Qualitative and Quantitative Tests for Tolnaftate

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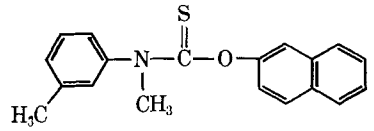
Provisional, unofficial monographs are developed by the Drug Standards Laboratory, in cooperation with the manufacturers of the drug concerned, for publication in the *Journal of Pharmaceutical Sciences*. The ready availability of this information affords discriminating medical and pharmaceutical practitioners 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.

2-NAPHTHYL-N-METHYL-N-(3-TOLYL)THIONOCARBAMATE; $C_{19}H_{17}NOS$; mol. wt. 307.42. The structural formula of tolnaftate may be represented as:



Physical Properties—Tolnaftate occurs as a white to creamy white fine powder, m.p. 110–113° (U.S.P., class I). It is freely soluble in chloroform and in acetone, slightly soluble in alcohol, sparingly soluble in ether, and practically insoluble in water.

Identity Tests—A 1 in 100,000 solution of tolnaftate in methanol exhibits an ultraviolet absorbance maximum at about 257 mμ [absorptivity (*a*) about 71] and a minimum at about 243 mμ. The spectrum is shown in Fig. 1.

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

Purity Tests—Dry about 1 Gm. of tolnaftate, accurately weighed, in vacuum at 65° for 3 hr.: it loses not more than 0.5% of its weight.

Char about 1 Gm. of tolnaftate, accurately weighed, cool the residue, add 1 ml. of sulfuric acid, heat cautiously until evolution of sulfur trioxide ceases, ignite, cool, and weigh: the residue does not exceed 0.1%.

Determine the heavy metals content of tolnaftate by the U.S.P. heavy metals test, method II: the heavy metals limit for tolnaftate is 20 p.p.m.

Assay—Dissolve 50 mg. of tolnaftate, accurately weighed, in sufficient methanol to make 250.0 ml. Dilute 5.0 ml. of this solution with methanol to 100.0 ml., and mix. Dissolve an accurately weighed quantity of tolnaftate reference standard in methanol, and dilute quantitatively and stepwise with methanol to obtain a standard solution having a concentration of about 10 mcg./ml. Concomitantly determine the absorbance of each solution in 1-cm. cells, at the wavelength of maximum absorbance at about 257 mμ, with a suitable spectrophotometer, using methanol as the blank. Calculate the quantity, in mg., of $C_{19}H_{17}NOS$ in the portion of tolnaftate taken by the formula $5\ C\ (A_u/A_s)$, in which C is the concentration, in mcg./ml., of tolnaftate in the standard solution, A_u is the absorbance of the sample solution, and A_s is the absorbance of the standard solution. The amount of tolnaftate found is not less than 98.0% and not more than 102.0% of the weight of the sample taken.

DOSAGE FORMS OF TOLNAFTATE

Tolnaftate Solution

Identity Test—The ultraviolet absorption spectrum of the chloroform solution obtained in the *Assay* exhibits an absorbance maximum and minimum at the same wavelengths as that of the standard solution.

Assay—Transfer an accurately measured volume of tolnaftate solution equivalent to about 10 mg. of tolnaftate, to a separator, add 50 ml. of chloroform, and extract with 50 ml. of 0.1 *N* sodium hydroxide. Filter the chloroform phase through chloroform-washed cotton into a 250-ml. volumetric flask and extract the aqueous phase with four 45-ml. portions of chloroform, filtering each portion into the flask. Make to volume with chloroform, and mix. Dilute 25.0 ml. of this solution to 100.0 ml. with chloroform, and mix. Concomitantly determine the absorbance of this solution and of a standard solution of tolnaftate reference standard, in the same medium, at a concentration of about 10 mcg./ml., in 1-cm. cells, at the maximum at about 260 mμ, with a suitable spectrophotometer, using chloroform as the blank. Calculate the quantity, in mg., of $C_{19}H_{17}NOS$ in each ml. of solution taken by the formula $(C/V) \times (A_u/A_s)$, in which C is the concentration, in mcg./ml., of tolnaftate in the standard solution, V is the volume, in ml., of solution taken, A_u is the absorbance of the sample solution, and A_s

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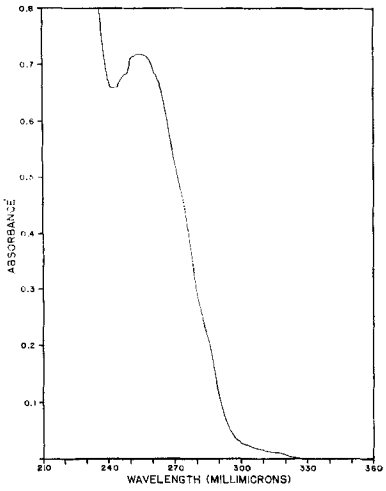

Fig. 1—Ultraviolet absorption spectrum of tolnaftate in methanol (10 mcg./ml.); Beckman model DK-2A spectrophotometer.

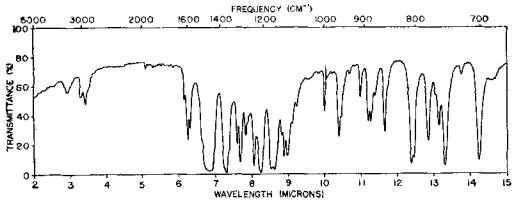

Fig. 2—Infrared spectrum of tolnaftate in potassium bromide disk (0.5%); Perkin-Elmer model 21 spectrophotometer, sodium chloride prism.

is the absorbance of the standard solution. The amount of tolnaftate found is not less than 90.0% and not more than 115.0% of the labeled amount.

Tolnaftate Cream

Identity Test—The ultraviolet absorption spectrum of the chloroform solution obtained in the *Assay* exhibits an absorbance maximum and minimum at the same wavelengths as that of the standard solution.

Assay—Weigh accurately an amount of tolnaftate cream equivalent to about 10 mg. of tolnaftate and transfer to a 250-ml. separator. Add 100.0 ml. of chloroform and shake the chloroform solution successively with two 25-ml. portions of 0.1 *N* sodium hydroxide, two 25-ml. portions of 0.1 *N* hydrochloric acid, and 25 ml. of water, transferring the bulk of the chloroform phase to a second separator after each extraction. Dilute 5.0 ml. of the chloroform solution to 50.0 ml. with chloroform, and mix. Concomitantly determine the absorbance of this solution and of a standard solution of tolnaftate reference standard, in the same medium, at a concentration of about 10 mcg./ml., in 1-cm. cells, at the maximum at about 260 mμ, with a suitable spectrophotometer, using chloroform as the blank. Calculate the quantity, in mg., of $C_{19}H_{17}NOS$ in the portion of cream taken by the formula $C\ (A_u/A_s)$, in which C is the concentration, in mcg./ml., of tolnaftate in the standard solution, A_u is the absorbance of the sample solution, and A_s is the absorbance of the standard solution. The amount of tolnaftate found is not less than 90% and not more than 110% of the labeled amount.

DISCUSSION

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

Tolnaftate[1] is an antifungal agent which is useful in the topical treatment of fungal infection caused by various species of *Trichophyton* and *Microsporum* (1–3). Tolnaftate, applied in a polyethylene glycol solution or cream, is particularly effective in the treatment of tinea pedis, tinea cruris, tinea corporis, and tinea manuum.

Identity Tests—Thin-layer chromatography may be included for testing the purity of bulk tolnaftate as well as an additional identity test for the drug and dosage forms. Benzene–alcohol (1:1) solutions of tolnaftate drug and reference standard are prepared at a concentration of about 1 mg./ml. The remainder of the *Assay* solutions obtained from tolnaftate solution and cream are evaporated to dryness and the residue dissolved in 1 ml. of benzene–alcohol (1:1). A 10-μl. portion of test and standard solutions is applied to a thin-layer plate prepared with Silica Gel G and the chromatogram developed using toluene as the mobile phase. The spots are visualized using ultraviolet light (254 mμ) and/or a 1 in 100 solution of iodine in carbon tetrachloride sprayed on the chromatogram and air dried.

Quantitative Tests—Analyses of bulk tolnaftate and tolnaftate solution and cream are based on ultraviolet spectrophotometric measurements. A solution of the basic drug in methanol compared to a similarly prepared reference standard solution gave an average recovery value of 100.5 ± 0.4%.[2] Absorbance measurements of tolnaftate in the commercial preparations are conveniently determined in chloroform solution. The ultraviolet absorption spectrum of tolnaftate in chloroform is similar to the spectrum shown in Fig. 1 with a slight shift in maximum absorbance to 260 mμ. Spectrophotometric analyses of tolnaftate solution and cream gave average values of 107.6 ± 1.3%[2] and 108.4 ± 0.7%[2] of the labeled amounts, respectively. The suitability of each procedure was verified by quantitative recovery of a standard tolnaftate solution carried through the extractive steps as included for the solution and cream.

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[1] Marketed as Tinactin by the Schering Corp., Bloomfield, N. J.

[2] Maximum deviation from the mean value.