Spectrophotometric Determination of Metoclopramide in Some Pharmaceutical Preparations via Oxidative Coupling Reaction

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الخلاصة

طورت طريقة طيفية بسيطة لتقدير الميتوكلوبرامايد بهيئته النقية وفي مستحضراته الصيدلانية باستخدام تفاعل الاقتران التأكسدي وتعتمد هذه الطريقة على أكسدة البروميثازين بوساطة أيون الهايبوكلورايت ثم اقترانه مع الميتوكلوبرامايد في وسط من حامض الخليك ليعطي ناتج أزرق اللون ذو أعلى امتصاص عند 596 نانوميتر وقد لوحظ أن قانون بيير يسري على الكميات التي تتراوح بين (3 - 30) مايكروغرام/ مللتر بامتصاصية مولارية x $1.1\ 10^4$ لتر. مول$^{-1}$. سم$^{-1}$. كان الانحراف القياسي النسبي للطريقة اقل من 1.2% ومعدل الاسترجاعية 99.6 % .وتم دراسة الظروف المثلى لتكوين المعقد وطبقت الطريقة بنجاح في تقدير الميتوكلوبرامايد في حالته النقية وفي بعض مستحضراته الصيدلانية. كما وجد ان لا تأثير للمضافات الدوائية في الطريقة المقترحة.

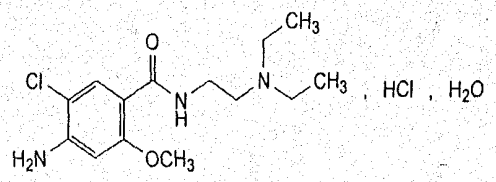
Abstract:-

A simple spectrophotometric method for the determination of metoclopramide in a pure form and in dosage forms pharmaceutical preparations has been developed. The proposed method is based on the oxidation of promethazine by sodium hypochlorite and the coupling of the resulting product with metoclopramide in acetic acid medium to form a blue product with maximum absorption at 596 nm. Beer's law is obeyed over the concentration range of(3-30)µg/ml,with molar absorptivity of $1.1x10^4$ $L.mol^{-1}.cm^{-1}$ .A relative standard deviation of the method was less than 1.2 % and accuracy was 99.6 %. The optimum conditions for all colour development are described and the proposed method has been successfully applied for the determination of metoclopramide in pure drug and pharmaceutical formulations.The common excipients and additives did not interfere in this method.

Keywords: Metoclopramide,spectrophotometric,oxidative coupling.

Introduction: -

Metoclopramide is the monohydrate of 4-amino-5-chloro-N-(2-diethylaminoethyl)-2-methoxybenzamide hydrochlorid



It is the active ingredient of many pharmaceutical preparations, which increases gastric motility and accelerates gastric emptying. This action is antagonized by atropine. It also has an anti-emetic action that is due to its local action on the gastro - intestinal tract or a direct action on the central nervous system(1).Metoclopramide is also used for the prophylaxis of vomiting associated with cisplatin or other cancer chemotherapeutic agents (2), it is also used to prevent nausea and vomiting induced by drug, radiation, anesthesia, or disease.

Many methods for the determination of metoclopramide have been described in the literature, among these the potentiometric titration(3),high performance liquid chromatography (4-6), chemiluminescence(7), and spectrophotometric methods (8-12),such as the coupling reaction of the diazotised metoclopramide with dibenzoyl methane (8), and with acety acetone (9), or coupling of diazotized aniline with metoclopramide (10). Another method depends on the interaction of metoclopramide with p-dimethylaminocinnamaldehyde to give a red color schiffs base (11).

The above methods show a lack of simplicity that is needed for routine analysis, long waiting times and instability of the colored species and complex procedures.This paper describe simple, rapid, accurate, and suitable analytical procedure for the routine determination of metoclopramide in a pure form and in different pharmaceutical preparations including tablet, syrup, drops and injection satisfactory results were obtained in comparison with official method (13).

Experimental: -

Apparatus:

Spectro - Scan 50 UV-Visible Spectrophotometer with 1.0-cm quartz cells was used for absorption measurements.

Reagents:

All chemicals used were of analytical grade.

Metoclopramide hydrochloride (Nineveh drug industry, NDI) (150 μg/ml): Dissolve 0.15 g of mtoclopramide hydrochloride in 1L distilled water

Promethazine hydrochloride solution ($1.68x10^{-3}$ M)

Dissolve 0.54g of reagent in 1L distilled water.

Acetic acid 0.1 N

Sodium hypochlorite: (0.1 %):This solution was prepared by dilution of 1.25ml of 8% sodium hypochloride to 100ml by distilled water in a volumetric flask with the same solvent.

Recommended procedure:

Aliquots of standard solution of metoclopramide (75-750 μg/ml) were transferred into a 25ml calibrated flask, 5ml of 0.1N acetic acid solution,a 3ml of ($1.6x10^{-3}$ M)

promethazine hydrochloride and 3ml of 0.1% sodium hypochlorite were added. The mixture was diluted to volume with distilled water, and allowed standing for 5min. The absorbance was measured at 596 nm against a reagent blank.

Procedures for pharmaceutical preparations:

Tablets: -

Ten tablets were weighed and ground into a fine powder. Shake a quantity of powder equivalent to 15 mg of metclopramide hydrochloride with 50ml of 0.1M NaOH for 15 min, neutralized with 0.1M HCl and filtered .The volume was made to 100ml with distilled water. A 3ml of this solution was treated as mentioned under the recommended procedure.

Syrup and mouth drops: -

A volume containing 15 mg of metoclopramide hydrochloride was diluted with distilled water and completed to 100 ml .A 3ml of this solution was treated as described under recommended procedure.

Injection: -

A 2ml vial containing 10-mg of metoclopramide hydrochloride was transferred into 100-ml volumetric flask and diluted to the mark with distilled water. A 4.5-ml of this solution was treated as described under the recommended procedure.

Results and discussion: -

Absorption spectra:

A blue coloured product with an absorption maximum at 596nm was formed when metoclopramide hydrochloride was allowed to react with promethazine hydrochloride in the presence of sodium hypochlorite in acidic medium of acetic acid. Fig [1] shows the spectrum of the dye formed and of the reagent blank.The maximum absorption at 596nm was selected for all subsequent experiments.

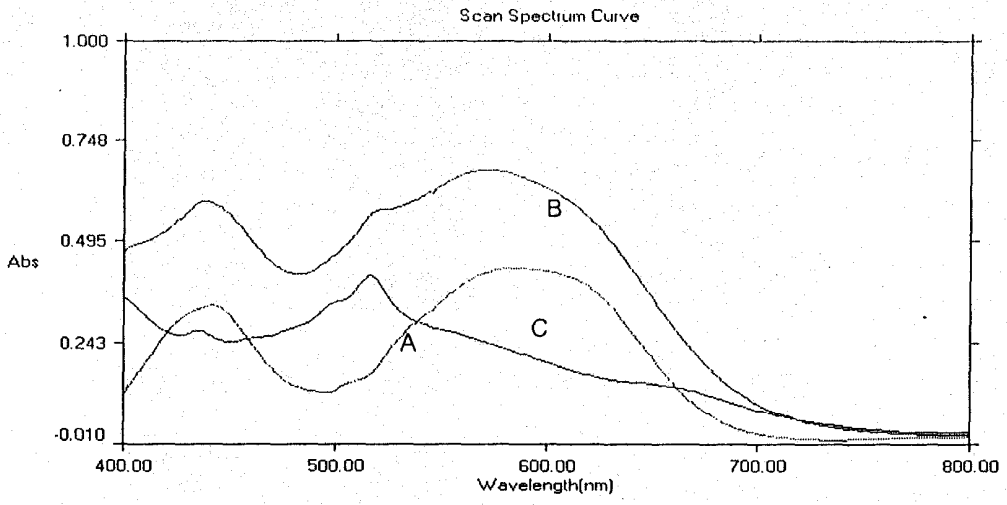


Fig [1]: Absorption spectra of 450 µg/25ml metoclopramide hydrochloride treated as described under the recommended procedure conditions

A-blank against water.
B- metoclopramide-promethazine product against water.
C- metoclopramide-promethazine product against reagent blank.

Study of the optimum reaction conditions.

The effect of various parameters on the absorption intensity of the dye formed was studied and the reaction conditions are optimized.

Effect of pH:

The effect of pH on the sensitivity of the product was examined. Only pH 3.5 (0.1N acetic acid) was found to be optimum. The effect of the amount of 0.1N acetic acid was also investigated and 5ml were found the optimal.

Effect of reagent concentration: -

The amount of promethazine solution ($1.68x10^{-3}$ M) for maximal colour intensity was examined. The maximum colour intensity was reached at 2ml and remained constant up to 5ml. However 3ml of the reagent solution was selected for the subsequent work.

Effect of oxidant concentration: -

The amount of sodium hypochlorite solution (0.1%) for maximal colour intensity was examined .The maximum colour intensity was reached when (2-5) ml were used. However 3ml of the hypochlorite solution was selected for further study.

Effect of reaction time: -

The maximum time for complex colour development was found to be 5min at room temperature and the absorbance was stable for at least 6 hours.

Effect of order of addition: -

To obtain optimum results the order of addition of reagent should be followed as given under the recommended procedure, otherwise a loss in color intensity was observed.

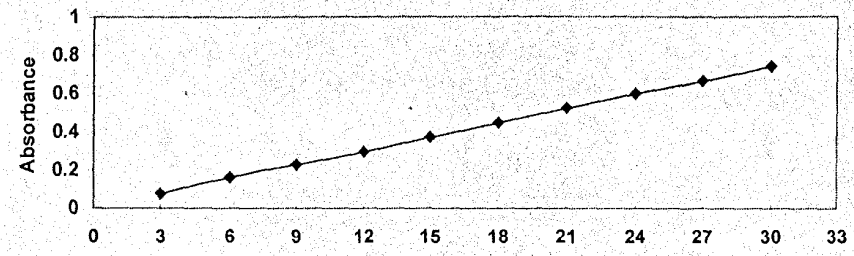
Beer's law: -

Employing the conditions described under recommended procedure, a linear calibration graph for metoclopramide hydrochloride is obtained Fig(2), which show that Beers law is obyed over the concentration range of 75-750 µg/25ml , with correlation coefficient of 0.9989 and intercept of 0.022 and the conditional molar absorptivity was found to be $1.1x10^{4}L.mol^{-1}.cm^{-1}$,with accuracy (average recovery) was 99.6 % and the relative standard deviation of less than 1.2 % .The optimum reaction conditions are given in Table (1).

Table(1): Optimum reaction conditions.

λ max nm	Temp. C°	pH	Amount of 1.68 x 10^{-3}M	Amount of oxidant 0.1 %	development Time (min)	Linearty range µg/25 ml
596	R.T	3.5	5ml	(3ml)	5 min	75-750

Fig(2): Calibration graph of metoclopramide hydrochloride.

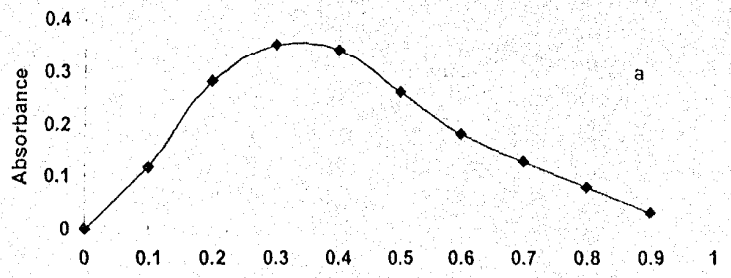


Concentration (µg/ml).

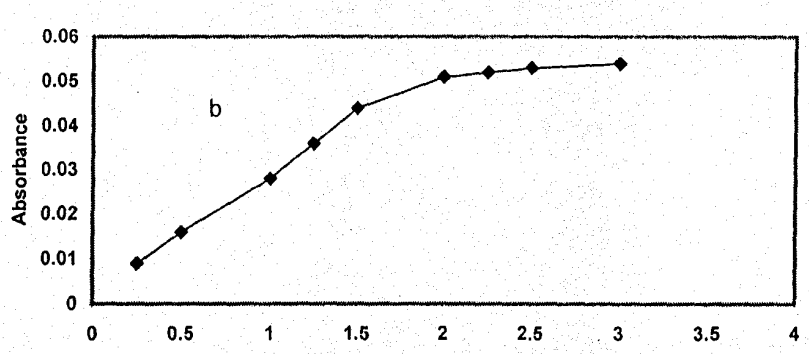
Structure of the dye :-

The stoichiometry of the reaction between metoclopramide and promethazine was investigated using continuous variation and mole ratio methods(14) of equimolar solutions ($4.2x10^{-4}M$) which were indicated that the product was formed in ratio of 1:2 (Fig.3).

Fig(3): Continuous variation (a) and mole ratio (b) plots for reaction of metoclopramide with promethazine (each $4.2x10^{-4}$ M) .

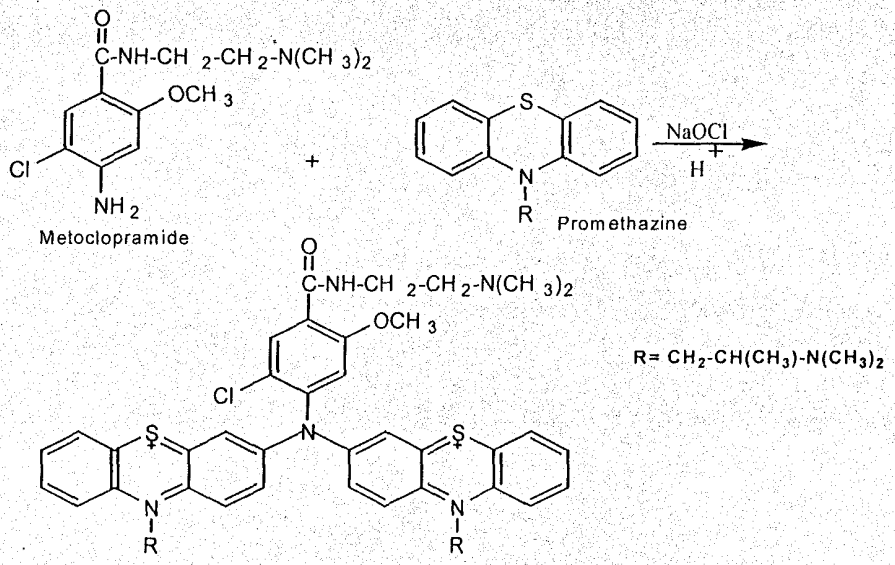


Metoclopramide]/[Metoclopramide]+[Promethazine]



Mole ratio of [promethazine]/[Metoclopramide]

Therefore the formation of the product probably occurs as follows.
Scheme 1.



Scheme.1. Probable product formation pathway

Apparent stability constant of the product: -

The conditional stability constant of the product can be estimated by using vargas method (15).The stability constant (mean of five values) is found to be 1.64×10^{9} $L^{2}.mol^{-2}$,indicating that the product is stable

Effect of interferences: -

The interfering effects of foreign species that often accompany with metoclopramide in pharmaceutical preparations were studied by adding different amounts of foreign species to 450µg/25ml of metoclopramide in solution and the recommended procedure for the determination of metoclopramide was followed. The species are considered to interfere seriously if they cause a change of more than 5% in the recovery percentage obtained for metoclopramide alone (16). It was observed that the starch ,lactose, magnesium stearate, methyl hydroxy benzoate, propyl hydroxy benzoate ,sodium saccharin and citric acid don't interfere with the determination method at levels found in dosage form. So that the selectivity of method is very good.

Analytical application: -

Four types of drugs containing metoclopramide hydrochloride (tablet, injection, syrup and mouth drop) had been analyzed .The results obtained in Table [2] showed that the found amount of metoclopramide in pharmaceutical preparation by both present and official method (13) agrees closely with the amount of metclopramide on the certified value.

Table [2]: Assay of metoclopramide hydrochloride in pharmaceutical preparations

by the proposed method and official method.

Pharmaceutical preparation supplied by NDI	Amount of metoclopramide .HCl*		
	Present method	B.p(official methodl)	certified value
Meclodine(tablets)	4.9	4.9	5mg/tablet
	9.9	9.8	10mg/tablet
Meclodine(syrup)	5.06	5.1	5mg/5cc
Meclodine(mouthdrops)	4.1	4.12	4mg/1cc
Meclodine (injection)	9.96	9.92	10mg/amp

*Mean of five determinations

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