramide increases the tone and peristalsis of the stomach and the duodenum and improves the pyloric activity, thus promoting gastric motility and reducing gastric emptying times[4].

Metoclopramide may be determined by several analytical techniques. Colorimetric assays have been the most widely used specially to determine metoclopramide in pharmaceutical formulations[5,6]. Among the other several methods of analysis are fluorimetry[7], thin layer chromatography[8] and liquid chromatography[9,10]. A non aqueous titration method was described, in B.P. 1988, for the determination of metoclopramide powder, while for tablets and injection, it described an ultraviolet spectrophotometric method[11].

Amines are excellent electron donors, and charge-transfer complexes of these compounds with chloranil and bromanil, π acceptors, have been reported[12-15]. These investigations revealed that the spectra produced were due to n- π charge-transfer complexes.

This paper describes the use of charge-transfer complex for the development of a simple and sensitive spectrophotometric method for the determination of metoclopramide in pure form and in pharmaceutical formulations.

EXPERIMENTAL

Samples

1. Metoclopramide hydrochloride authentic sample was kindly supplied by Memphis Chemical Co., Cairo, A.R.E. It was assayed according to the B.P. 1988 method. The percentage purity was found to be 100.30± 0.32.

2. Meclopram tablets and ampoules, produced by the Alexandria Co. for Pharmaceuticals and Chemical Ind., Alexandria, A.R.E. Each tablet or ampoule is labelled to contain 10mg metoclopramide hydrochloride.

3. Plasil tablets, produced by the Nile Co. for Pharmaceuticals and Chemical Industries, Cairo, A.R.E. Under licence of Gruppo Lepetit. S.P.A. Milan, Italy. Each tablet is labelled to contain 10mg metoclopramide hydrochloride.

4. Plemazol tablets and ampoules, produced by Cid Co., Cairo, Egypt. Each tablet or ampoule is labelled to contain 10mg metoclopramide hydrochloride.

5. Primperan tablets and ampoules, produced by Memphis Chemical Co., Cairo, A.R.E. Under licence of Laboratoires Delagrange, Paris. Each tablet or ampoule is labelled to contain 10mg metoclopramide hydrochloride.

Reagents and Materials

The reagents used were of analytical-reagent grade and the solvents were of spectroscopic grade.

Chloranil solution. Chloranil (purified by recrystallisation from acetone) was dissolved in chloroform to obtain $1X10^{-2}M$ solution.

Bromanil solution Bromanil (purified by recrystallisation from acetone) was dissolved in chloroform to obtain $1X10^{-2}M$ solution.

Reference drug solution. Transfer an accurately weighed amount of metoclopramide hydrochloride equivalent to 50 mg of the base into a separating funnel. Dissolve in about 20ml of distilled water, make alkaline with a few drops of 10% sodium hydroxide solution, 1ml being added in excess. Extract the liberated metoclopramide base with four successive 10-ml portions of chloroform with shaking for 3 minutes each time. Pass the chloroform extracts sequentially over anhydrous sodium sulphate supported on absorbent cotton previously moistened with chloroform. Collect the combined chloroform extracts in a 50-ml calibrated flask. Complete to volume with chloroform.

Apparatus

Beckman DU-7 Spectrophotometer.

Procedures

1. General Procedure and Preparation of Calibration Graph.

Transfer an accurately measured volume of reference or sample solution of the metoclopramide free base (in the concentration range 0.4 - 1.6 mg) into a series of 10-ml calibrated flasks. Add 1ml of chloranil or bromanil solution and heat on a water-bath at 80°C until almost dry. Dissolve the residue and complete to

volume with chloroform. Measure the absorbance at 675 nm against a reagent blank.

2. Molar Ratio of Reactants in Complex.

A. The Continuous Variation Method[16].

Prepare a series of 10-ml calibrated flasks containing complementary proportions of 10^{-2}M metoclopramide solution and 10^{-2}M chloranil or bromanil solution (0.0:1.0, 0.1: 0.9 .....1.0: 0.0). Then proceed as under **General Procedure** starting from "heat on a water-bath ...".

B. The Mole-Ratio Method[16].

Introduce 0.4ml aliquots of 10^{-2}M chloranil or bromanil solution in a series of 10-ml calibrated flasks containing different volumes of 10^{-2}M Metoclopramide solution (0.2, 0.3, ...1.2 ml). Then proceed as under **General procedure** starting from "heat on a water-bath ...".

3. Determination of Molar Absorptivity and Association Constant[17].

Introduce 0.4 ml aliquots of 10^{-2}M chloranil or bromanil solution in a series of 10-ml calibrated flasks containing different volumes of 10^{-2}M metoclopramide solution (0.8, 1.0, ... 1.8ml). Then proceed as under **General procedure** starting from "heat on a water-bath ...".

4. Assay of Pharmaceutical preparations.

A. Procedure For Tablets

Weigh accurately not less than twenty tablets and calculate the average weight of each tablet. Transfer

an aliquot of the powdered tablets equivalent to about 100 mg metoclopramide base to a 100-ml calibrated flask and treat it with 50ml 0.1N hydrochloric acid. Heat the solution on a water-bath at 70°C for about 15 minutes with occasional shaking. Cool the flask and complete to the mark with water then filter. Transfer an aliquot of the filterate equivalent to 50 mg base to a separating funnel. Then proceed as described under **Reference drug solution** starting from "make alkaline with ...".

B.**Procedure For Injection**.

Transfer an accurately measured volume of the mixed content of ten ampoules, equivalent to 50mg metoclopramide base into a separating funnel. Then proceed as described under **Reference drug solution** starting from "make alkaline with....".

RESULTS AND DISCUSSION

Metoclopramide having tertiary amino group can acts as an electron donor and participate in n- π charge - transfer complexation with acceptors, e.g., chloranil and bromanil. The spectra of the complexes exhibit maximum absorption at about 675 nm as shown in figure 1.

Reactions between tertiary amines N-ethyl groups and some halogenated quinones have been previously studied in the course of investigating molecular complexes[18-20]. The interaction can result in dehydrogenation to enamines, which condense with a second molecule of the halo-quinone to yield blue dialkylaminovinylquinones.

Variable parameters affecting the complexation process were studied. Different solvents were tried,

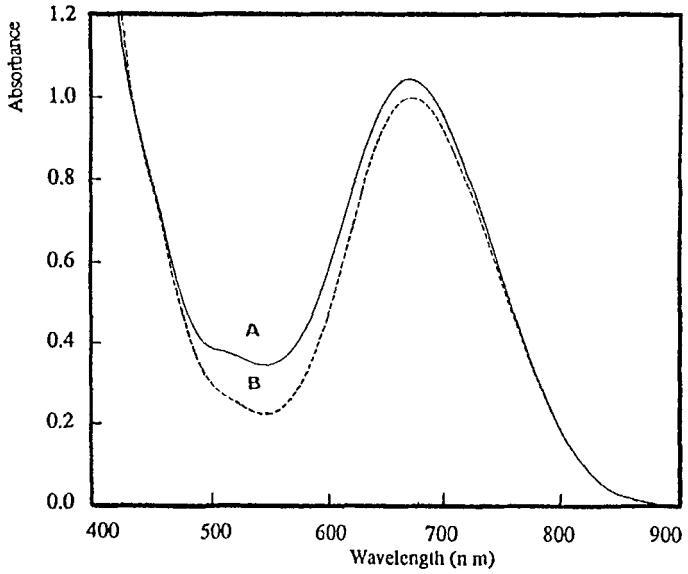

Figure (1) : Absorption spectra of the color reaction of metoclopramide with chloranil (A), bromanil (B).

e.g., chloroform, Dioxane, ethanol, methanol and methylene chloride. Chloroform afforded a higher sensitivity than the other solvents and proved to be the most suitable one with maximum absorbance at 675 nm. Because the reaction with chloranil or bromanil at room temperature is slow[21], the effect of heating temperature and heating time were studied. Trials were made in order to accelerate the reaction by heating in a water-bath at different temperatures for different times. It was found that heating on a water-bath at 80 °C until almost dry produced maximum color intensity. The absorbance of the complexed metoclopramide is stable for more than 3 hours, thus permitting the quantitative analysis to be carried out with good reproducibility.

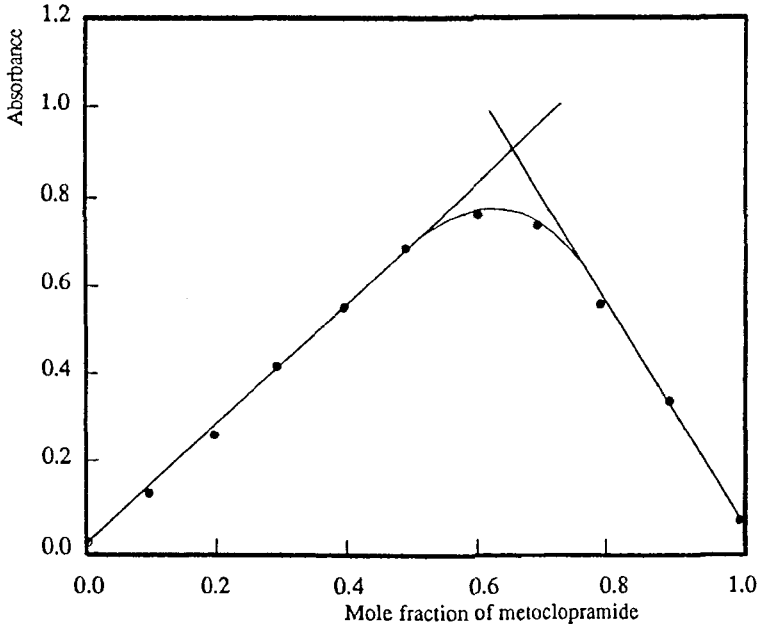

Figure (2) : Determination of thê stoichiometry of the reaction of metoclopramide and chloranil by the continuous variation method.

The continuous variation method and the mole ratio method were applied to determine the molar ratio of metoclopramide and chloranil or bromanil in both complexes. Both methods revealed a donor to acceptor ratio of 2:1 under the described condition as shown in figures 2 - 4.

Molar Absorptivities and Association Constants.

These were evaluated by the Benesi-Hildebrand equation[17].

$$[A]_o / A = 1 / k_c^{AD} \varepsilon_\lambda^{AD} \times 1/[D]_o + 1 / \varepsilon_\lambda^{AD}$$

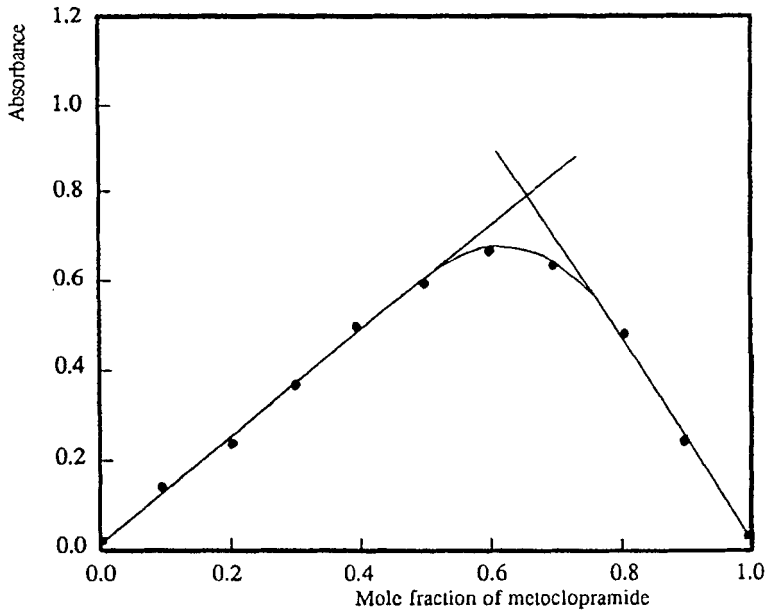

Figure (3) : Determination of the stoichiometry of the reaction of metoclopramide and bromanil by the continuous variation method.

where $[A]_o$ and $[D]_o$ indicate the total (Free and complexed) concentration of acceptor A and donor D; A is the absorbance; ε_λ^{AD} is the molar absorptivity of AD at a wavelength λ ; and K_c^{AD} is the association constant of the complex. The Benesi-Hildebrand method depends on the experimental condition that one of the two component species is present in large excess, so that its concentration is virtually unaltered on the formation of a complex. The graph for complexed metoclopramide is illustrated in figure 5.

For a series of solutions in which $[D]_o >> [A]_o$, a graph of $[A]_o/A$ against $[D]_o^{-1}$ is linear. The intercept

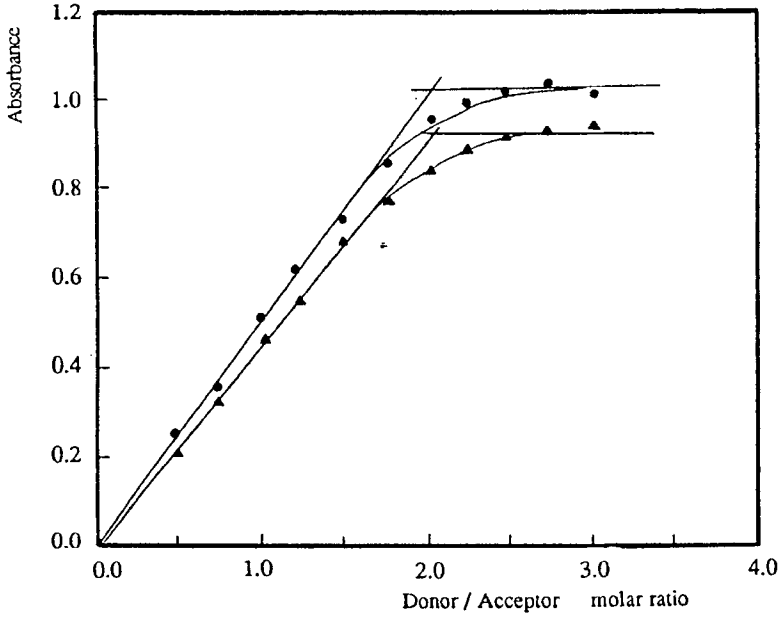

Figure (4) : Determination of the stoichiometry of the reaction of metoclopramide - chloranil (—●—●—) and metoclopramide - bromanil (—▲—▲—) by the mole - ratio method.

of the line with the ordinate is $(\varepsilon_{\lambda}^{AD})^{-1}$ and the slope is $[\varepsilon_{\lambda}^{AD} K_c^{AD})^{-1}$, a value which is independent of concentration, and therefore the value of K_c^{AD} can be calculated. By using the method of the least squares[22], the graphs of $[A]_o/A$ versus $[D]_o^{-1}$ can be described by the following regression equations:

$[A]_o/A = 2.661 \times 10^{-4} + 1.286 \times 10^{-7} \times 1/[D]_o$ (For chloranil)

$[A]_o/A = 2.732 \times 10^{-4} + 1.484 \times 10^{-7} \times 1/[D]_o$ (For bromanil)

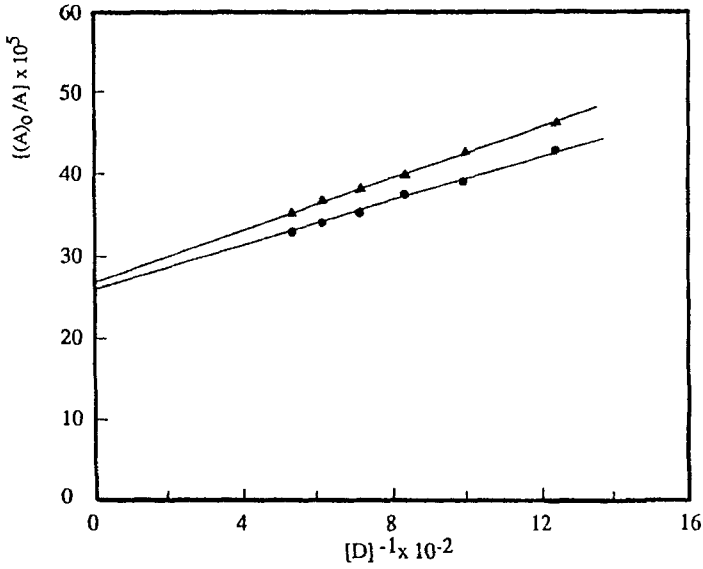

Figure (5) : Benesi - Hildebrand graph for metoclopramide - chloranil complex (—●—●—) and metoclopramide - bromanil complex (—▲—▲—).

Thus, the values for metoclopramid-chloranil are ε_λ^{AD} of 3758 and K_c^{AD} of 2069 mol^{-1}, while for metoclopramide.-bromanil the values obtained are 3660 and 1840 respectively.

The proposed method was successfully applied for the determination of pure metoclopramide, the results obtained were compared with the official B.P. 1988 method. Statistical analysis of the results revealed no significant difference between them as shown in table 1.

Beer's law is obeyed for drug concentrations ranging from 0.04-0.16 $mg.ml^{-1}$ for metoclopramide -

TABLE 1

Results of metoclopramide hydrochloride in raw materials and tablets using the proposed and the official B.P. 1988 methods.

Preparation	Chloranil Method	Bromanil Method	Official B.P. 1988 Method
Powder Mean ± C.V. Student's t* F**	100.02 ± 0.54 1.180 2.848	99.88 ± 0.43 2.073 1.806	100.30 ± 0.32
Meclopram tablets Mean ± C.V. Student's t* F**	100.98 ± 0.65 0.734 3.182	101.41 ± 0.25 1.304 2.190	101.19 ± 0.37
Plasil tablets Mean ± C.V. Student's t* F**	100.68 ± 0.36 1.574 1.235	100.53 ± 0.63 1.666 2.481	101.00 ± 0.40
Plemazol tablets Mean ± C.V. Student's t* F**	99.44 ± 0.49 2.111 1.126	99.64 ± 0.91 0.934 3.063	100.01 ± 0.52
Primperan tablets Mean ± C.V. Student's t* F**	99.46 ± 0.67 1.203 1.382	100.23 ± 0.74 1.048 1.685	99.86 ± 0.57

* t-Tabulated (n=7) at (n1+n2-2) df and P=0.05 is 2.179

** F-Tabulated (n=7) at P=0.05 is 4.28

TABLE 2

Results of metoclopramide hydrochloride in ampoules using the proposed and the official B.P. 1988 methods.

Preparation	Chloranil Method	Bromanil Method	Official B.P. 1988 Method
Meclopram ampoules Mean ± C.V. Student's t* F**	99.20 ± 0.80 2.095 1.477	99.84± 1.10 0.352 2.864	100.01 ± 0.65
Plemazol ampoules Mean ± C.V. Student's t * F **	99.47 ± 0.77 1.168 1.162	99.12 ± 0.82 1.939 1.050	99.97 ± 0.83
Primperan ampoules Mean ± C.V. Student's t* F**	98.76 ± 0.97 1.769 1.405	99.10 ± 1.03 1.016 1.586	99.60 ± 0.81

* t-Tabulated (n=7) at (n1+n2-2) df and P=0.05 is 2.179

** F-Tabulated (n=7) at P=0.05 is 4.28

TABLE 3

Application of the standard addition technique to the determination of metoclopramide hydrochloride in pharmaceutical preparations.

Preparation	Chloranil Method (Mean* ± C.V)	Bromanil Method (Mean* ± C.V)
Meclopram tablets	99.14 ± 0.84	99.02 ± 0.98
Plasil tablets	99.68 ± 0.34	99.80 ± 0.63
Plemazol tablets	99.89 ± 0.72	99.41 ± 0.69
Primperam tablets	100.20 ± 0.31	99.66 ± 0.50
Meclopram ampoules	100.80 ± 0.29	100.61 ± 0.12
Plemazol ampoules	99.82 ± 0.63	100.44 ± 0.89
Primperam ampoules	100.91 ± 0.80	101.02 ± 0.73

* Each mean recovery % is the average of six recovery experiments.

chloranil and metoclopramide - bromanil. The regression equations and correlation coefficients derived, using the least squares method, were:

$A_{675} = 0.0048 + 5.1677C \quad r = 0.9992$ for chloranil

$A_{675} = 0.0028 + 4.7919C \quad r = 0.9996$ for chloranil

where C is the concentration in mg. ml^{-1} in the final solution.

The coefficient of variation was calculated for the results of each procedure and found not exceeding 2%. This indicates the reproducibility of the proposed method.

Before dealing with the analysis of different pharmaceutical dosage forms, the effect of common additives, adjuvants and excepients on the proposed method were experimentally studied, the results obtained revealed no interference. Different pharmaceutical dosage forms containing metoclopramide were analysed by the proposed method and compared with the official B.P. 1988 method as shown in tables 1 & 2. Statistical analysis of the results revealed that the proposed method was equally precise and accurate as the official method.

The precision and validity of the results obtained was assessed by applying the standard addition technique as shown in table 3.

The proposed method is simple, time saving sensitive and encourages its applicalion in the analysis and quality control of this drug in different pharmaceutical dosage forms.

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