Spectrophotometric Micro Determination of Promethazine Hydrochloride in Pharmaceutical Dosage forms Via Oxidative Coupling Reaction with P-Aminobenzoic acid and N-Bromosuccinimide

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Abstract

A simple, accurate and sensitive spectrophotometric method for the determination of promethazine.HCl has been developed. The method is based on the oxidative coupling reaction of promethazine.HCl with P-aminobenzoic acid and in the presence of N-bromosuccinimide to form an intense bluish-green water soluble dye that is stable and has a maximum absorption at 600nm.A graph of absorbance versus concentration shows that Beer's law is obeyed over the concentration range of 50-750 μg of promethazine.HCl in a final volume of 25ml.(i-e 2-30ppm) with a molar absorptivity of $1.0*10^4$ L $mol^{-1}cm^{-1}$, a recovery% of 98.10-101.00 and a relative standard deviation of better than 1.2% depending on the concentration .The optimum conditions for full colour development are described and the proposed method was applied satisfactorily to the pharmaceutical dosage forms.

Introduction

Promethazine.HCl[10-2-dimethylaminopropyl)phenothiazine] is a phenothiazine derivative and is extensively used as tranquilliser and anti-histaminics in various dosage form (1). Several titrimetric (2) , spectrophotometric (3) , polaroqraphic (4) , qas chromatographic (5) and High-performance liquid chromatograply (HPLC) (6) methods for the determination of promethazine . HCl have been described. The official methods (7) generally include non -aqueous titration for bulk drugs and an ultraviolet spectrophotometric method for dosage forms.

Oxidative coupling organic reactions seems to be one of the most popular spectrophotometric methods for the determination of several drugs such as sulphonamids (8) paracetamol (9) , phenylphrine . HCl (10) , methyldopa (11) and folic acid (12).

The objective of the investigation reported in this paper was to evaluate a spectrophotometric method for the determination of promthazine . HCl based on the reaction of promethazine . HCl with p -aminobenzoic acid in the presence of N-bromosuccinimide as oxidizing agent. A stable water soluble bluish-green coloured product was formed which can be measured at 600nm .The method dose not require temperature control or solvent extraction and can be applied successfully to pharmaceutical dosage forms containing promethazine . HCl.

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Procedure

In to aseries of 25ml calibrated flask,transfer increasing volumes of promethazine.HCl solu tion(100µgml^{-1}).Add 3ml of 2*10^{-3}M of N-bromosuccinimide solution and shake well ,followed by 2 ml of 4*10^{-3}M of p-amino benzoic acid solution .Dilute the solution to the mark with distilled water and allow the reaction mixture to stand for 30 min at room temperature.Measure the absorbance at 600nm against a reagent blank prepared in the same way but containing no promethazine .Hcl .
The colour of the formed dye is stable for about 120 min.For the optimization of conditions and in all subsequent experiments, a solution of 500 µgml^{-1} promethazine.Hcl was used and the final volume was 25ml.

Experimental

Apparatus

All spectral and Absorbance measurements were carried out on a Shimadzu UV-visible- 260 digital double beam recording spectrophotometer using 1 cm silica cell.

Reagents

All chemicals were of analytical reagent grade unless other wise stated. promethazine.HCl standard material was provided from the state company for drug industries and medical appliances (SDI) Sammara-Iraq.Histazine tablets and syrup were obtained from the united pharmaceutical M .Fg.co. Amman,Jordan.

Promethazine hydrochloride stock solution. (500 µg ml^{-1}).

A 0.0500 gm . amount of promethazine.HCl was dissolved in distilled water; the solution was then made up to 100ml in volumetric flask with distilled water. More dilute solutions were prepared by simple dilution with distilled water.

N-Bromosuccinimide solution. (10^{-2} M).

Prepared by dissolving 0.1779 gm of N-bromosuccinimide in distilled water and made up to 100 ml volumetric flask with distilled water. More dilute solutions were prepared by simple dilution with distilled water

P-Aminobenzoic acid solution. (4×10^{-3} M).

Prepared by dissolving 0.0540 gm of P-aminobenzoic acide in distilled water and made up to 100 ml volumetric flask with distilled water .

Procedure

In to aseries of 25ml calibrated flask,transfer increasing volumes of promethazine.Hcl solution (100 µgml^{-1}).Add 3ml of 2*10^{-3}M of N-bromosuccinimide solution and shake well ,followed by 2 ml of 4*10^{-3}M of p-amino benzoic acid solution .Dilute the solution to the mark with distilled water and allow the reaction mixture to stand for 30 min at room temperature.Measure the absorbance at 600nm against a reagent blank prepared in the same way but containing no promethazine .HCl . The colour of the formed dye is stable for about 120 min.For the optimization of conditions and in all subsequent experiments, a solution of 500 µgml^{-1} promethazine.HCl was used and the final volume was 25ml.

Procedure of pharmaceutical preparations

Tablets:

Each tablet containing 25 mg of promethazine.Hcl weigh and finally powdered 10 tablets, extract and accurately weighed portion of the powder equivalent to a bout 0.0500 gm of drug and dissolved in distilled water, shake and filter the solution into 100 ml volumetric flask and wash the

resi due with distilled water and dilute to volume with distilled water to obtain (500 ppm) solution of the drug .A concentration of 100 ppm of the drug was prepared by simple dilution of the above solution with distilled water.

Syrup: (1mg ml^{-1})

Each 1 ml of syrup containing 1 mg of promethazine.HCl. Transfer 50 ml of the syrup solution to a 100 ml volumetric flask and diluted to 100 ml with distilled water to obtain (500 ppm) solution of promethazine.HCl. More dilute solutions were prepared by simple dilution with distilled water.

Results and Discussion

Absorption spectra:

When a very diluted aqueous solution of promethazine.HCl was mixed with P-aminobenzoic acid reagent and oxidized with N-bromosuccinimide an intense bluish-green colour forms after 5 min, which became stable after 30 min.The colour has a maximum absorption at λ max 600 nm. Fig (1) shows the spectra of the bluish-green colour formed (A) and of the reagent blank (B)

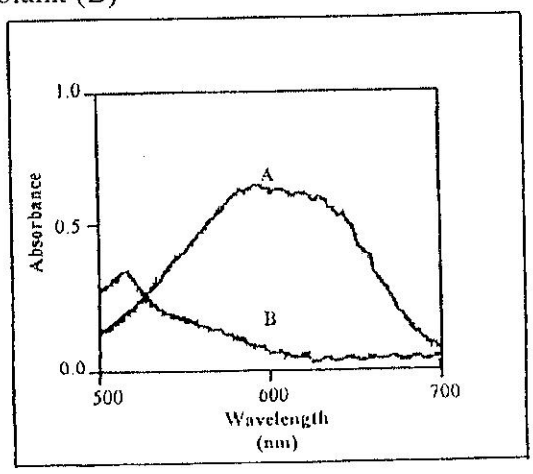


Fig.1 Absorption spectra of A (20 µg/ml) of promethzine.HCl treated as described under procedure and measured against reagent blank and B the reagent blank measured against distilled water.

Study of the optimum reaction conditions:

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

Effect of reagent concentration:

When various concentrations of P-aminobenzoic acid solution were added to a fixed amount of promethazine.Hcl, 2ml of ($4*10^{-3}$M) solution was found enough to develop the colour to its full intensity and give a minimum blank value and was considerd to be optimum.

Effect of oxidant concentration:

The dye formation reached maximum with about 3ml of ($2*10^{-3}$M) of N-bromo succinimide solution, therefore, a 3 ml of N-bromosuccinimide solution was used in the procedure since it gives high sensitivity, minimum blank value and ensure a quatitative determination at the upper limit of the calibration graph.

Effect of reaction time

The colour intensity reached maximum after drug had been reacted with P-amino benzoic acid and N-Bromosuccinimide for 30 min, therefore, a 30 min development time was selected as optimum in the general procedure.The colour obtained was stable for 120 min.

Effect of the order of the addition

To obtain optimum results the order of addition of reagents should be followed as given under the procedure, otherwise a loss in colour intensity and stability was observed.

Effect of temperature:

The effect of temperature on the colour intensity of the dye was studied. In practice , higher absorbance was obtained when the colour was developed at room temperature (30 ^{0}C) than when the calibrated flasks were placed in an ice-bath at (0 ^{0}C) or in a water-bath at (60 ^{0}C) therefore it is recommended that the colour reaction should be carried out of room temperature (30 ^{0}C).

Calibration graph

Employing the conditions described in the above procedure, a liner calibration graph for promethazine.HCl was obtained (Fig.2),which shows that beer's law is obeyed over the concentration range of (2-30 µg/ml) with a correlation coefficient of 0.9984

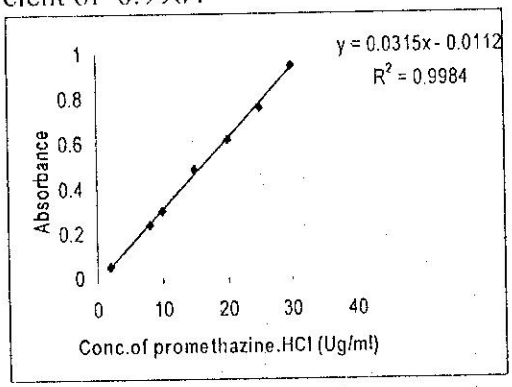


Fig.2 Calibration graph for promethazine.HCl.

Accuracy and precision:

To determine the accuracy and precision of the method, promethazine.HCl was determined at three different concentrations.The results obtained are shown in table (1). It indicated that a satisfactory precision and accuracy could be obtained with the proposed method.

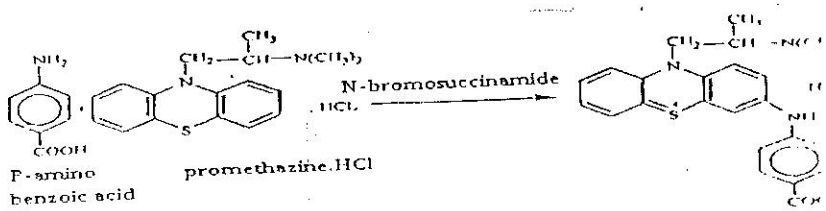
Table.1 Accuracy and precision of the proposed method

Promethazine .HCl (µg/ml)	Recovery ,%*	RSD,%*
10	98.10	1.00
20	99.20	0.50
30	100.50	0.16

* Average for five determinations.

Structure of the dye

The stoicheiometry of the reaction was investigated using molar ratio method (13). The results obtained (Fig.3) shows a 1:1 drug to reagent product was formed at 600 nm and agreed well with the literature(8). The formation of the dye may probably occur as follows:



The dye formed is soluble in water. The apparent stability constant was calculated by comparing the absorbance of a solution containing stoichiometric amounts of promethazine.HCl and P-aminobenzoic acid with that of a solution containing five-fold excess of P-aminobenzoic acid. The average conditional stability constant of the dye in water under the described experimental conditions was $1.7*10^7$ molc/L

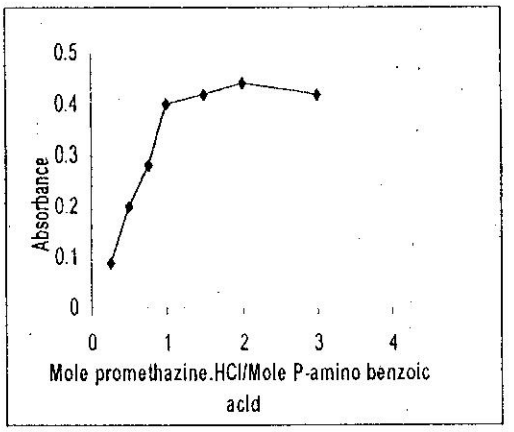


Fig.3 Study of the mole ratio of the reaction between promethazine.HCl and P-aminobenzoic acid

Analytical application

Histazine drug tablets and histazine syrup containing promethazine.HCl has been analyzed and it is gave a good accuracy and precision (table 2) The proposed method was compared successfully with British Pharmacopoeia(7) standard method (table 2).

Table 2. Application of the proposed and official methods to the determination of promethazine.HCl in its dosage forms.

Drug form	Proposed method Recovery,%*	RSD,%*	Official Method Recovery,
Histazine Tablet	99.80	0.83	99.10
Histazine Syrup	101.0	1.20	98.50

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التقدير الطيفي لدواء البروميثازين هيدروكلوريد في المستحضرات الصيدلانية بوساطة تفاعل الإزدواج التاكسدي مع P- امينو حامض البنزويك و N-بروموسكسين أماید

لؤي قاسم عبد الرحمن، انس مؤيد العباجي ، ميادة القيسي

الخلاصة

تم تطوير طريقة بسيطة وحساسة لتقدير دواء البروميثازين هيدروكلوريد في المحاليل المائية والمستحضرات الصيدلانية. تتضمن الطريقة مفاعلة البروميثازين هيدروكلوريد مع بارا امينو حامض البنزويك وبوجود بروموسكسين اماید كعامل مؤكسد لتكوين صبغة زرقاء مخضرة مستقرة وذائبة في الماء اعطت اقصى إمتصاصية لها عند طول موجي 600 نانوميتر. طبق قانون بير في المدى الخطي بين 50 إلى 750 مايكروغرام/25 مل (2-30 جزء بالمليون) وبمعامل إمتصاصي مولاري مقداره 10000 لترمول$^{-1}$ سم$^{-1}$. بلغت قيمة الإسترداد المئوي بين 98,1 -101 وقيمة الإنحراف القياسي النسبي المئوي افضل من 1,2 % . تم دراسة الظروف المثلى للتفاعل وطبقت الطريقة المقترحة بنجاح على المستحضرات الصيدلانية الحاوية على دواء البروميثازين هايدروكلوريد.