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Original Article

Flame Emission and Molecular Absorption Spectrophotometric Determination of Promethazine Hydrochloride via Potassium Dichromate as Oxidant Reagent

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ABSTRACT

Two simple, rapid and sensitive Flame Atomic Emission and Molecular Absorption Spectrophotometric method for determination of trace amount of promethazine hydrochloride in pure and its pharmaceutical preparations were described. The methods were based on the oxidation of promethazine hydrochloride by potassium dichromate in acid solution to form an intense yellow soluble product and in first method the intensity emission measured of potassium at emission line of potassium 766 nm using flame emission spectrophotometer, the second methods used Molecular Absorption UV-Vis for oxidant reagent potassium dichromate at λmax. 440 nm. Beer's law is obeyed over the concentration range of 1-18 µg/mL for two methods, and relative standard deviation RSD% were (1.01, 1.29), and (1.37, 1.45), for tablets and injections in first and second methods respectively. The two proposed methods have been successfully applied for the determination of promethazine hydrochloride in bulk drug and pharmaceutical formulations. The common excipients and additives did not interfere in these methods.

Keyword: promethazine hydrochloride, Flame Atomic Emission, Molecular Absorption Spectrophotometry.

INTRODUCTION

Promethazine hydrochloride , (2RS) – N , N-dimethyl -1- (10H-phenothiazine-10-yl) propan-2-amine hydrochloride or N ,N,α-Trimethyl-10H-Phenothiazine-10-ethanamine or 10 (2-dimethylaminopropyl) phenothiazine is commonly known as neuroleptic tranquilizer and commonly used as a sedative, antihistamine, antiemitic ,anaesthetic, and psychic sedative ,molecular formula $C_{17}H_{29}N_2S.HCl$, C=71.79%, H=7.09%, N=9,85%, S=11.27% ,another names Atosil, Fenazil, Fenergan, Lergigan, Phenergan, Promantine. Protazine and Prothazine ,crystals from ethylene chloride ,turns blue on prolonged exposure to air and moisture ,mp 230-232°C (some decomposition), absorption maximum 249 nm , freely soluble in water , slightly acid to litmus, pH for 10% solution 5.3 ,soluble in alcohol, chloroform, practically insoluble in acetone ,ether, ethyl acetate ,LD_{50} s.c. in rates :400 mg/kg (Fig.1) [1-3]. The vital importance of this drug prompted the development of various analytical methods for its determination. These methods include nephelometric titration for precipitation promethazine with tetra phenyl boron [4].

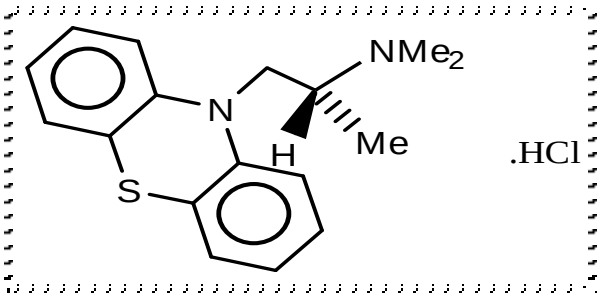

Figure 1: Structure of promethazine hydrochloride

Flow injection spectroelectroanalytic determination of promethazine hydrochloride is based on the in situ detection of a coloured cationic radical formed during electroxidation at a gold electrode in sulfuric acid medium (0.1 mol /L) [5]. Resonance Rayleigh scattering In a weak acidic medium, promethazine hydrochloride reacted with Pd(II) to form cationic chelate, it further reacted with Na_2WO_4 by virtue of electrostatic attraction and hydrophobic force to form 1:1 ternary ion-association complex [6]. Capillary zone electrophoreses for determination of structurally related phenothiazines with Micellar Electrokinetic Chromatography [7].

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Determination of thiazinamium, Promazine and Promethazine in Pharmaceutical Formulations by also CZE [8]. Fluorimetric Determination of Promethazine by a Stopped-Flow Mixing Technique [9]. Turbidimetric Determination of Promethazine Hydrochloride with Bromophenol Blue with Flow Injection Analysis [10]. Beside the spectrophotometric methods which included charge-transfer complex formation reactions by using chloranil [11] and chloranilic acid [12], as π-acceptors reagents in organic medium, or by extractive spectrophotometric determination using dipicrylamine and picric acid reagents for the determination of promethazine hydrochloride [13]. Spectrophotometric determination by atomic absorption spectrometry, the formation of promethazine reineckat ion-association complexes allows an indirect determination of low concentrations of this drug by atomic absorption spectrometry. The AAS measurement is based on the determination of the chromium content of the reineckate counter-anion [14].

Two methods for the estimation in pharmaceutical dosage form, the methods are based on the formation of chloroform extractable complex of Promethazine Hydrochloride with Bromothymol Blue and bromocresol green [15]. An flow injection spectrophotometric method for the assay of promethazine was developed using cerium (IV) as an oxidant [16]. An indirect titrimetric method and an indirect spectrophotometric method for the determination of six phenothiazine drugs using chloramine-T as an oxidant are described [17]. Two spectrophotometric methods for quantitative determination of paracetamol and promethazine hydrochloride in tablet dosage form, the absorption maxima were found to be at 244 nm and 254 nm in distilled water for both the drugs [18].

A new procedure for determination Promethazine HCl in phosphate buffer saline pH 7.4 [19]. Spectrophotometric techniques were developed for the determination of single and binary mixture Promethazine hydrochloride and Paracetamol by Normal and first derivative spectroscopy [20]. Spectrophotometric determination of Chlorpromazine HCl in pure and pharmaceutical formulations based on the formation of violet color product as a result to interaction of mentioned drug with P-amino acetanilide as new chromogenic reagent in the presence of ferric chloride hexahydrate [21].

In this work, a flame emission and molecular absorption spectrophotometric methods for the determination of promethazine hydrochloride were proposed and based on its oxidation by potassium dichromate and then determination of the potassium ion content of the potassium dichromate in flame photometry and molecular UV-Vis absorption for potassium dichromate . The proposed method was applied to determine the promethazine hydrochloride in its drug formulations including tablet and injection and satisfactory results were obtained in comparison with official method of British Pharmacopoeia.

EXPERIMENTAL

Apparatus:

1-Flame emission spectrophotometer (CORNIN G400) was used for emission measurements.
2- Double-beam UV-Visible spectrophotometer: Varian Gary 100 UV-Vis spectrophotometer.
3- Analytical balance: DENVER Instrument Max 220 gm, d=.0001g.

Reagents: All chemicals used were for analytical reagent grade and promethazine hydrochloride standard material was provided from State Company for Drug Industries and medical appliance (SDI) Samarra-Iraq. Distilled water was used throughout the experiment.

Promethazine Hydrochloride (1000µg/mL): A stock solution of 1000 µg/mL of promethazine hydrochloride was prepared by dissolving of 1g in distilled water and then made up to 1000 mL in volumetric flask with the same solvent. The working solution of 100 µg/mL was prepared by simple dilution of stock solution and kept protected from sun light in ambient bottle.

Potassium dichromate (0.003 mol/L): Potassium dichromate solution prepared by dissolving 0.8825 gm potassium dichromate in 1000 mL of distilled water.

Sulphuric acid (8 mol/L): Sulphuric acid solution prepared by diluting of 44 mL of concentrated sulphuric acid (94%, Sp.gr. =1.84) to 100 mL with distilled water.

Proposed procedures: After a 5.0 mL aliquot of promethazine hydrochloride solution containing 1-18 µg/mL was transferred into a 100 mL conical flask and 10 mL of 8 mol/L sulfuric acid was added. The dichromate solution (0.003 mol/L) was added slowly from a 10 mL burette with continuous stirring by a magnetic stirrer. At first, a purple color developed, and the titration was continued until the color completely disappeared after that the intensity of potassium was measured against a reagent blank. Based on the intensity of potassium at 766 nm in the first method. In the second method the absorbance of potassium dichromate was measured at λmax 440 nm, the

amount of the promethazine drug were calculated according two procedures.

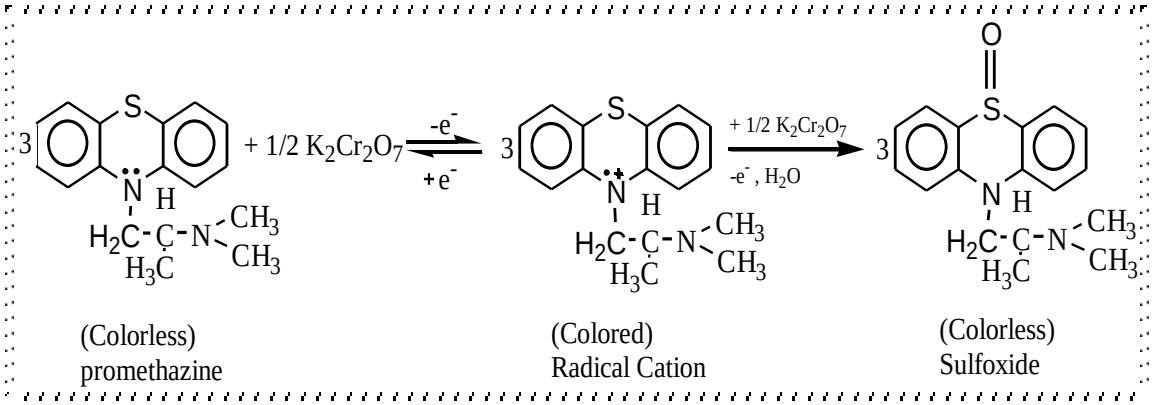
Procedure for assay of promthazine hydrochloride in pharmaceutical preparations:

Tablets (10 mg per unit): Twenty tablets were weighed and ground into a fine powder. An amount of powder equivalent to about 200 mg of the pure drug was weighed. The powder was extracted with three 30 mL portions of water and filtered into a 100 ml volumetric flask. The filtrate was washed and diluted to the mark with distilled water. An aliquot of this solution was analyzed by the two procedures detailed above.

Injections (25 mL per unit): The contents of twenty ampoules were mixed. After an a accurately measured volume equivalent to 20 mL of pure drug was transferred into a 100 mL standard flask and completed to the mark with distilled water, an aliquot was analyzed as was done for tablets.

RESULTS AND DISCUSSION

The proposed method is based on the fact that potassium dichromate in an acid medium directly oxidizes promethazine hydrochloride first to colored promethazininium free radicals and finally to colorless sulfoxide after that the intensity of potassium ion content of the potassium dichromate was measured against a reagent blank. The oxidation of promethazine hydrochloride is generally represented by scheme (1) based on the mechanism adopted from [22-23].



Scheme (1): Reaction scheme of promethazine hydrochloride

The number of moles of dichromate consumed per mole of the drug was 0.333, in conformity with the formation of sulphoxides [24] as illustrated in scheme above (1).

Estimation of optimum conditions: Three parameters affected on measurement were studied in this work.

Oxidant reagent concentration effect: It was found that a 0.003 mol/L solution of potassium dichromate was recommended for all measurements, as illustrated in figure (1) bellow.

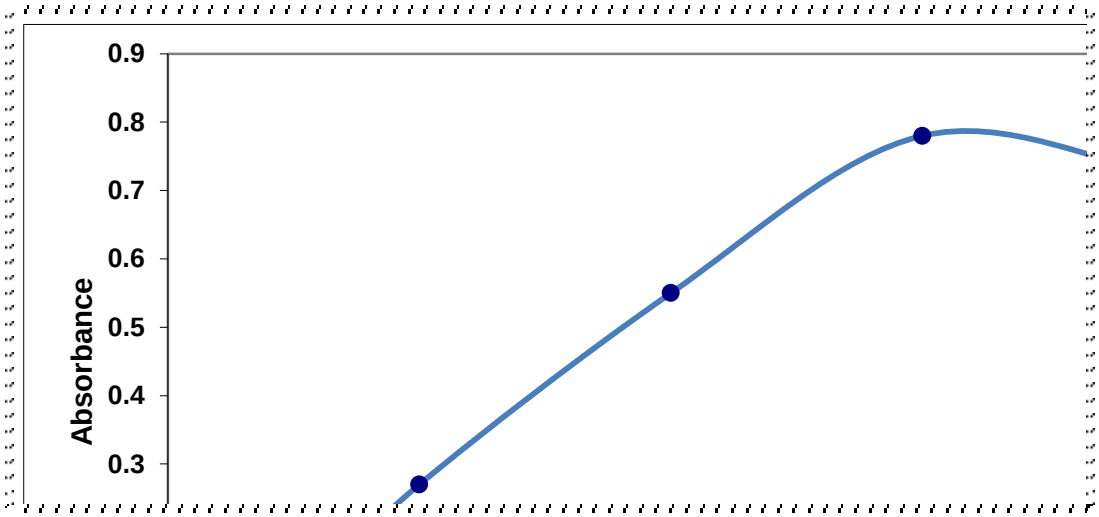


Figure (1): Effect of oxidant concentration on the absorbance of promethazine hydrochloride using the proposed method.

Strength of sulphuric acid effect: When various concentrations of sulphuric acid solution were added to fixed amount of the drug solutions, 10 mL of 8 mol/L solution was found enough to produce the higher absorbance and was considered to be optimum for concentration rang 1-18 µg/mL of promethazine hydrochloride, figure (2) showing that.

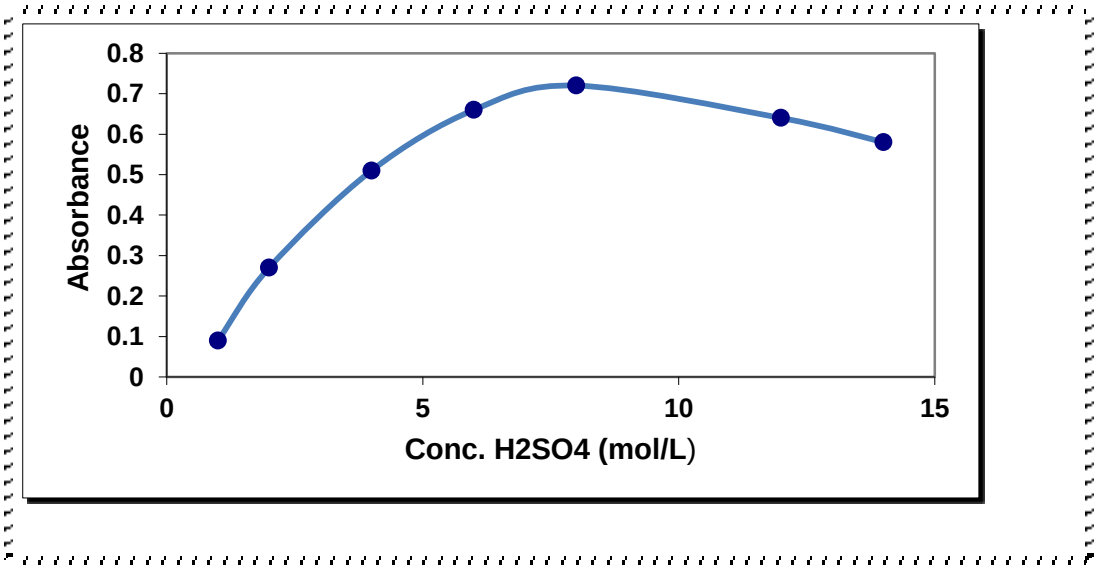


Figure (2): Effect of sulphuric acid concentration on the absorbance of promethazine hydrochloride.

Temperature effect: The results of the proposed methods were studied at different temperatures. The results indicate that the absorbance values reduced after 25 °C. Therefore room temperature (25ºC) is selected in this method, as in figure (3).

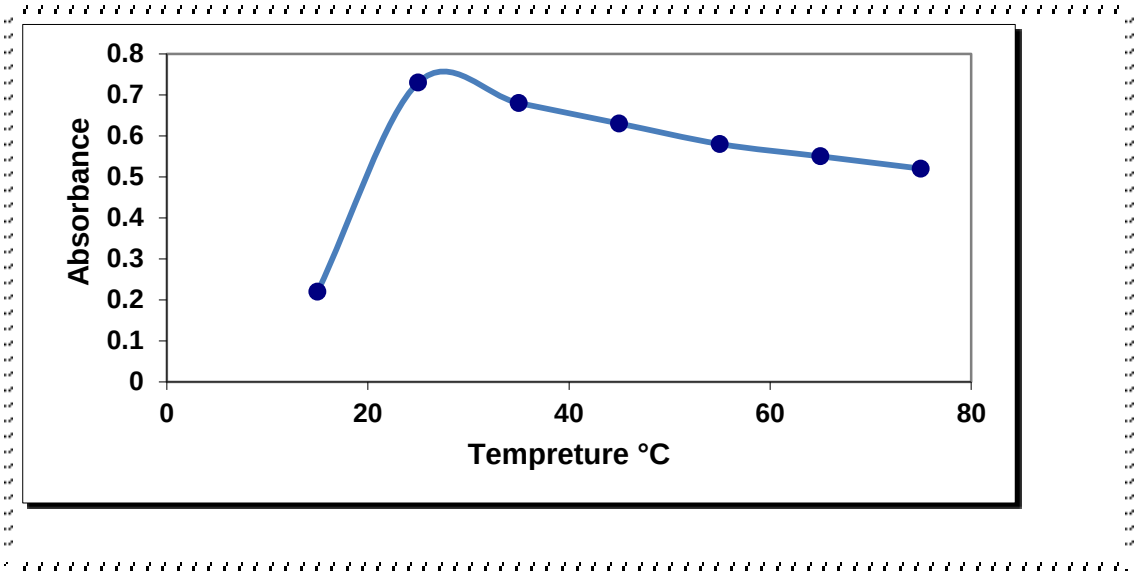


Figure (3): Effect of temperature on the absorbance of promethzine hydrochloride using the proposed method.

Interference: Interference from the common additives and excipients likely to be present with the promethazine hydrochloride in formulations was investigated. Starch, Talc, Dextrose, Gelatin, Stearate and Alginate at the levels found in formulations did not interfere under the described experimental conditions, as shown by the results of the recovery study compiled in table (1).

Employing the conditions described in the procedure, a linear calibration graphs for promethazine HCl were obtained (Figure 2, 3), which shows that Beer's law were obeyed over the concentration range of 1-18 µg/mL with correlation coefficient of 0.9956 , 0.9991and an intercept of +6.5821, -0.0467 for first and second methods respectively .

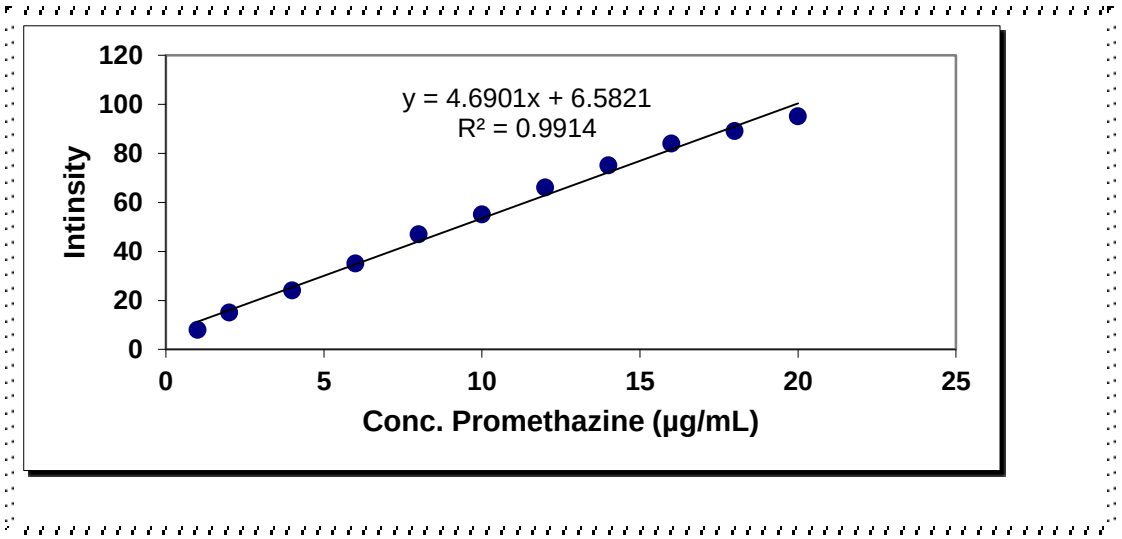


Figure 2: Calibration graph of promethazine hydrochloride by flame emission photometry.

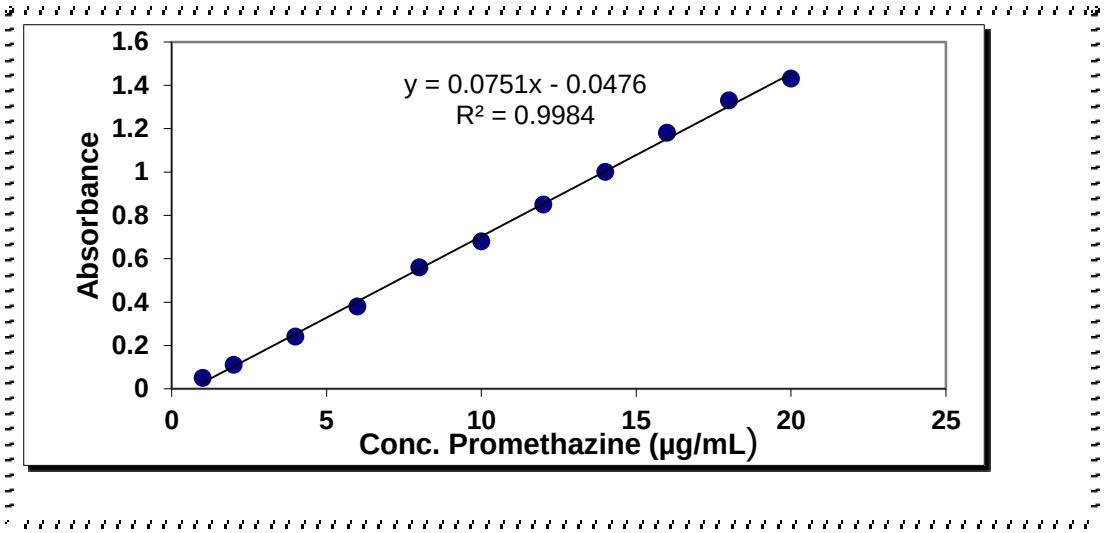


Figure 3: Calibration graph of promethazine hydrochloride by molecular UV-Vis spectrophotometry.

Table (1): Assay of promethazine hydrochloride in pharmaceutical preparation by proposed methods and reference method.

Formulation	Taken (mg)	Reference Method			Proposed Methods		
		S.D	Recovery (%)	Found (mg)	S.D	Recovery (%)	Found (mg)
Phenergan (Tablet)	10	0.72	99.60	9.96	0.62[a], 0.74[b]	98.40[a], 97.07[b]	9.84[a], 9.70[b]
Phenergan (Injection)	25	0.70	98.32	24.58	1.32[a], 1.81[b]	98.16[a], 97.28[b]	24.54[a], 24.32[b]

(a) (b) Indicates for first and second methods respectively.

Table (2): Values of Analytical Data, Correlation Coefficient, Relative Standard Deviation, and Relative Error for two methods with F-test.

Figure of merit	Range (µg/mL)	Regression equation	Corr.Coef. (r)	RSD [(*)](%)	Relative Error (%)	F-test
Flame Photometric method	1-18	Y=4.6901+6.5821	0.9956	1.01[C], 1.29[d]	1.60[c], 1.84[d]	1.42
UV-Vis molecular absorption method	1-18	Y=0.0751-0.0476	0.9991	1.37[c], 1.45[d]	3.00[c] ,2.72[d]	1.88

[(*)] Average of five emission and absorbance measurement for drug.
(c) (d) Indicates for tablet and injection respectively.

CONCLUSION

Although promethazine hydrochloride has been determined by a variety of techniques, the method described here is simple, rapid, accurate and sensitive flame emission spectrophotometric without temperature control or solvent extraction step. Potassium dichromate considered moderately oxidizing agent at acidic medium for oxidize vary chemical compounds, makes its used for determination phenathaiazens drugs such as promethazine hydrochloride by oxidizing to sulfoxides derivatives after formation free radical intermediate compound as showing in scheme (1).

$Cr_2O_7^{-2} + 14H^+ + 6e \Longleftrightarrow 2Cr^{+3} + 7H_2O$ $E°=1.33V(1.11Vin\ 2M\ H_2SO_4)$ [25]

The proposed methods were applied to the determination of studied drug in their dosage forms. The results in tables (1, 2) indicate that the methods give good accuracy and precision with satisfactory agreement with the results obtained by the official method of British Pharmacopoeia. These methods were applied successfully for determination promethazine hydrochloride in pure or pharmaceutical formulations.

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