

A new spectrophotometric method for the determination of promethazine–HCl from pure and pharmaceutical preparations

Muhammad Jawwad Saif*, Jamil Anwar

Institute of Chemistry, University of the Punjab, Quid-e-Azam Campus, Lahore-54590, Pakistan

Accepted 9 March 2005

Available online 23 May 2005

Abstract

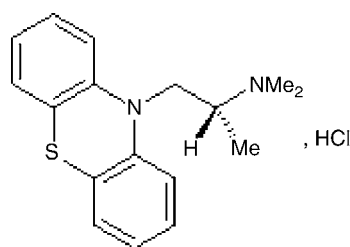
Promethazine–HCl reacts with potassium persulphate to give a pinkish red color complex exhibiting maximum absorbance at 515 nm. The reaction is selective for promethazine–HCl, with 1 µg/mL as visual limit of identification and provides a basis for a new spectrophotometric determination method. The color forming reaction obeys Beer's Law from 0.001 to 0.125 mg/mL of promethazine–HCl. The relative standard deviation does not exceed 0.005 mg/mL. The method is successfully applied to pure and pharmaceutical formulations of promethazine–HCl. The quantitative assessment of tolerable amounts of possible interferants was also studied. The results are reproducible within ±1% and in good agreement with those obtained by the standard procedure.

© 2005 Elsevier B.V. All rights reserved.

Keywords: Promethazine–HCl; Potassium persulphate; Spectrophotometry

1. Introduction

Promethazine–HCl is the generic name of (2*RS*)-*N,N*-dimethyl-1-(10*H*-phenothiazin-10-yl)propan-2-amine hydrochloride.



and enantiomer

It is a white or faintly yellowish, crystalline powder, very soluble in water, freely soluble in alcohol and in methylene chloride [1]. Promethazine–HCl has been reported to be incompatible with solutions of a number of compounds including aminophylline, barbiturates, benzylpenicillin salts, car-

benicillin, heparin, hydrocortisone sodium succinate, morphine sulphate, alkalis, and some contrast media. Adverse effects include bradycardia, tachycardia, transient minor increases in blood pressure and occasional hypotension. Jaundice and thrombocytopenic purpura have also been reported, and extrapyramidal effects may occur at high doses [2].

Many analytical techniques have been employed for the determination of promethazine–HCl. The majority of the titrimetric procedures are based on the redox properties of the *S*-atom. Chloramine-T [3], hexacyanoferrate(III) [4], *N*-bromosuccinimide [5], dibromodimethyl hydantoin [6], hexamine–cobalt(III) tricarbanato cobaltate(III) [7], metavanadate [8], etc., are used as oxidimetric titrants for the determination of promethazine hydrochloride. Numerous spectrophotometric methods have also been described for the estimation of the drug. Most of these are based on the chemical oxidation of promethazine–HCl to the colored radical cation using oxidizing agents [9–13]. Various other methods, like spectrofluorometry [14], HPLC [15], and absorptive stripping voltammetry [16], have also been employed.

Many of these methods are unsatisfactory. The chloramine-T method is partly non-aqueous and not applicable

* Corresponding author.

E-mail address: jawwadsaif@hotmail.com (M.J. Saif).

for micro-determination. The hexacyanoferrate(III) [4] procedure uses 50 mL of syrupy phosphoric acid for each titration besides employing a screening indicator. In a method using *N*-bromosuccinimide [5], the intense purple color of the promethazine radical cation interferes with the color change of the methyl-red screening indicator. Some spectrophotometric methods [9–13] suffer from instability of the colored radical cation and some others require a very long heating time [17,18]. The HPLC technique, though rapid and sensitive, is relatively expensive involving costly instruments and solvents. The stripping voltammetric technique [16] though quite good for the determination of promethazine–HCl at low levels (ng/mL), involves a rigid control of the surface area of the hanging-drop mercury electrode (HMDE). Moreover, the procedure is time consuming due to prolonged deposition and stripping processes. The purpose of this investigation was to develop a simple, rapid, accurate and inexpensive spectrophotometric procedure for the determination of promethazine–HCl in pure and pharmaceutical preparations.

2. Experimental

2.1. Apparatus

A Hitachi U-2000 spectrophotometer with 1 cm silica cells was used for absorption measurements. Graduated pipettes and flasks were employed during the work.

2.2. Reagents

All reagents used were of BDH grade where otherwise not mentioned. Deionized water was used to prepare all the solutions. Freshly prepared solutions were always used. Standard solution (w/v) of promethazine–HCl (1000 $\mu\text{g/mL}$) was prepared by dissolving 100 mg of the drug in distilled water and diluting to the mark with the same in a 100 mL calibrated flask to give a stock solution, which was diluted, further as required. A 2% (w/v) potassium persulphate (BDH) was prepared by dissolving 2.00 g of potassium persulphate in sufficient quantity of distilled water in a 100 mL measuring flask and then volume was made up to the mark with distilled water.

2.3. General procedure

To an aliquot (1 mL) of promethazine–HCl containing 0.01–2.5 mg/mL, 0.5 mL of 2% potassium persulphate was added. A red color resulted which was diluted up to 10 mL with distilled water. The absorbance of this red solution was measured at 515 nm. The experiment was repeated with different concentrations of promethazine–HCl and a calibration curve was plotted. The color reaction obeyed Beer's Law in the concentration range 0.001–0.25 mg/mL of promethazine–HCl.

2.4. Interferences

In order to check the tolerable limits of various possible interferences, different quantities of the interfering compounds were added to an aliquot containing 1 mg/mL of promethazine–HCl and potassium persulphate until the solution showed the same absorbance as that of pure promethazine–HCl solutions (Blank). The interference studies were carried out under all the experimental conditions as described in Section 2.3. The permissive values of interfering compounds were calculated as percentage with respect to the amount of promethazine–HCl.

2.5. Determination of promethazine–HCl

2.5.1. Tablets

Tablets containing 10 and 25 mg of promethazine–HCl were powdered, weighed and dissolved in distilled water. The resulting solution was filtered to separate any suspended particles. The filtrate was diluted further to get 1 mg/mL solution of promethazine–HCl. An aliquot containing 0.01–2.5 mg/mL was treated according to the procedure as described above and the absorbance was measured at 515 nm. The quantity per tablet was calculated from the standard calibration graph of promethazine–HCl.

2.5.2. Syrup

Syrup containing 5 and 1 mg/mL of promethazine–HCl was diluted with distilled water and filtered. If turbidity persisted the contents were centrifuged until a clear supernatant was obtained. After filtration a 1 mg/mL solution of promethazine–HCl was prepared in distilled water. An aliquot containing 0.01–2.5 mg/mL was taken, the above procedure was followed and the absorbance was measured at 515 nm. The quantity of promethazine–HCl per mL of syrup was calculated from the standard calibration graph. The excipients did not show any effect on potassium persulphate.

2.5.3. Injection

To determine the drug in injectable dosage form, the contents per injection were diluted with distilled water to get 1 mg/mL solution of promethazine–HCl. The general procedure was followed using an aliquot containing 0.01–2.5 mg/mL of drug and the absorbance was measured at 515 nm. The quantity per injection was calculated from the standard calibration curve.

3. Results and discussion

3.1. Optimum conditions for complex formation

In order to establish the optimum conditions necessary for a rapid and quantitative formation of the colored product with maximum stability and sensitivity, the absorbance of a series of solutions was measured by varying one parameter

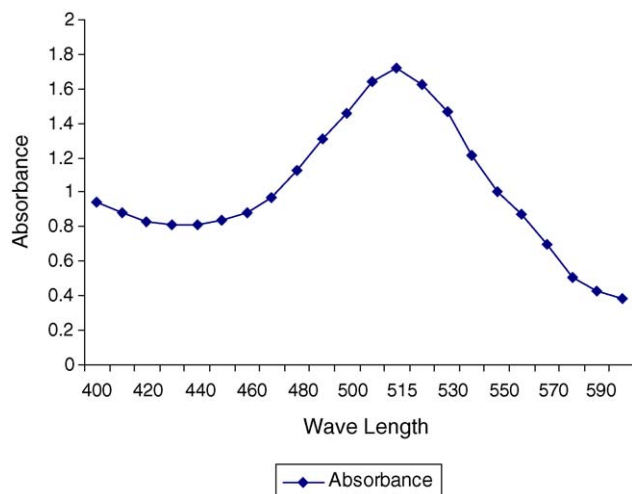


Fig. 1. Absorption spectra of promethazine-HCl with potassium persulphate.

while keeping the others constant at 515 nm (Fig. 1). It was found that 0.5 mL of 2% potassium persulphate was necessary to achieve the maximum color intensity of the product (Fig. 2). Above and below this concentration, the color intensity diminished. The probable mechanism is that potassium persulphate instantaneously oxidizes the PMH at room temperature giving a red colored species that is believed to be a radical cation. Most probably, the excess of persulphate causes an irreversible oxidation of the colored product to a colorless sulphoxide with the loss of one or more electrons.

The red color was found stable in different solvents like water, methanol and ethanol. There was no significant effect of pH on the intensity of the color. However, a sharp decrease in the stability of the colored product with respect to time was observed. The reaction was almost instantaneous. At room temperature, time duration of 5 min was given to complete the reaction. On boiling the solution, the color was slowly diminished. At room temperature (25 °C), the colored product was stable for 12 h and the reproducible results were obtained.

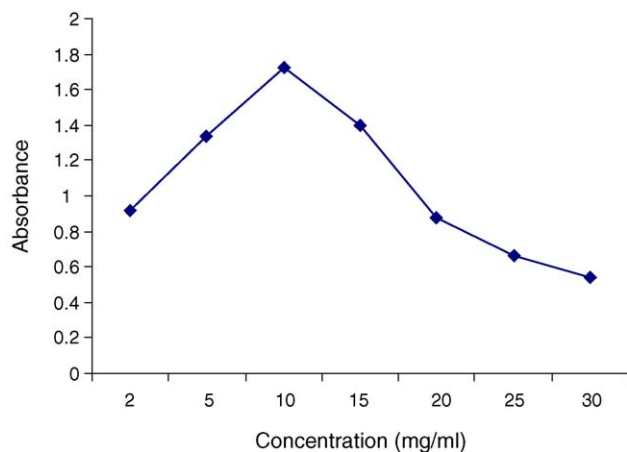


Fig. 2. Effect of potassium persulphate.

Table 1

Optical characteristics, precision and accuracy of the proposed method

Parameters	Results
Wavelength, λ (nm)	515
Beer's Law limit, C (mg/mL)	0.001–0.25
Molar absorptivity ($\text{mol}^{-1} \text{cm}^{-1}$)	0.2207×10^4
Regression equation, Y^a	
Slope, b	–0.0493
Intercept, a	0.505
Correlation coefficient (r)	0.987
Relative standard deviation, R.S.D. ^b (%)	0.67
% Range of error (confidence limits) at 95% confidence level	24.39 ± 0.02

^a $Y = a + bC$, where C is the concentration of analyte (mg/10 mL) and Y is the absorbance unit.

^b Calculated from five independent measurements.

3.2. Quantification, sensitivity, accuracy and precision

The results for the determination of promethazine-HCl are shown in Table 1, which show the sensitivity, validity and reproducibility of the method. It is also reasonably precise and accurate as the amount taken from identical samples is known and the amount found by the above procedure does not exceed the relative standard deviation 0.32%. The low relative standard deviation value and the range of error at 95% confidence level indicated good precision and accuracy of the proposed method.

The calibration graph is linear in the range of 0.001–0.25 mg/mL. The apparent molar absorptivity was

Table 2

Quantitative assessment of tolerable amounts of possible interferents

Possible interfering drug	Maximum amount not interfering ^a (%)
Lorazepam	300
Choral hydrate	125
Buscopan	150
Acetyl salicylic acid	300
Paracetamol	400
Dextromethorphan	200
Paracetamol	350
Fluoxetine-HCl	400
Naproxen	400
Metamezol-Na	250
Brufen	350
Mesoridazine	250
Triprolidine HCl	300
Hydroxyzine-HCl	250
Benzodiazepine	400
Barbituric acid	400
Ibuprofen	350
Mepazine	250
Perazine	250
Sucrose	400
Glucose	400
Lactose	450
Fructose	350

^a The value is the percentage of the drug with respect to 1 mg/10 mL of promethazine-HCl that causes +0.01 change in absorbance.

Table 3
Assay of promethazine–HCl in pharmaceutical preparations

Trade name	Label claim (mg/tablet or mg/mL)	Proposed method			BP method [19]				
		Amount Found (mg)	Recovery (%)	S.D.	Amount found (mg)	Recovery (%)	S.D.	<i>t</i> -Value	<i>f</i> -Value
Diprozine (tablet)	25	25.21	100.84	0.32	25.3	101.2	0.42	0.40	1.72
Diprozine (elixir)	5	5.01	100.2	0.46	4.99	99.8	0.20	0.08	2.69
Melamine (injection)	5	5.02	100.4	0.32	4.98	99.6	0.32	0.11	3.16
Phenergan (tablet)	10	10.04	100.4	0.42	10.01	100.1	0.82	0.05	3.81
Phenergan (tablet)	25	25.51	102.0	0.50	25.42	101.7	0.50	0.30	1.00
Phenergan (injection)	25	25.30	101.2	0.26	25.21	100.84	0.54	0.37	4.33

Average of five determinations.

$0.2207 \times 10^4 \text{ mol}^{-1} \text{ cm}^{-1}$. The regression equation was calculated by the method of least squares from fourteen points, each of which was the average of five independent determinations. The correlation between absorbance and concentration in terms of correlation coefficient (*r*) was 0.987 (cf. Table 1).

3.3. Interferences

The quantitative assessment of tolerable amounts of different organic compounds (w/v) under experimental conditions is given in Table 2. Various amounts of diverse interfering compounds were added to a fixed amount of promethazine–HCl (1 mg/mL) studied and the recommended procedure for the spectrophotometric determination was followed. Other compounds like ibuprofen, metamizol–Na and triprolidine hydrochloride did not show any interference.

3.4. Application of the method

The applicability of the method for the assay of pharmaceutical formulations was examined by employing it for standard samples. The average recoveries obtained by the proposed method ranged from 97% to 100.4% (cf. Table 3), which indicates adequate accuracy and precision. Comparison with the BP method [19] revealed that the proposed method is comparable in accuracy. The excipients like sucrose, glucose, lactose and the color in the tablets and syrup did not interfere with the color or with potassium persulphate.

4. Conclusion

This method is simple, rapid and offers the advantages of high sensitivity and a wide range of determination without the need for heating or extraction. The statistical analyses are in good agreement with those of the British Pharmacopoeia. The method can be applied to micro

determination of promethazine–HCl in pure as well as in pharmaceutical preparations. The other advantages of the present method include low detection limit with high accuracy and precision, freedom from experimental variables, which influence the sensitivity and reliability of the method. The method described in this work for the assay of promethazine–HCl formulations offers a distinct possibility of quality control in the assay of pharmaceutical dosage formulations.

References

- [1] The British Pharmacopoeia, Her Majesty's Stationary Office, London, 1993, pp. 1100.
- [2] J.E.F. Reynold, Martindale the Extra Pharmacopoeia, 28 ed., The Pharmaceutical Press, London, 1982, pp.1294, 1504.
- [3] A.N. Nayak, H.S. Rangaswamy, P.G. Yathirajan, Ramappa, Indian Drugs (1982), 19, 202.
- [4] A.S. Issa, M.S. Mahous, Talanta 31 (1984) 287.
- [5] A.M. Taha, N.A. El-Rabbat, M.E. El-Kommas, Analyst 108 (1983) 1500.
- [6] M.I. Walsh, M. Rizk, A. Abdel-Malik, F. Bilal, Analyst 108 (1983) 626.
- [7] M.I. Walsh, F. Belal, F.A. Aly, Talanta 35 (1988) 320.
- [8] M. Satan, F. Dima, G. Ghimicescu, Rev. Med. Chir. 82 (1978) 337.
- [9] W. Misiuik, M. Tarasiewicz, Pharmazie 51 (1996) 62.
- [10] V.P. Kalashnikov, A.I. Shkadova, T.G. Popova, Farm. Zh. (Kiev) 5/6 (1992) 68.
- [11] L. Kuzmicka, L. Puzanowska-Tarasiewicz, M. Tarasiewicz, Pharmazie 43 (1988) 288.
- [12] M.M. El-Kerdway, S.M. Hassan, S.M. El-Ashy, Mikrochim. Acta 108 (1992) 323.
- [13] H. Puzanowska-Tarasiewicz, J. Karpinskaa, Pharmazie 44 (1989) 35.
- [14] F.A. Mohamed, Anal. Lett. 28 (1995) 2491.
- [15] D. De Orsi, L. Gagliardi, D. Tonelli, J. Pharm. Biomed. Anal. 14 (1996) 1635.
- [16] T. Peng, R. Yang ad, R. Lu, Zhongguo Yaoux Zazhi 25 (1990) 277.
- [17] S.R. El-Shabouri, A.F. Yossef, F.A. Mohammad, J. Assoc. Off. Anal. Chem. 69 (1986) 821.
- [18] M.S. Mahrous, M.M. Abdel Khalek, Talanta 31 (1984) 289.
- [19] Xsc, The British Pharmacopoeia, H.M. Stationary Office, London, 1993, pp. 1902.