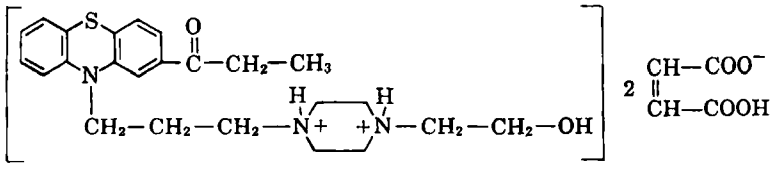
# Qualitative and Quantitative Tests for Carphenazine Maleate

**Provisional, unofficial monographs are developed by the Drug Standards Laboratory, in cooperation with the manufacturers of the drugs concerned, for publication in the *Journal of Pharmaceutical Sciences*. The ready availability of this information affords discriminating medical and pharmaceutical practitioners with an added basis for confidence in the quality of new drug products generally, and of those covered by the monographs particularly. Such monographs will appear on drugs representing new chemical entities for which suitable identity tests and assay procedures are not available in the published literature. The purity and assay limits reported for the drugs and their dosage forms are based on observations made on samples representative of commercial production and are considered to be reasonable within expected analytical and manufacturing variation.** ***Drug Standards Laboratory***

1 - {10 - (3 - [4 - (2 - HYDROXYETHYL) - 1 - PIPERAZINYL] - PROPYL)PHENOTHIAZIN - 2 - YL} - 1 - PROPANONE BIS(HYDROGEN MALEATE); $C_{24}H_{31}N_3O_2S \cdot 2C_4H_4O_4$; M.W. 657.75. The structural formula of carphenazine maleate may be represented as



**Physical Properties.**—Carphenazine maleate occurs as a finely divided, odorless, yellow powder, m.p. 162–167°, with decomposition, U.S.P. XVI Class Ia. It is slightly soluble in alcohol and in water, and practically insoluble in ether. The pH of a 1% suspension in carbon dioxide–free water is between 2.5 and 3.5.

**Identity Tests.**—Dissolve 15 mg. of carphenazine maleate in 10 ml. of water. Place 5 drops of the solution in a depression of a white spot plate and add 1 drop of a solution of chloramine-T (1 in 10): a violet precipitate forms, slowly changing to gray. To another 5 drops of the solution add 1 drop of the buffered palladous chloride solution used in the *Assay:* a permanent red develops.

Dissolve 15 mg. of carphenazine maleate in 10 ml. of alcohol and place 1 drop of the solution on a piece of filter paper. Allow the solvent to evaporate and examine the residue under a short wavelength ultraviolet lamp (maximum emission at about 254 mμ): a yellow fluorescence is observed.

A 1 in 50,000 solution of carphenazine maleate in 0.1 *N* hydrochloric acid exhibits ultraviolet absorbance maxima at about 243 mμ [absorptivity (1%, 1 cm.) about 385] and 277 mμ, and minima at about 228 and 260 mμ. The ratio of the absorbances at 243 and 277 mμ is between 1.27 and 1.41. The spectrum is shown in Fig. 1.

The infrared spectrum of a 0.5% dispersion of carphenazine maleate in potassium bromide, in a disk of about 0.82-mm. thickness, is shown in Fig. 2.

**Purity Tests.**—Determine the water content of carphenazine maleate by the titrimetric (Karl Fischer) method: carphenazine maleate contains not more than 1% water.

Char about 1 Gm. of carphenazine maleate, accurately weighed, cool the residue, add 1 ml. of sulfuric acid, heat cautiously until the evolution of sulfur trioxide ceases, ignite, cool, and weigh: the residue does not exceed 0.2%.

### Assay

**Palladous Chloride Stock Solution.**—Transfer 500 mg. of palladous chloride to a 250-ml. beaker, add 5 ml. of hydrochloric acid, and warm the mixture on a steam bath. Add 200 ml. of hot water in small portions until solution is complete, cool, transfer the solution to a 500-ml. volumetric flask, dilute to volume with water, and mix.

**Buffered Palladous Chloride Solution.**—Transfer 75 ml. of the *Palladous chloride stock solution* to a 500-ml. volumetric flask, add 50 ml. of 1 *N* sodium

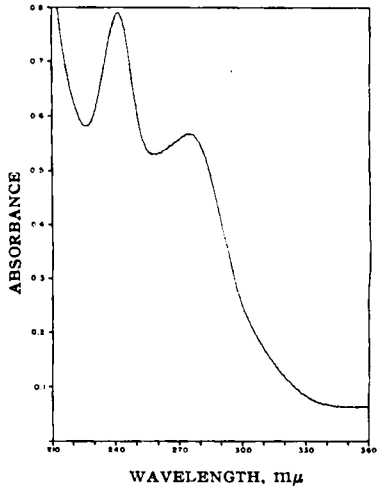



Fig. 1.—Ultraviolet absorption spectrum of carphenazine maleate in 0.1 *N* hydrochloric acid (2 mcg. per ml.); Beckman model DK-2A spectrophotometer.

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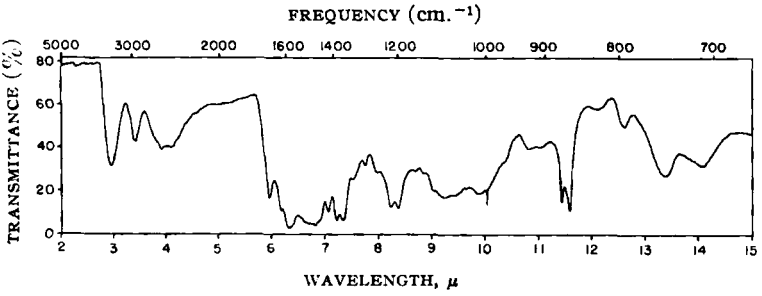


Fig. 2.—Infrared spectrum of carphenazine maleate in potassium bromide disk (0.5%): Perkin-Elmer model 21 spectrophotometer, sodium chloride prism.

acetate solution and 44 ml. of 1 *N* hydrochloric acid, dilute to volume with water, and mix.

**Standard Preparation.**—Transfer about 50 mg. of carphenazine maleate reference standard, previously dried in vacuum over phosphorus pentoxide for 18 hours and accurately weighed, to a 250-ml. volumetric flask. Dissolve it in about 100 ml. of diluted alcohol, add diluted alcohol to volume, and mix.

**Procedure.**—Transfer about 50 mg. of carphenazine maleate, accurately weighed, to a 250-ml. volumetric flask; dissolve it in about 100 ml. of diluted alcohol, add diluted alcohol to volume, and mix. Pipet 4 ml. of *Buffered palladous chloride solution* into each of three glass-stoppered test tubes. Pipet 3 ml. of the assay solution and of the *Standard preparation*, respectively, into separate tubes and prepare a blank by adding 3.0 ml. of diluted alcohol to the remaining tube. Mix the contents of each tube thoroughly; within 10 minutes spectrophotometrically determine the absorbances of the solutions containing carphenazine maleate, in 1-cm. cells, at the wavelength of maximum absorbance at about 490 mμ, using the blank to set the instrument to zero absorbance. Record the absorbance of the solution from the *Standard preparation* as $A_s$ and that from the assay solution as $A_u$ and calculate the weight, in milligrams, of carphenazine maleate in the portion of carphenazine maleate taken by the formula $W \times A_u/A_s$, where $W$ is the weight, in milligrams, of carphenazine maleate reference standard taken. The amount of carphenazine maleate found, on the anhydrous basis, is not less than 98.0% and not more than 102.0% of the weight of the sample taken

## DOSAGE FORMS OF CARPHENAZINE MALEATE

### Carphenazine Maleate Tablets

**Identity Tests.**—Transfer to a glass-stoppered 250-ml. conical flask an amount of powdered tablets equivalent to about 25 mg. of carphenazine maleate. Add 100 ml. of alcohol, shake occasionally during 15 minutes, and filter through a medium porosity sintered-glass filter, discarding the first few milliliters of filtrate. Evaporate 6 ml. of the filtrate to dryness on a water bath with the aid of a current of air and dissolve the residue in 1 ml. of water: the solution responds to the two color identity tests under carphenazine maleate.

Evaporate 4 ml. of the filtrate obtained in the previous test to dryness on a water bath with the aid of a current of air and dissolve the residue in 50 ml. of 0.1 *N* hydrochloric acid: the solution exhibits ultraviolet absorbance maxima at about 243 and 277 mμ, and the ratio of the absorbances at these wavelengths is between 1.27 and 1.41.

**Assay.**—Weigh and finely powder not less than 20 carphenazine maleate tablets. Transfer an amount of powder equivalent to about 20 mg. of carphenazine maleate, accurately weighed, to a medium porosity sintered-glass funnel. Fit the funnel into the neck of a vacuum bell jar so that the stem discharges into a 100-ml. volumetric flask containing 50.0 ml. of water. Extract the powder with successive 5-ml. portions of alcohol until the flask is filled almost to the mark. Dilute to volume with alcohol, mix, and readjust the volume to the mark with alcohol. Proceed as directed in the *Assay* under carphenazine maleate, beginning with "Pipet 4 ml. of *Buffered palladous chloride solution*. . . ." The amount of carphenazine maleate found is not less than 95.0% and not more than 110.0% of the labeled amount.

## DISCUSSION

U.S.P. and N.F. terminology for solubility, melting range, reagents, etc., have been used wherever feasible.

Carphenazine maleate[1] is a phenothiazine derivative which is used in the management of chronic psychosis.

**Identity Tests.**—Carphenazine maleate was found to undergo the typical color reactions of phenothiazines with the eight test reagents described by Yung and Pernarowski (1). The reactions obtained with the chloramine-T and palladous chloride reagents are particularly distinctive and together serve to differentiate carphenazine maleate from the 13 phenothiazine tranquilizers reported in their paper. The fluorescence test is nonspecific and represents a typical class property. Identification is further aided by the characteristic ultraviolet and infrared spectra.

Attempts to prepare sharp-melting solid derivatives of carphenazine maleate were unsuccessful. The picrate, reineckate, and 2,4-dinitrophenylhydrazone derivatives were obtained but could not be recrystallized to yield sharp-melting products.

When the ultraviolet absorption identity test was performed on commercial 25-mg. tablets, the ratio of the absorbances at 243 and 277 mμ was 1.310. A similar test sample was purified by extraction with ether from alkaline medium, evaporation of the solvent, and dissolution of the residue in dilute hydrochloric acid. The ratio of absorbances obtained with this solution was 1.316. Purification, therefore, was not necessary for identification purposes.

[1] Marketed as Proketazine Maleate tablets by Wyeth Laboratories, Philadelphia, Pa.

**Quantitative Methods.**—The red palladium (II)–carphenazine color complex developed in the colorimetric assay forms immediately on addition of the test solution to the palladous chloride reagent and is stable for about 15 minutes. The color fades slowly thereafter, and the absorbance of the solution decreases about 2.5% in 3.5 hours. With reagent containing 0.015% palladous chloride, the colors produced by solutions of carphenazine maleate obeyed Beers law in the concentration range of 0.0 to 0.3 mg. per ml. Reagents containing 0.005 and 0.010% palladous chloride failed to produce linear concentration-absorbance plots with the same concentration range of carphenazine maleate. The acidity of the reagents was kept constant throughout these tests (pH 2.1 to 2.2). Analysis of commercial tablets labeled to contain 25 mg. of carphenazine maleate gave an average value of 96.7 ± 1.0%.[2]

[2] Maximum deviation from the mean value.

Repetitive analyses performed on the same tablet extracts were more precise so that the gross deviation may be attributed mainly to variations in the extraction procedure.

Samples of carphenazine maleate dissolved in glacial acetic acid and in a 4:1 mixture of chloroform and acetonitrile were titrated potentiometrically with 0.1 *N* perchloric acid in glacial acetic acid and in dioxane, respectively. The former system gave a sharp break (about 100 mv.) in the curve, equivalent to 98.1% of the amount of carphenazine maleate taken; the latter solvent system was unsatisfactory. In both systems a small amount of a dark gummy precipitate (soluble in acetone) formed as the titration progressed.

## REFERENCE

(1) Yung, D. K., and Pernarowski, M., This Journal, 52, 365(1963).

# Technical Articles

# Improved Viable Counting Method for Petrolatum-Based Ointments

By W. T. SOKOLSKI and C. G. CHIDESTER

**A filtration method for recovery of viable micro-organisms from petrolatum-based ointments is described. In this method the ointment is dissolved in isopropyl myristate and passed through a filter. Advantages of the method are that all the micro-organisms in the ointment sample are concentrated on the filter pad, and the filter pad can be rinsed to remove antibacterial agents and traces of petrolatum. Markedly higher recoveries were obtained by the proposed method than by methods in common use.**

Current viable counting methods for petrolatum-based ointments involve either (*a*) smearing the ointment directly on the surface of an agar plate (1, 2) or (*b*) extracting the micro-organisms from ointment by shaking with water (3, 4) and plating the aqueous phase. There have been conflicting reports concerning the sterility of ophthalmic ointments. Using an extraction method, Vander Wyk and Granston (3) found that 85% of the ointments they tested were contaminated with micro-organisms; Bowman and Holdowsky (4) found only 10% contaminated in a similar method. Neither report included a test of the effectiveness of the extraction method—such as an attempt to recover a known inoculum from ointment.

One objection to the use of aqueous extraction methods for ointments that contain antimicrobial agents is that the resulting concentrations

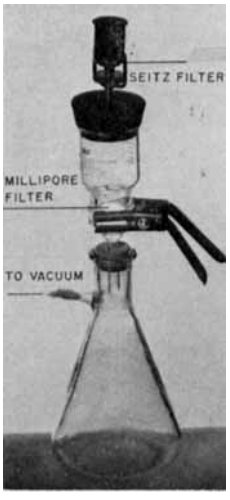


Fig. 1.—Filter unit for viable count or sterility testing of petrolatum-based ointments.

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