Analysis of Promethazine Hydrochloride in Syrups

By ALBERT R. SPERLING

An improved method for the determination of promethazine hydrochloride in official syrups is presented. Column chromatography has been used to separate the active ingredient from those of its degradation products that interfere with the present official analysis. Determination and identification are by ultraviolet and infrared spectrophotometry, respectively. The procedure is rapid and accurate. One of the major breakdown products of promethazine hydrochloride in aqueous solution is identified.

THE U.S.P. XVII (1) assay for promethazine hydrochloride syrup is not adaptable to all commercial products. The viscosity of some syrups prevents efficient extraction, and the results of analysis are poor. Another disadvantage of the assay is that certain degradation products of promethazine hydrochloride which may be present will interfere with the analysis. No provision has been made for the separation or removal of these materials. Steele (2) attempted an analysis of various phenothiazine derivatives by using a strongly acidic ion-exchange resin. Good results were obtained on pure materials but the application to dosage forms was less successful. Turi (3) used a diatomaceous earth[1] chromatographic column with 1% tartaric acid as the stationary phase to separate promethazine hydrochloride and other phenothiazines from mixtures containing other therapeutic agents. Only tablet and capsule dosage forms were studied.

The present paper describes a simple method for the chromatographic separation, on diatomaceous earth columns, of promethazine hydrochloride from official syrups, and the removal of interfering degradation products. The active principle is determined and identified by ultraviolet and infrared spectrophotometry, respectively. Also identified is the major degradation product from an aqueous solution of promethazine hydrochloride.

METHOD

Apparatus.—A Beckman DK-2 recording spectrophotometer and chromatographic columns, 20 × 200 mm., were used.

Received July 29, 1966, from the Spectrophotometric Research Branch, Division of Pharmaceutical Chemistry, Bureau of Science, Food and Drug Administration, U. S. Department of Health, Education, and Welfare, Washington, D. C. 20204.

Accepted for publication October 5, 1966.

[1] Marketed as Celite 545 by Johns-Manville Corp., New York, N. Y.

Reagents.—Chloroform, A.C.S., reagent grade; chloroform, A.C.S., reagent grade saturated with water, containing 1% v/v acetic acid; ether U.S.P., saturated with water; 1 *N* sulfuric acid solution; 1 *N* sodium hydroxide solution; diatomaceous earth.

Preparation of Chromatographic Column.—Place a pledget of glass wool at the bottom of a chromatographic column. To 4 Gm. of diatomaceous earth, add 1 ml. of 1 *N* sulfuric acid, and mix well. Transfer to the column and tamp down moderately.

Preparation of Standard Solution.—Dissolve 6 mg. of U.S.P. promethazine hydrochloride reference standard, accurately weighed, in 200 ml. of water-saturated chloroform containing 1% v/v acetic acid.

Preparation of Sample Solutions.—For syrups containing 1 to 2 mg./ml. of active ingredient, dilute the syrup with an equal volume of water in a volumetric flask. For syrups containing about 5 mg./ml. of active ingredient, dilute 1 part of syrup with 4 parts of water in a volumetric flask. To measure the viscous syrup more easily, pipet the appropriate volume of water into the flask and then bring to volume with syrup.

Procedure.—*Assay.*—Transfer a 10-ml. aliquot of sample solution to a 125-ml. separator and allow the pipet to drain well. If necessary flush the pipet with a small amount of water (less than 2 ml.). Extract the solution with three 45-ml. portions of chloroform and filter the extracts through a pledget of glass wool. Evaporate the filtrate to dryness on a steam bath with the aid of a stream of air. Remove immediately from the steam bath, add 2 ml. of water to the residue, and mix well. The entire residue will not dissolve. To this mixture add 3 Gm. of diatomaceous earth and mix thoroughly. Transfer this diatomaceous earth-sample mixture to the previously prepared chromatographic column, tamp moderately, and add a pledget of glass wool. Wash the column with 150 ml. of water-saturated ether and discard this eluate. Rinse the sample beaker and elute the column with water-saturated chloroform containing 1% v/v acetic acid; collect the eluate in a 200-ml. volumetric flask. Dilute to volume with chloroform. Determine the absorbances of the chloroform solutions of the sample and standard solutions in

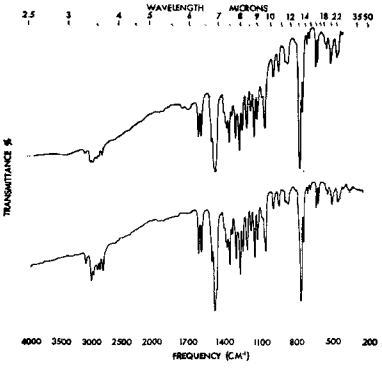

Fig. 1.—Infrared spectra of promethazine standard (bottom) and promethazine isolated from the sample (top).

1-cm. cells at the wavelength of maximum absorption at about 302 mμ and at the wavelength of minimum absorption at 360 mμ, using water-saturated chloroform containing 1% v/v acetic acid as a blank. Calculate the quantity of promethazine hydrochloride in milligrams by the formula

$$\frac{C(A_u^{302} - A_u^{360})}{V(A_s^{302} - A_s^{360})} = \text{mg./ml. of syrup}$$

where A_u and A_s are the absorbances of the unknown and standard solutions at the specified wavelengths, C is the concentration of the standard solution in mg./200 ml., and V represents the volume of syrup present in the 10-ml. aliquot of the sample solution.

Identification.—Transfer a volume from both standard and sample chloroform solutions, equivalent to about 1 to 2 mg. of promethazine, to 125-ml. separators. Wash each solution successively with 10 ml. of 1 *N* sodium hydroxide and 10 ml. of water. Evaporate each chloroform layer to dryness in an agate mortar and dry the residue for 30 min. in a vacuum desiccator over phosphorus pentoxide. Prepare a potassium bromide disk of the residue. Identify the sample by comparing the infrared absorption spectrum of the sample with that of the standard (Fig. 1).

RESULTS AND DISCUSSION

Table I gives the recoveries of U.S.P. reference standard promethazine hydrochloride which was added to a simulated and a commercial syrup. The recoveries agree within 1.4% of the amounts added. Table II shows the average results of analysis of various commercial samples. Samples *A*, *B*, *C*, *E*, and *F* are declared to contain 1.25 mg./ml. and sample *D* 5 mg./ml. Very low results were obtained when syrups *B* and *F* were analyzed by the U.S.P. method, but after dilution with an equal volume of water, results were satisfactory. All of the results agreed within 3.2% of the declared content except sample *A*, which assayed only 70% of the declared amount. Preliminary investigation showed that this low result was due to partial decomposition of the syrup. When an attempt was made to analyze this syrup by the present U.S.P. (1) method, degradation products

Table I.—Recovery of Reference Standard Added to Simulated and Commercial Syrups

Sample	Recoveries, %
A[a]	100.2
	99.7
B[a]	100.0
	100.0
E[a]	98.1
	98.6
F[b]	98.9
	99.5

[a] Commercial syrups. [b] Simulated syrup.

Table II.—Analysis of Promethazine Hydrochloride in Commercial Syrups

Sample	Found, mg./ml.	Labeled Amt., % Proposed Method	Labeled Amt., % U.S.P. Method	Labeled Amt., % Modified U.S.P. Method[a]
A	.882	70.6		
	.881	70.5		
B	1.259	100.7	49.5	96.3
	1.252	100.1	51.8	95.6
C	1.255	100.4		
	1.252	100.1		
D	5.057	101.1		
	5.097	101.9		
E	1.233	98.6		
	1.229	98.3		
F	1.210	96.8	69.5	96.9
	1.216	97.3	62.4	96.2

[a] The syrup was diluted with an equal volume of water, then analyzed by the official U.S.P. method

interfered with the analysis because no provision had been made for their removal or separation. This interference (Fig. 2, curve 2) can be seen by the change in the ultraviolet spectrum from that of the reference standard (Fig. 2, curve 1). An interfering peak occurs at about 335 mμ and the main peak is shifted to about 292 mμ with an increase in absorptivity. With the proposed procedure, the promethazine is trapped on the diatomaceous earth in the sulfuric acid layer while the ether wash removes the interfering degradation products. The eluate is then determined and identified.

According to Waaler (4) the thermal decomposition products of promethazine in aqueous solution are 10-methylphenothiazine, acetaldehyde, and dimethylamine. Yamamoto and Fujisawa (5) report the same decomposition when a 0.5% solution is

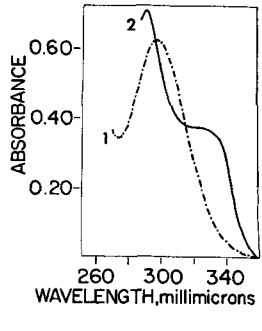

Fig. 2.—Ultraviolet spectra of promethazine in 0.1 *N* acid (curve 1) and in the presence of degradation products (curve 2).

exposed to 20-w. cool white fluorescent light in the presence of air, for a period of 2 or 3 days. In the course of this investigation it has been found that when an aqueous solution of promethazine hydrochloride of similar concentration is exposed to sunlight for longer periods of time, phenothiazine is one of the major degradation products. After extraction of the aqueous solution, this compound was identified by thin-layer chromatography and by its infrared spectrum.

SUMMARY

A procedure has been developed for the analysis of promethazine hydrochloride in syrups. Column chromatography is combined with extraction to separate the active ingredient from interfering degradation products and excipients. Phenothiazine has been identified as one of the degradation products of promethazine.

REFERENCES

(1) "United States Pharmacopeia," 17th rev., Mack Publishing Co., Easton, Pa., 1965, p. 529.
(2) Steele, J. W., *Can. Pharm. J.*, **February 1964**, 59.
(3) Turi, P., *J. Pharm. Sci.*, **53**, 369(1964).
(4) Waaler, T., *Pharm. Acta Helv.*, **35**, 168(1960).
(5) Yamamoto, R., and Fujisawa, S., Proceedings: 23rd Congress of Pharmaceutical Science, Münster, Germany, 1963.

Technical Articles

Evaluation of the Suitability of Butadiene–Acrylonitrile Rubbers as Closures for Parenteral Solutions

By J. SHANKER, M. GIBALDI*, J. L. KANIG, A. P. PARKER†, and L. LACHMAN

The sorption, leaching, tensile, and other properties of a series of butadiene–acrylonitrile rubbers from the medium-high acrylonitrile group were evaluated to determine the suitability of this copolymer system as elastomer closures for multiple-dose vial injectable preparations. These elastomers were found to exhibit considerable sorption of antibacterial preservatives from solution and leaching of extractives to the solutions when compared with a butyl rubber control. Partial identification of the leached materials was possible by chemical analysis. By reducing the amount of accelerator in one of the elastomer formulations by 25 per cent, a 35 per cent reduction in the amount of extractive leached from the elastomer resulted. This rubber formulation also exhibited a lower tensile strength and greater ultimate elongation. The butadiene-acrylonitrile elastomers possessed very low porosity and exhibited a low degree of water vapor transmission.

THERE HAS been considerable development in elastomer chemistry and technology during the last two decades, and a variety of synthetic elastomers are now in common use. A few of the more important uses of elastomers by the pharmaceutical industry are as packaging materials, surgical gloves, tubing for medical use, and vial closures.

These materials make excellent closures for multidose vials containing parenteral solutions because of their unique combination of properties—namely, pierceability and resealability (1). Unfortunately, the favorable qualities are also accompanied by various undesirable characteristics. It has long been known that rubber closures may yield substances to the preparation for which it is used as a stopper, a property known as leaching (2, 3). The closure can also sorb components from the preparation (3). In addition, it has been reported that materials can be lost by vapor transmission through the closure, chemical incompatibility between the product and closure could take place, physical instability of the elastomer could result, and coring or cutting away of rubber particles by the hypodermic needle is a frequent occurrence (1, 4, 5–7).

It is evident from the foregoing brief literature review that most of the studies appearing in the

Received June 13, 1966, from the College of Pharmacy, Columbia University, New York, N. Y., and the Research Department, Ciba Pharmaceutical Co., Summit, N. J.
Accepted for publication August 24, 1966.
The authors express their appreciation to the B. F. Goodrich Chemical Co. for its cooperation in this investigation.

* Present address: School of Pharmacy, State University of New York at Buffalo.
† Present address: Reed and Carnrick Laboratories, Kenilworth, N. J.