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Spectrophotometric Determination of Promethazine Hydrochloride in bulk powder and in its dosage forms

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A simple spectrophotometric method for the determination of promethazine hydrochloride is described. The method is based on the oxidation of promethazine hydrochloride with acidic potassium permanganate to liberate formaldehyde which reacts *in situ* with acetylacetone in presence of ammonium acetate to give a colored product exhibiting maximum absorbance at 412 nm. The Lambert-Beer's law is obeyed in the concentration range of 10-80 µg of promethazine hydrochloride per ml of reaction mixture. The results obtained are comparable with those obtained by official methods.

Phenothiazine derivatives are one of the most important group of drugs. Promethazine, a phenothiazine derivative is used as antihistaminic, antiemetic and as a tranquillizer. Various methods employed for the estimation of promethazine hydrochloride are reviewed by Blazek[1] and Fairbrother[2]. The Pharmacopoeial methods are based on UV spectrophotometry and nonaqueous titrimetry[3,4]. The spectrophotometric methods[5-14] are based on the measurement of color chromogen obtained on oxidation of promethazine hydrochloride. Various colorimetric methods involved in the estimation of phenothiazine moiety are based on its reaction with molybdophosphoric acid[5], molybdoarsenic acid[6], chloramine T[7], Van Urk's reagent[8], acid dye,[9], Pd (II)[10], Ce (IV)[11], Fe (III)[12] and N-bromosuccinimide[13].

The method developed in this investigation is based on the oxidation of promethazine hydrochloride with acidic potassium permanganate to liberate formaldehyde which reacts *in situ* with acetylacetone in presence of ammonium acetate to give a yellow colored chromogen with λ_{max} 412 nm. Reaction conditions were optimized to obtain the maximum color intensity. The results are in good agreement with those obtained by official procedures. The method is applied successfully to the analysis of this drug from the dosage forms.

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EXPERIMENTAL

Double beam Beckman Model 25 spectrophotometer having two matched cells with 1 cm light path was employed for the spectral measurements. Constant temperature water bath (Townson and Mercer Ltd. England) was used to control temperature of reaction mixture at required level. Promethazine hydrochloride B.P., potassium permanganate (Glaxo), sodium thiosulphate (Glaxo), sulphuric acid (98%w/w, sp.gr. 1.84, (Glaxo), acetylacetone (Freshly distilled), ammonium acetate (Excel R), glacial acetic acid (aldehyde free, SD's) and double distilled water were also used in the study. The dosage forms of promethazine hydrochloride were procured from local market.

Sulphuric acid (5.3 ml) was measured accurately and mixed with water and diluted to 1000 ml with water. Potassium permanganate (3.16 g) was weighed accurately and dissolved in and diluted to 1000 ml with water. Sodium thiosulphate (250 g) was dissolved in and diluted to 1000 ml with water. A coloring reagent solution was prepared by mixing ammonium acetate (300 g) with freshly distilled acetylacetone (10.0 ml) in water (800 ml). The

Table 1 - Analysis of Promethazine Hydrochloride in Powdered form and in its dosage forms

Sr. No.	Formulations of Promethazine hydrochloride	Strength in mg	% Recovery[a]	
			Proposed method	B.P. method
1.	Powder		98.28 ±1.13*	98.71 ±0.87*
2.	Tablets			
	i	10	99.15 ±1.02*	98.95 ±0.85*
	ii	25	99.78	99.51
3.	Injection	25 mg/ml	101.70	101.73

a : Average value of five determinations, * Avg ± SD

final volume was adjusted to 1000 ml with water and the solution was kept in a refrigerator. Promethazine hydrochloride (50.0 mg) was weighed accurately and dissolved in dilute hydrochloric acid solution (5.0 ml) and diluted to 100 ml with water. The final solution contained 500 µg of promethazine hydrochloride per ml of the solution.

Assay procedure

Standard promethazine hydrochloride solution (2.0 ml) was pipetted out in to 25 ml volumetric flask. Sulphuric acid solution (2.0 ml) potassium permanganate solution (1.25 ml) were added to it. The reaction mixture was allowed to stand for 3 minutes at 37°. Sodium thiosulphate solution was added dropwise till the reaction mixture became colorless. The reagent solution (5.0 ml) was added to it and mixed thoroughly. The reaction mixture was immersed in a water bath at 37° for 30 minutes. The volume was adjusted to the mark with water. The absorbance of the colored solution was measured at 412 nm against reagent blank.

Promethazine hydrochloride (50.0 mg) was weighed accurately and dissolved in dilute hydrochloric acid solution (5.0 ml) and diluted to 100 ml with water. The solution (2.0 ml) was analysed as described in the assay procedure. The amount of promethazine hydrochloride was determined from calibration curve (Table 1).

Analysis of promethazine hydrochloride from tablets

Twenty tablets were weighed and powdered. The powder equivalent to 50 mg of promethazine hydrochloride was weighed accurately and treated with dilute hydrochloric acid (5.0 ml) and water (50.0 ml). The reaction mixture was shaken for 15 minutes and the mixture filtered through Whatman filter paper No. 40 and the residue was washed thoroughly with water. The filtrate and washings were combined in a 100 ml volumetric flask and diluted to the mark with water. The solution (2.0 ml) was analysed as described in the assay procedure.

Analysis of promethazine hydrochloride from injection

The injection solution was diluted suitably with water to contain promethazine hydrochloride equivalent to 500 µg/ml of the solution. An aliquot (2.0 ml) was analysed as described in the assay procedure.

RESULTS AND DISCUSSION

It is known that potassium permanganate oxidises N-methyl group to formaldehyde[15]. Promethazine contains an N-methyl group in its side chain which can be oxidized with acidic potassium permanganate to liberate formaldehyde. The liberated formaldehyde is determined by acetylacetone reagent. The yellow colored product obtained exhibit maximum absorbance at 412 nm.

During preliminary studies it was observed that the precipitate of manganese dioxide and the color of unreacted potassium permanganate interfere in the color development with reagent. In order to overcome the interference, various reducing agents including sodium metabisulfite, hydrogen peroxide, ascorbic acid and sodium thiosulphate were used. All were found to be effective for the removal of above interference, however, studies on effect of these reducing agents on colored

product, 3,5-diacetyl-1,4-dihydrolutidine showed that only sodium thiosulphate is suitable for the reaction. Other reducing agents reduce the color intensity of the product.

Various reaction conditions, viz. concentration of sulphuric acid solution, potassium permanganate solution, reagent solution, time required for oxidation and maximum color development were optimized to obtain maximum color intensity. The color remained stable for more than two hours. The method of least square was employed to fit a mathematical equation to the analytical data. The Lambert-Beer's law was obeyed in the concentration range of 10.0 to 80.0 µg of promethazine hydrochloride per ml of the reaction mixture (r = 0.999). The equation of straight line was found to be y=0.01x-0.0057.

Pure sample of promethazine hydrochloride was analysed by the proposed method. The results are in good agreement with those obtained by pharmacopoeial method[4] (Table-1). The proposed procedure was applied to assay promethazine hydrochloride in the dosage forms. The results obtained compare favourably with labelled amount of the drug as well as with those obtained by pharmacopoeial methods[4]. None of the usual diluents, lubricants and solvents employed in the preparation of the dosage forms were found to interfere in the proposed procedure (Table-1). The proposed method, hence, is specific, precise, accurate and reliable.

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