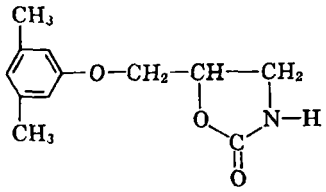
Qualitative and Quantitative Tests for Metaxalone

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.

5-(3,5-DIMETHYLPHENOXYMETHYL)-2-oxazolidinone; $C_{12}H_{15}NO_3$; mol. wt. 221.26. The structural formula of metaxalone may be represented as



Physical Properties.—Metaxalone occurs as a white, odorless, bitter, crystalline powder, m.p. 121–125°, U.S.P. Class I. It is freely soluble in chloroform, soluble in alcohol and in propylene glycol, and very slightly soluble in water.

Identity Tests.—Dissolve about 10 mg. of metaxalone in 10 ml. of sulfuric acid solution (65 in 100). To 1 ml. of this solution add 2 ml. of a 1 in 1000 solution of vanillin in sulfuric acid solution (65 in 100): a cherry-red color develops within about 10 minutes.

A 1 in 10,000 solution of metaxalone in alcohol exhibits ultraviolet absorbance maxima at about 280 [absorptivity (1%, 1 cm.) about 55] and 272 mμ [absorptivity (1%, 1 cm.) about 52] and a minimum at about 277 mμ. The spectrum is shown in Fig. 1.

The infrared spectrum of a 0.3% dispersion of metaxolone in potassium bromide, in a disk of about 0.82 mm. thickness, is shown in Fig. 2.

Purity Tests.—Dry about 1 Gm. of metaxalone, accurately weighed, under vacuum at 80° for 3 hours: it loses not more than 0.5% of its weight.

Char about 1 Gm. of metaxalone, 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 0.3%. Retain the residue for the heavy metals test.

Dissolve the sulfated ash obtained from 1 Gm. of metaxalone in a small volume of hot nitric acid and evaporate to dryness on a steam bath. Dissolve the residue in 2 ml. of diluted acetic acid, dilute to 25 ml. with water, and determine the heavy metals content of this solution by the U.S.P. XVI heavy metals test, method I: the heavy metals limit for metaxalone is 20 p.p.m.

Determine the nitrogen content by the U.S.P. XVI nitrogen determination, method II, using about 300 mg. of metaxalone, previously dried under vacuum at 80° for 3 hours and accurately weighed, and 0.1 *N* sulfuric acid for the titration. Each milliliter of 0.1 *N* sulfuric acid is equivalent to 1.401 mg. of nitrogen (N). The amount of nitrogen found is not less than 6.20% and not more than 6.46% of the weight of the sample taken.

Assay.—Transfer about 100 mg. of metaxalone, previously dried under vacuum at 80° for 3 hours and accurately weighed, to a 100-ml. volumetric flask, dissolve in alcohol, dilute to volume with alcohol, and mix. Transfer 10.0 ml. of this solution to a second 100-ml. volumetric flask, dilute to volume with alcohol, and mix. Prepare a solution of metaxalone reference standard in alcohol by dissolving a suitable quantity, previously dried and accurately weighed, and diluting quantitatively and stepwise to a concentration of about 100 mcg./ml. Concomitantly determine the absorbance of the two solutions in 1-cm. cells with a suitable spectrophotometer at the wavelength of maximum absorbance at about 280 mμ, using alcohol as the blank. Calculate the weight of $C_{12}H_{15}NO_3$, in milligrams, in the amount of metaxalone taken by the formula $C(A_u/A_s)$, where C is the exact concentration, in micrograms per milliliter, of metaxalone in the solution of the reference standard, A_u is the absorbance of the solution of the sample, and A_s is the absorbance of the solution of the reference standard. The amount of metaxalone found is not less than 98.0% and not more than 102.0% of the weight of the sample taken.

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A. H. Robins Co., Inc., Richmond, Va., has cooperated by furnishing samples and data to aid in the development and preparation of this monograph.

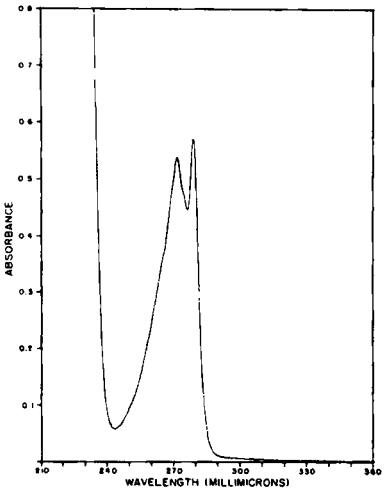

Fig. 1.—Ultraviolet absorption spectrum of metaxalone in alcohol (100 mcg./ml.). Beckman model DK-2A spectrophotometer.

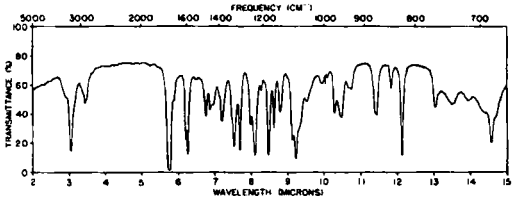

Fig. 2.—Infrared spectrum of metaxalone in potassium bromide disk (0.3%). Perkin-Elmer model 21 spectrophotometer; sodium chloride prism.

DOSAGE FORMS OF METAXALONE

Metaxalone Tablets

Identity Tests.—The ultraviolet absorption spectrum of the chloroform solution obtained in the *Assay* shows absorbance maxima (280 and 272 mμ) and a minimum (277 mμ) at the same wavelength as that of the *Standard Preparation*. The spectrum of metaxalone in chloroform is similar to the spectrum in alcohol (Fig. 1).

Evaporate to dryness 1 ml. of the initial chloroform solution obtained in the *Assay*. Dissolve the residue in 1 ml. of sulfuric acid solution (65 in 100) and add 2 ml. of a 1 in 1000 solution of vanillin in sulfuric acid solution (65 in 100): a cherry-red color develops within about 10 minutes.

Assay.—*Standard Preparation.*—Transfer about 100 mg. of metaxalone reference standard, previously dried under vacuum at 80° for 3 hours and accurately weighed, to a 100-ml. volumetric flask, dissolve in chloroform, dilute to volume with chloroform, and mix. Transfer 10.0 ml. of this solution to a second 100-ml. volumetric flask, dilute to volume with chloroform, and mix.

Procedure.—Weigh and finely powder not less than 20 metaxalone tablets and transfer a portion of the powdered tablets equivalent to about 200 mg. of metaxalone to a 60-ml. separator. Add 10 ml. of water, agitate to suspend the powder, and extract with five 25-ml. portions of chloroform. Filter the chloroform extracts through a pledget of chloroform-washed purified cotton into a 200-ml. volumetric flask, dilute to volume with chloroform, and mix. Transfer 10.0 ml. of this solution to a 100-ml. volumetric flask, dilute to volume with chloroform, and mix. Concomitantly determine the absorbance of this solution and that of the *Standard Preparation* in 1-cm. cells with a suitable spectrophotometer at the wavelength of maximum absorbance at about 280 mμ, using chloroform as the blank. Calculate the weight of $C_{12}H_{15}NO_3$, in milligrams, in the amount of powdered tablets taken by the formula $2C(A_u/A_s)$, where C is the exact concentration, in micrograms per milliliter, of metaxalone in the *Standard Preparation*, A_u is the absorbance of the solution from the tablets, and A_s is the absorbance of the *Standard Preparation*. The amount of metaxalone found is not less than 95.0% and not more than 105.0% of the weight of the sample taken.

DISCUSSION

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

Metaxolone,[1] synthesized by Lunsford *et al.* (1), is a skeletal muscle relaxant for treatment of acute muscle spasm related to sprains and strains, fractures, dislocations, and trauma to tendons and ligaments.

Identity Tests.—Metaxalone reacts with certain aldehydes in acid medium to form colored products. Formaldehyde and *p*-dimethylaminobenzaldehyde gave yellow colors, while vanillin gave a bright cherry-red.

Alcohol is a particularly convenient solvent for the ultraviolet absorbance identity test and the assay test for bulk metaxalone. On the other hand, it is more convenient to use the extracting solvent, chloroform, directly for the absorbance measurement of metaxalone in the tablet assay, thereby avoiding the necessity of chloroform evaporation and subsequent solution in alcohol.

Quantitative Methods.—Analysis for both the bulk metaxalone and metaxalone tablets is based on ultraviolet absorption properties. Analysis of commercial tablets (400 mg.) gave an average value of 99.4 ± 0.2%[2] of the labeled amount.

REFERENCE

(1) Lunsford, C. D., *et al.*, *J. Am. Chem. Soc.*, **82**, 1166 (1960).

[1] Marketed as Skelaxin by A. H. Robins Co., Inc., Richmond, Va.

[2] Maximum deviation from the mean value.