Qualitative and Quantitative Tests for Chlorphenesin Carbamate

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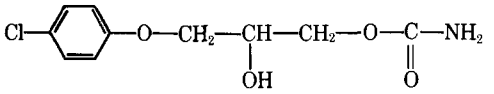
Provisional, unofficial monographs are developed by the Drug Standards Laboratory, in cooperation with the manufacturers of the drug concerned, for publication in the *Journal of Pharmaceutical Sciences*. The ready availability of this information affords discriminating medical and pharmaceutical practitioners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

3-(P-CHLOROPHENOXY)-2-HYDROXYPROPYL CARBAMATE; $C_{10}H_{12}ClNO_4$; mol. wt. 245.67. The structural formula of chlorophenesin carbamate may be represented as:



Physical Properties—Chlorphenesin carbamate occurs as a white to off-white, odorless powder, m.p. 86–92° (U.S.P. class Ia). It is very slightly soluble in water, freely soluble in alcohol, and sparingly soluble in chloroform.

Identity Tests—Mix 500 mg. of chlorphenesin carbamate with 1 ml. of acetic anhydride, add 1 drop of sulfuric acid, stir until solution is effected, and allow the solution to stand at room temperature for 30 min., stirring occasionally. Pour the solution into 50 ml. of water while stirring the mixture vigorously, and allow to crystallize. Filter off the crystals, wash with water until the odor of acetic acid is no longer perceptible, and dry at about 60°: the acetyl chlorphenesin carbamate so obtained melts at about 133°.

A 1 in 100,000 solution of chlorphenesin carbamate in alcohol exhibits ultraviolet absorbance maxima at about 227 mμ [absorptivity (*a*) about 53], 280 mμ, and 288 mμ and absorbance minima at about 245 mμ and 284 mμ. The spectrum is shown in Fig. 1.

The infrared spectrum of a chlorphenesin carbamate dispersion in liquid petrolatum is shown in Fig. 2.

Purity Tests—Dry about 2 Gm. of chlorphenesin carbamate, accurately weighed, over silica gel and at a pressure not exceeding 5 mm. of mercury for 6 hr.: it loses not more than 0.5% of its weight.

Char about 1 Gm. of chlorphenesin carbamate, 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 0.5%.

Received October 28, 1966, from the *Drug Standards Laboratory, AMERICAN PHARMACEUTICAL ASSOCIATION, Washington, DC 20037

Accepted for publication December 19, 1966.

† The Upjohn Co., Kalamazoo, MI 49002. The Upjohn Co. has cooperated by furnishing samples and data to aid in the development and preparation of this monograph.

The Drug Standards Laboratory gratefully acknowledges the assistance of Miss Carolyn Damon and Miss Hannah Klein.

Weigh accurately about 600 mg. of chlorphenesin carbamate and transfer to a Kjeldahl flask with 20 ml. of sulfuric acid, 200 mg. of selenium, and 15 Gm. of anhydrous sodium sulfate. After the mixture has become colorless, digest for 1 hr., cool, and dilute to about 300 ml. with water. Cool, make alkaline with sodium hydroxide solution (1 in 2), and distil the liberated ammonia into 40.0 ml. of 0.1 *N* sulfuric acid. Add methyl red T.S. and titrate the excess acid with 0.1 *N* sodium hydroxide. 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 5.50% and not more than 5.90% calculated on the dried basis.

Using about 20 mg. of chlorphenesin carbamate, accurately weighed, proceed as directed under "Oxygen Flask Combustion," U.S.P. XVII, p. 884, using a mixture of 1 ml. of sodium hydroxide T.S., 5 ml. of hydrogen peroxide T.S., and 15 ml. of water as the absorbing liquid. After the combustion is complete, rinse the stopper and sample holder with water and boil the solution for about 5 min. Cool, acidify with diluted nitric acid adding 2 ml. in excess, add 10.0 ml. of 0.05 *N* silver nitrate, 2 ml. of nitrobenzene, and 2 ml. of ferric ammonium sulfate T.S. Shake well, and titrate the excess silver nitrate with 0.05 *N* ammonium thiocyanate. Each milliliter of 0.05 *N* silver nitrate is equivalent to 1.773 mg. of chlorine (Cl). The chlorine content is not less than 13.9% and not more than 14.9%, calculated on the dried basis.

Assay—Dissolve about 125 mg. of chlorphenesin carbamate, accurately weighed, in 25 ml. of chloroform in a 50-ml. volumetric flask, add the solvent to volume, and mix. Similarly, dissolve an accurately weighed quantity of chlorphenesin carbamate reference standard in chloroform to obtain a standard solution having a concentration of about 2.5 mg./ml. Concomitantly determine the absorbances of both solutions in 1.0-mm. cells at the wavelength of maximum absorbance at about 5.80 μ, with a suitable infrared spectrophotometer, using chloroform as the blank. Calculate the quantity, in milligrams, of $C_{10}H_{12}ClNO_4$ in the portion of chlorphenesin carbamate taken by the formula $50C \times (A_u/A_s)$, in which C is the concentration, in milligrams per milliliter, of chlorphenesin carbamate reference standard in the standard solution, and A_u and A_s are the absorbances of the solution of chlorphenesin carbamate and the standard solution, respectively. The amount of chlorphenesin carbamate found is

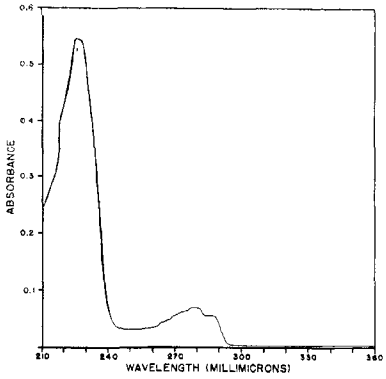


Fig. 1—Ultraviolet absorption spectrum of chlorphenesin carbamate in alcohol (10 mcg./ml.); Beckman model DK-2A spectrophotometer.

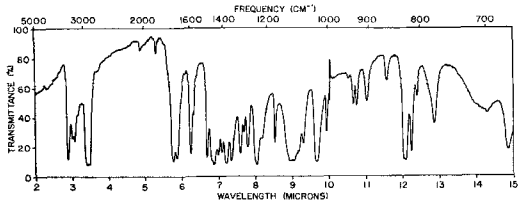


Fig. 2—Infrared spectrum of a chlorphenesin carbamate dispersion in liquid petrolatum; Perkin-Elmer model 21 spectrophotometer, sodium chloride prism.

not less than 97.0% and not more than 103.0%, calculated on the dried basis.

DOSAGE FORMS OF CHLORPHENESIN CARBAMATE

Chlorphenesin Carbamate Tablets

Identity Test—Triturate a quantity of finely powdered chlorphenesin carbamate tablets, equivalent to about 400 mg. of chlorphenesin carbamate, with 50 ml. of chloroform, and filter. Evaporate the clear filtrate on a steam bath to dryness: a liquid petrolatum dispersion of the residue exhibits infrared absorption maxima only at the same wavelengths as that of a similar preparation of chlorphenesin carbamate shown in Fig. 2.

Assay—*Standard Preparation*—Transfer 50.0 mg. of chlorphenesin carbamate reference standard to a glass-stoppered, 50-ml. conical flask and dissolve in 20.0 ml. of chloroform.

Assay Preparation—Weigh and finely powder not less than 10 chlorphenesin carbamate tablets. Weigh accurately a portion of the powder, equivalent to about 50 mg. of chlorphenesin carbamate, and transfer to a glass-stoppered, 50-ml. conical flask. Add 20.0 ml. of chloroform, stopper, and shake mechanically for 15 min. Filter a portion through paper into a glass-stoppered flask.

Procedure—Determine the absorbance of the *Assay Preparation* and that of the *Standard Preparation* in 1.0-mm. cells at the wavelength of maximum absorbance at about 5.80 μ, with a suitable infrared spectrophotometer, using chloroform as the blank. Calculate the quantity, in milligrams, of $C_{10}H_{12}ClNO_4$ in the portion of the tablets taken by the formula $50 \times (A_u/A_s)$, in which A_u is the absorbance of the *Assay Preparation* and A_s is the absorbance of the *Standard Preparation*. The amount of chlorphenesin carbamate found is not less than 92.5% and not more than 107.5% of the labeled amount.

DISCUSSION

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

Chlorphenesin carbamate[1] is an orally active skeletal muscle relaxant useful in the relief of discomfort associated with skeletal muscle trauma and inflammation.

Purity Tests—The synthesis of chlorphenesin carbamate involves the opening of a cyclic carbonate intermediate (1). An isomeric secondary carbamate is also formed in the reaction and constitutes a possible impurity in the final product. The limit of 3-(*p*-chlorophenoxy)-1-hydroxypropyl carbamate as a contaminant in chlorphenesin carbamate is controlled by quantitative nuclear magnetic resonance (NMR) spectroscopy (2) and should not exceed 1.5% of the weight of the bulk material.

Quantitative Methods—The nitrogen content of chlorphenesin carbamate as determined by the Kjeldahl procedure and the chlorine content by oxygen flask combustion gave average values of 5.61 ± 0.05%[2] and 14.2 ± 0.1%,[2] respectively.

Analyses for bulk chlorphenesin carbamate and the tablet formulation are based on infrared absorption properties of the carbonyl group in the molecule. Commercial tablets (400 mg.) gave an average recovery value of 99.7 ± 0.4%[2] of the labeled amount. Infrared analysis of the bulk drug yielded assay results of 100.2 ± 0.2%[2] which compares favorably to the recoveries (100.3 ± 0.3%[2]) obtained by the assay procedure reported for tybamate (3). A 500-mg. sample of chlorphenesin carbamate is subjected to sodium methoxide cleavage in a nonaqueous medium and the excess alkali determined by back titration with standard acid.

REFERENCES

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[1] Marketed as Maolate by The Upjohn Co., Kalamazoo, Mich.
[2] Maximum deviation from the mean value.