Spectrophotometric Promethazine Hydrochloride Determination Using Bromcresol Green

ABDOL-ALI M. EMAMI KHOI

Received May 17, 1978, from the *Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Tehran University, Tehran, Iran.* Accepted for publication October 30, 1978.

Abstract □ A spectrophotometric method was developed for determining promethazine hydrochloride (I) complexed with bromcresol green and then extracted with chloroform. The complex in chloroform showed maximum absorption at 415 nm and obeyed Beer's law over 1.2–8.5 μg/ml. The complex molar absorptivity was 1.93×10^4 *M*. Complex formation and extraction were complete and quantitative over pH 2.7–2.8. The promethazine hydrochloride–bromcresol green molar ratio was 1:1. Excipients, coloring matter, flavoring agents, and other substances likely to be present in promethazine preparations did not interfere in the determination. Direct determination in tablet, syrup, and injection preparations were carried out satisfactorily.

Keyphrases □ Promethazine hydrochloride—spectrophotometric analysis, color complex with bromcresol green, various pharmaceutical formulations □ Bromcresol green—promethazine hydrochloride spectrophotometric analysis, various pharmaceutical formations □ Spectrophotometry—analysis, promethazine hydrochloride, various pharmaceutical formulations □ Antihistaminic agents—promethazine hydrochloride, spectrophotometric analysis, various pharmaceutical formulations

Various methods have been described for promethazine hydrochloride (I) determination. The official nonaqueous USP titration method (1) is not applicable to microgram I determinations. Volumetric (2), ion-exchange (3), chromatographic (4), polarographic (5), gravimetric (6), complexometric (7), and luminescence (8) methods all lack simplicity and sensitivity.

Spectrophotometric methods also have been used for the analysis of the base. Eriochrome black T (9), perchloric acid–nitromethane (10), sodium 1,2-naphthoquinone-4-sulfonate in 50% H_2SO_4 (11), and ferric chloride (12) were employed to create a colored product that could be determined spectrophotometrically. Some of these methods are not simple; others are not sensitive.

This report describes a direct, simple, and sensitive spectrophotometric determination for I. This method is applicable to powder, syrup, injection, and tablet forms. The procedure depends on complex formation between I and bromcresol green (II) which is extractable by chloroform at pH 2.7–2.8. This method can be carried out successfully in the presence of caffeine and many other substances.

Bromcresol green has been used for determining small amounts of long-chain tertiary alkylamines and quaternary ammonium salts (13). It was recently used for the direct determination of thebaine in *Papaver bracteatum* Lindl Arya II papulation capsules (14) and to determine diphenhydramine hydrochloride (15).

Table I—Effect of Other Compounds on the Determination of Promethazine Hydrochloride

Substance	Amount Ratio[a]	Recovery %[b]
Ascorbic acid	50	100.0
Sodium saccharin	250	100.9
Cinnamon oil	10	100.0
Orange oil	60	100.5
Clove oil	70	100.0
Amaranth	120	100.2

[a] The ratio of the amount of substances to promethazine hydrochloride in the determination. [b] Promethazine hydrochloride concentration = 3.2×10^{-4} *M*.

EXPERIMENTAL[1]

Apparatus and Reagents.—All glassware was washed with 0.1 *N* HCl followed by distilled water. All reagents were analytical grade.

Bromcresol Green (10^{-4} M)—Accurately weighed bromcresol green powder was dissolved in 2 ml of 0.1 *N* NaOH, and the volume was brought to 1 liter with citric acid-sodium hydrogen phosphate buffer, pH 2.7–2.8. The resulting solution was adjusted to pH 2.7–2.8.

Promethazine Hydrochloride (10^{-4} M) *Standard*—Accurately weighed, dry, pure promethazine hydrochloride powder USP (32.09 mg) was dissolved in water and diluted to 1 liter.

Buffer Solution—A citric acid–sodium hydrogen phosphate buffer (pH 2.2–2.8) was used (16).

Determination—A solution containing 12–80 μg of I was pipetted into a 100-ml separatory funnel followed by 20 ml of 10^{-4} *M* II, and the two solutions were mixed. The yellow complex that formed was extracted with 5-, 3-, and 2-ml portions of chloroform by vigorous shaking. The extracts were collected in a 10-ml volumetric flask. The volume was adjusted with chloroform, and the absorbance was measured within 0.5 hr against chloroform at 415 nm. The amount of I was calculated by comparison with a standard curve.

RESULTS AND DISCUSSION

The yellow I–II complex in chloroform showed maximum absorption at 415 nm. Complex formation and extraction were complete and quantitative over the pH 2.7–2.8 range citric acid-sodium hydrogen phosphate buffer solution. The complex composition was studied by the molar ratio method (17). The ratio of I to II was 1:1, but the required ratio for complete complexation and quantitative extraction was 1:3.

Eight standard series of six samples, 1.0–9.0 μg I/ml, were analyzed. The optimum concentration range for the measurements at 415 nm and 1.00-cm optical path length was 1.2–8.5 μg of promethazine hydrochloride/ml. The complex solution molar absorptivity in chloroform at 415 nm was 1.93×10^4. The relative standard deviation of the calculated absorptivities in the optimum concentration range was ±1%.

To determine the effect of compounds commonly present with I in pharmaceutical preparations, known volumes of standard solutions containing caffeine (23 mg), sodium gentisate (20 mg), ammonium chloride (20 mg), menthol (90 mg), sodium citrate (20 mg), acetaminophen (200 mg), and alcohol (1 ml) were studied at different concentrations. There was no interference in the determinations. Ascorbic acid, sodium saccharin, cinnamon oil, orange oil, clove oil, and amaranth (Table I) also did not interfere and produced slight deviation in the determination only at high concentrations.

Under acid conditions, most substances with a tertiary amine group or quaternary ammonium salts form yellow complexes with II that are extractable with chloroform. Pharmaceutical I preparation from different manufacturers were free of such substances, so a confirmatory test was not needed.

To test the method validity, I was added to pharmaceutical preparations[2] and determined by the proposed procedure. The recovery (99–100.25%) (Table II) proved the selectivity and specificity of the method for direct I determination in pharmaceutical preparations.

[1] A Beckman DB-GT spectrophotometer with 1.00-cm glass cells, a Bausch & Lomb Spectronic 21, and a Beckman H_3 pH meter were used.

[2] Phenergan tablets, syrup, and injection, France.

0022-3549/83/0600-0704$01.00/0

Table II—Determination and Recovery of Promethazine Hydrochloride (Micrograms) in Pharmaceutical Preparations

Preparation	Present	Added	Determined	Recovery, %
Tablet	37.97	41.76	41.30	99.00
Syrup	30.00	23.64	23.70	100.25
Injection	35.00	32.65	32.70	100.15

ACKNOWLEDGMENT

The author thanks Mr. Rostam H. Maghssoudi for support and encouragement in the preparation of this manuscript.

REFERENCES

(1) "The United States Pharmacopeia," 19th rev. U.S. Pharmacopeial Convention, Rockville, Md., 1975, p. 412.

(2) Z. Kurzawa, L. Balcerkiewicz, and A. Kryzminska, *Chem. Anal. (Warsaw)*, **1974**, 333.

(3) J. Jarzebinski, Z. Zakrezewski, and M. J. Szatynska, *Farm. Pol.* **9**, 335 (1973).

(4) S. Ebel, B. Dobmeier, M. Fick, H. Kussmaul, *Arch. Pharm. (Weinheim, Germany)*, **307**, 878 (1974).

(5) E. Pungor, K. Toth, and M. Papay, *Chem. Anal. (Warsaw)*, **17**, 947 (1972).

(6) J. Blazek and M. Travnickova, *Cesk. Farm.*, **22**, 207 (1973).

(7) B. Dembinski and K. Nowakowski, *Farm. Pol.*, **30**, 423 (1974).

(8) N. Kosta and S. Leposava, *Tehnika (Belgrade)*, **22**, 693 (1967).

(9) F. Pellerin, J. A. Gautier, O. Barat, and D. Demay, *Chim. Anal. (Paris)*, **45**, 395 (1963).

(10) L. G. Chatten and F. D. Semaka, *Can. J. Pharm. Sci.*, **5**, 4 (1970).

(11) H. T. Fawzy, I. A. Saad, and L. N. Gadel-Rub, *Pharmazie*, **28**, 322 (1973).

(12) M. K. Youssef and I. A. Attia, *Indian J. Pharm.*, **37**, 121 (1975).

(13) H. M. N. H. Irving and J. J. Markham, *Anal. Chim. Acta*, **39**, 7 (1967).

(14) R. H. Maghssoudi and A. B. Fawzi, *J. Pharm. Sci.*, **67**, 32 (1978).

(15) R. H. Maghssoudi, A. B. Fawzi, and M. A. N. Moosavi Meerkalaie, *J. Assoc. Off. Anal. Chem.*, **60**, 926 (1977).

(16) A. I. Vogel, "A Text-Book of Macro and Semimicro Qualitative Inorganic Analysis," 4th ed., Longmans, London, England, 1964, p. 644.

(17) J. H. Yoe and A. L. Jones, *Ind. Eng. Chem. Anal. Ed.*, **16**, 111 (1944).

NMR Studies and GC Analysis of the Antibacterial Agent Taurolidine

B. I. KNIGHT *, G. G. SKELLERN *, G. A. SMAIL *, M. K. BROWNE ‡, and R. W. PFIRRMANN§ ˣ

Received December 9, 1981, from the **Department of Pharmacy, University of Strathclyde, Glasgow G1 1XW, U.K.*; ‡*Monklands District General Hospital, Airdrie ML6 0JS, U.K.*; and §*Geistlich-Pharma, 6110 Wolhusen, Switzerland.* Accepted for publication June 10, 1982.

Abstract □ The NMR spectrum of taurolidine in deuterium oxide was compared with spectra obtained from model experiments with amines and formaldehyde. Head-space analysis combined with capillary GC showed that there was <0.004% free formaldehyde present in 2% solutions of taurolidine. This value is comparable to the concentration of formaldehyde found when the taurolidine solutions were injected directly onto GC columns.

Keyphrases □ Taurolidine—NMR spectral analysis, head-space analysis–GC methods for the determination of formaldehyde □ NMR spectroscopy—analysis of taurolidine □ GC analysis—direct or combined with head-space analysis, quantitation of formaldehyde concentration in taurolidine □ Head-space analysis—with capillary GC, quantitation of formaldehyde concentration in taurolidine

Taurolidine [4,4′-methylenebis(tetrahydro-1,2,4-thiadiazine 1,1-dioxide), I] is a broad spectrum bactericide and antiendotoxin (1–3) which is being used widely in clinical trials to counteract bacterial infections following GI surgery and to treat peritonitis (4–6). It is administered intraperitoneally *via* a catheter inserted when the abdomen is closed, as a 2% aqueous solution[1] containing 5% povidone[2] (added to increase the solubility of taurolidine).

As a result of NMR studies (7) of aqueous solutions of taurolidine, equilibria are considered to exist between taurolidine, 4-hydroxymethyltetrahydro-2*H*-1,2,4-thiadiazine 1,1-dioxide (II), tetrahydro-2*H*-1,2,4-thiadiazine 1,1-dioxide (III)[3], and formaldehyde.

The existence of such equilibria was studied with the aid of solutions of morpholine–formaldehyde and III–formaldehyde as models. Also, because of the concern regarding toxicity, the determination of the formaldehyde concentration in solutions of taurolidine (which have been used in large volumes for the treatment of septicemia) is of considerable interest. Thus, this paper also describes the quantitative determination of formaldehyde using combined head-space analysis–capillary GC and direct GC.

EXPERIMENTAL

NMR—The NMR spectra of taurolidine were determined in deuterium oxide and deuterodimethylsulfoxide. Taurolidine (20 mg/ml) together with 1-vinyl-2-pyrrolidinone polymer (50 mg/ml) in deuterium oxide, and morpholine and III in deuterium oxide (before and after gaseous formaldehyde had been passed through the solution), were also determined[4]. The reference standard was sodium 3-trimethylsilylpropionate-2,2,3,3-$^2H_4$.

GC Analysis of Formaldehyde—*Head-Space Analysis*—Aqueous solutions (10 ml) of formaldehyde (0.005–0.01%) containing sodium chloride (5 g) were added to 100-ml injection vials which were tightly stoppered. The vials were incubated at 20, 40, or 60° for 1 hr to allow the

[1] Taurolin.
[2] Polyvinylpyrrolidone-17, mol. wt. 11,000, BASF (Germany).
[3] Taurultam.
[4] Perkin-Elmer R32 90-MHz NMR spectrometer.

0022-3549/83/0600-0705$01.00/0