Qualitative and Quantitative Tests for Tybamate

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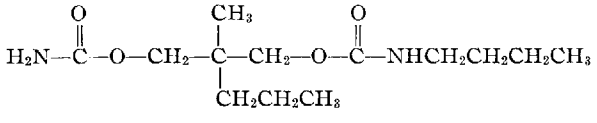
Provisional, unofficial monographs are developed by the Drug Standards Laboratory, in cooperation with the manufacturers of the drug concerned, for publication in the *Journal of Pharmaceutical Sciences*. The ready availability of this information affords discriminating medical and pharmaceutical practitioners 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-METHYL-2-PROPYLTRIMETHYLENE BUTYLCARBAMATE CARBAMATE; $C_{13}H_{26}N_2O_4$; mol. wt. 274.36. The structural formula of tybamate may be represented as



Physical Properties.—Tybamate occurs as a white crystalline powder or a clear viscous liquid which may congeal to a solid form on standing. It has a mild characteristic odor and a bitter taste. The dried powder melts within a range of 2° between 49° and 54°, U.S.P. class I. It is very slightly soluble in water, very soluble in alcohol and in acetone, and freely soluble in ether.

Identity Tests.—Transfer 1 ml. of a 0.04% chloroform solution of tybamate into a glass-stoppered test tube and add 1 ml. of a mixture of acetone–glacial acetic acid (3:1), 1 ml. of a 1 in 100 solution of *p*-dimethylaminobenzaldehyde in benzene, and 5 ml. of antimony trichloride solution (dissolve 3.6 Gm. of antimony trichloride in 20 ml. of chloroform and add 5 ml. of acetic anhydride). Heat the solution at about 55° for 15 min.: a red color is produced.

Dissolve 1 Gm. of tybamate and 0.8 Gm. of xanthydrol in a mixture of 10 ml. of dehydrated alcohol and 10 ml. of glacial acetic acid. Heat the solution on a steam bath for 90 min., taking care to avoid excessive evaporation. Cool and add cold water: an oil, which may crystallize on standing, separates from solution. Filter the mixture through paper, wash the residue with water until free from acetic acid odor, and dry at 105° for 2 hr. The dried residue when recrystallized from a mixture of trichloroethylene–hexane (1:2) melts between 127° and 130°.

The infrared spectrum of a 0.5% dispersion of tybamate in potassium bromide, in a disk of about 0.82 mm. thickness, is shown in Fig. 1.

Purity Tests.—Dry about 1 Gm. of tybamate, accurately weighed, in vacuum at 30–35° for 4 hr.; it loses not more than 0.5% of its weight.

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

Dissolve the sulfated ash obtained from 1 Gm. of tybamate 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. heavy metals test, method 1: the heavy metals limit for tybamate is 10 p.p.m.

Assay.—Transfer about 750 mg. of tybamate, accurately weighed, into a conical flask, add 20 ml. of pyridine, and neutralize the solution with 0.1 *N* sodium methoxide to the first pink color of phenolphthalein T.S. Add 50.0 ml. of 0.1 *N* sodium methoxide, a few boiling chips, and reflux with an air condenser on a steam bath for 30 min. Cool, add 40 ml. of neutralized alcohol, and titrate with 0.1 *N* hydrochloric acid to the absence of a pink color. Perform a blank determination. The difference between the two titrations represents the volume of 0.1 *N* sodium methoxide equivalent to

Received June 20, 1966, from the *Drug Standards Laboratory, AMERICAN PHARMACEUTICAL ASSOCIATION FOUNDATION, Washington, D.C. 20037.

Accepted for publication September 15, 1966.

† Wallace Laboratories, Cranbury, N. J. Wallace Laboratories has cooperated by furnishing samples and data to aid in the development and preparation of this monograph.

The authors express their appreciation to Mervin Meyer and Stephen M. Lipcsey, Wallace Laboratories, and Carolyn Damon, Drug Standards Laboratory, for valuable contributions to the monograph.

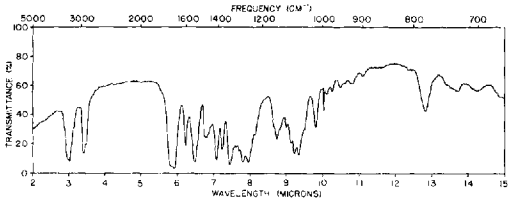


Fig. 1.—Infrared spectrum of tybamate in potassium bromide disk (0.5%); Perkin-Elmer model 21 spectrophotometer, sodium chloride prism.

the weight of $C_{13}H_{26}N_2O_4$ in the sample. Each milliliter of 0.1 *N* sodium methoxide is equivalent to 27.44 mg. of $C_{13}H_{26}N_2O_4$. The amount of tybamate found is not less than 98% and not more than 102% of the weight of the sample taken.

DOSAGE FORMS OF TYBAMATE

Tybamate Capsules

Identity Tests.—Transfer a sample of the capsule content, equivalent to about 10 mg. of tybamate, into a separator containing 75 ml. of water. Shake the aqueous solution with 25 ml. of chloroform and filter a portion of the chloroform extract. Transfer 1 ml. of the filtrate into a glass-stoppered test tube and add 1 ml. of a mixture of acetone–glacial acetic acid (3:1), 1 ml. of a 1 in 100 solution of *p*-dimethylaminobenzaldehyde in benzene, and 5 ml. of antimony trichloride solution (dissolve 3.6 Gm. of antimony trichloride in 20 ml. of chloroform and add 5 ml. of acetic anhydride). Heat the solution at about 55° for 15 min.: a red color is produced.

Transfer a sample of the capsule content, equivalent to about 1 Gm. of tybamate, into a separator containing 100 ml. of cold water. Shake vigorously for 2 min. and discard the aqueous layer. To the oily layer in the separator add 25 ml. of chloroform, 75 ml. of cold water, and shake vigorously. Allow the layers to separate, transfer the chloroform extract into a beaker, and add anhydrous sodium sulfate. The chloroform solution filtered through paper exhibits infrared absorption maxima only at the same wavelengths as that of a similar preparation of tybamate standard.

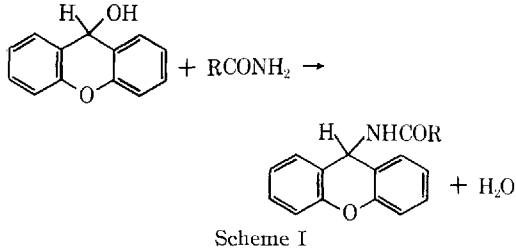
Assay.—Transfer an accurately weighed sample of the capsule content, equivalent to about 750 mg. of tybamate, into a conical flask, add 20 ml. of pyridine, and neutralize the solution with 0.1 *N* sodium methoxide to the first pink color of phenolphthalein T.S. Add 50.0 ml. of 0.1 *N* sodium methoxide, a few boiling chips, and reflux with an air condenser on a steam bath for 30 min. Cool, add 40 ml. of neutralized alcohol, and titrate with 0.1 *N* hydrochloric acid to the absence of a pink color. Perform a blank determination. The difference between the two titrations represents the volume of 0.1 *N* sodium methoxide equivalent to the weight of $C_{13}H_{26}N_2O_4$ in the sample. Each milliliter of 0.1 *N* sodium methoxide is equivalent to 27.44 mg. of $C_{13}H_{26}N_2O_4$. The amount of tybamate found is not less than 95% and not more than 105% of the labeled amount.

DISCUSSION

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

Tybamate,[1] synthesized by Berger and Ludwig (1), is a tranquilizing agent which affords symptomatic improvement in a variety of psychoneurotic disorders, especially in the treatment of the anxiety and tension components of psychoneuroses.

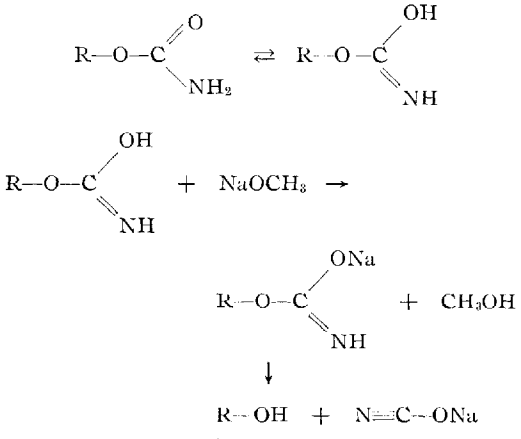
Identity Tests.—Crystalline derivatives of primary amides can be prepared with xanthydrol in glacial acetic acid. (Scheme I.)



Scheme I

The reaction is useful in characterizing aliphatic amides or carbamates (xanthylamides) and sulfonamides (*N*-xanthylsulfonamides).

Quantitative Tests.—Analysis for bulk tybamate and tybamate capsules is based on the reaction of alkali on carbamates of the general type $ROOCNH_2$ in nonaqueous media. Cerri *et al.* (2) have postulated the reaction sequence shown in Scheme II.



Scheme II

In anhydrous pyridine, the equilibrium shown in the first equation is shifted strongly to the right and the enolic species is reacted with the sodium methoxide. In aqueous systems the equilibrium favors the keto form and the reaction with alkali is no longer quantitative. The presence of small quantities of water in the solvents can induce errors in the procedure, but this effect can be nullified by increasing the methanol content in the reaction mixture by about 5% and increasing the reflux time to 55 min. (3).

The assay of bulk tybamate by the volumetric procedure gave an average recovery of 100.2 ±

[1] Marketed as Solacen by Wallace Laboratories, Cranbury, N. J.

1.2%.[2] The titration can be conducted with 0.1 *N* benzoic acid in benzene using thymol blue T.S. eliminating the addition of neutralized alcohol. In this instance, care must be exercised to prevent absorption of atmospheric carbon dioxide during the titration. Analysis of commercial tybamate capsules gave an average value of 97.2 ± 1.2%[2] of the labeled amount of tybamate.

[2] Maximum deviation from the mean value.

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(2) Cerri, O., Spialtini, A., and Gallo, U., *Pharm. Acta Helv.*, **34**, 13(1959).
(3) Wright, F., Wallace Laboratories, private communication.

Technical Articles

Particle Size Distribution and Hopper Flow Rates

By EDWARD D. SUMNER*, HERMAN O. THOMPSON, WILLIAM K. POOLE, and JAMES E. GRIZZLE

The rate of flow of varying ratios of four sieve size fractions of rock salt through the hopper of a rotary press was represented by a second degree polynomial equation. This fitted polynomial accounted for 90 per cent of the variation in the mean flow rates. No correlation was found between the tangent of the angle of repose and flow rate. High positive correlation was found between flow rate and bulk density, while high negative correlation between flow rate and porosity was observed. There was no significant increase or decrease in flow rates with regard to the quantity of rock salt remaining in the hopper.

One of the most important considerations in pharmaceutical manufacturing is the flow of particulate solids through hoppers and feeders. Capsules, divided powders, and tablets are examples of solid dosage forms which require measured filling for the production of each unit. Thus, the uniformity of the final product requires a uniform flow rate of these solid mixtures. Modern tablet machines are capable of compressing from 5000 (1) to 22,000 (2) tablets per minute. Uniformity of flow rate and flow rate of particulate solids must be considered in order to meet the requirements of these high speed units.

The laws which govern static pressures of fluids do not apply to particulate masses. Some properties of liquids in containers are: pressure is identical throughout at the same depth, pressure exerted on any point is transmitted undiminished to every portion of the enclosed liquid, and pressure exerted by a liquid on the walls of the container is always at right angles to the surface of the container.

Unlike liquids, pressures of bulk solids contained in hoppers varies with direction at different points, pressure is dependent on the shape and size of the receptacle, and the weight of a solid is transferred to the walls by shearing between particles in addition to pressure.

The principal factors affecting flow rates of particulate solids are: particle size, particle size distribution, particle shape, density, surface characteristics, and relative size and geometry of the hopper (3).

A review of the literature (3–15) reveals that the majority of the investigations and research on flow of particulate solids have been conducted on monodisperse systems and hoppers of much larger or smaller dimensions than those ordinarily used in some pharmaceutical manufacturing processes. This work was conducted to ascertain what relationship existed between particle size distribution, bulk density, porosity, and tangent of angle of repose in regard to flow rates and uniformity of flow rates.

MATERIALS AND METHODS

Material.—The particulate solid used was rock salt in the following sieve size fractions: 8/10, 10/20, 20/40, 40/60.

Received April 25, 1966, from the School of Pharmacy and Department of Biostatistics, University of North Carolina, Chapel Hill.
Accepted for publication August 15, 1966.
Presented to the Pharmaceutical Technology Section, A.Ph.A. Academy of Pharmaceutical Sciences, Dallas meeting, April 1966.
Abstracted in part from a thesis submitted by E. D. Sumner to the Graduate College, University of North Carolina, Chapel Hill, in partial fulfillment of Doctor of Philosophy degree requirements.
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