Qualitative and Quantitative Tests for Alverine Citrate

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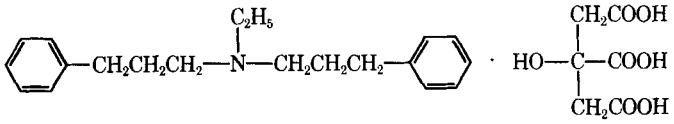
Provisional, unofficial monographs are developed by the Drug Standards Laboratory, in cooperation with the manufacturers of the drug concerned, for publication in the *Journal of Pharmaceutical Sciences*. The ready availability of this information affords discriminating medical and pharmaceutical practitioners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

BIS-γ-PHENYLPROPYLETHYLAMINE CITRATE; $C_{26}H_{27}N \cdot C_6H_8O_7$; mol. wt. 473.57. The structural formula of alverine citrate may be represented as:



Physical Properties—Alverine citrate occurs as a white to off-white powder having a sweet odor and a slightly bitter taste, m.p. 100–102° (U.S.P. class I). It is slightly soluble in water and in chloroform, sparingly soluble in alcohol, and very slightly soluble in ether. The pH of a solution of alverine citrate in carbon dioxide-free water (1 in 200) is between 3.5 and 4.5.

Identity Tests—A 1 in 1500 solution of alverine citrate in 0.1 *N* hydrochloric acid exhibits ultraviolet absorbance maxima at about 253 mμ, 258 mμ [absorptivity (*a*) about 0.9], and 267 mμ and absorbance minima at about 233, 255, and 265 mμ. The spectrum is shown in Fig. 1.

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

Suspend about 500 mg. of alverine citrate in 10 ml. of water, add a slight excess of sodium hydroxide to liberate alverine base, allow to stand 5 min. with occasional swirling, and filter: the clear filtrate responds to the U.S.P. tests for citrate.

Purity Tests—Dry about 1 Gm. of alverine citrate, accurately weighed, at 80° for 2 hr.: it loses not more than 0.5% of its weight.

Char about 1 Gm. of alverine citrate, 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%.

Assay—Transfer about 360 mg. of alverine citrate, accurately weighed, to a separator, add 25 ml. of water, 5 ml. of sodium hydroxide T.S., and extract with four 25-ml. portions of chloroform. Wash the combined extracts with 10 ml. of water and filter the chloroform solution through a layer of chloroform-moistened anhydrous sodium sulfate contained on a pledget of cotton, collecting the filtrate in a titrating beaker. Wash the aqueous phase with 10 ml. of chloroform and filter as before into the beaker. Add methanolic methyl red T.S. and titrate with 0.1 *N* perchloric acid in dioxane. Perform a blank determination, and make any necessary correction. Each milliliter of 0.1 *N* perchloric acid is equivalent to 47.36 mg. of $C_{26}H_{27}N \cdot C_6H_8O_7$. The amount of alverine citrate found is not less than 99% and not more than 102%.

DOSAGE FORMS OF ALVERINE CITRATE

Alverine Citrate Tablets

Identity Test—Powder a suitable number of tablets and transfer an amount equivalent to about 120 mg. of alverine citrate to a 200-ml. volumetric flask. Add about 100 ml. of 0.1 *N* hydrochloric acid, allow to stand unstoppered until effervescence ceases, stopper and shake for 30 min., dilute to volume with the acid, and mix. Filter a portion of the solution, discarding the first 20 ml. of filtrate. The filtrate exhibits ultraviolet absorbance maxima and minima at the same wavelengths as the bulk drug as shown in Fig. 1.

Assay—Weigh and finely powder not less than 20 alverine citrate tablets. Weigh accurately a portion of the powder, equivalent to about 360 mg. of alverine citrate, and transfer to a separator. Add 5 ml. of water and 5 ml. of sodium hydroxide T.S., swirl occasionally for 5 min., and extract with four 25-ml. portions of chloroform. Wash the combined extracts with 10 ml. of water and filter the chloroform solution through a layer of chloroform-moistened anhydrous sodium sulfate contained on a pledget of cotton, collecting the filtrate in a titrating

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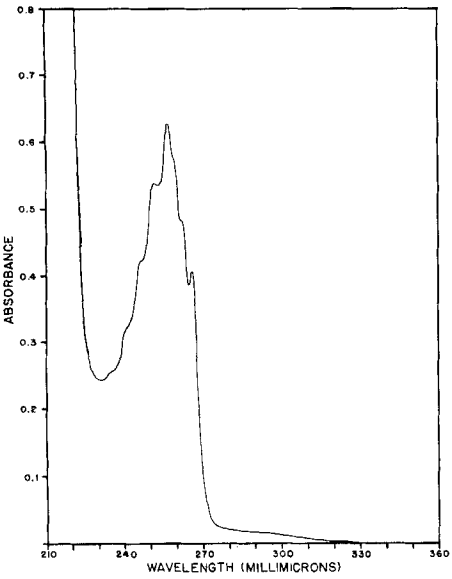

Fig. 1—Ultraviolet absorption spectrum of alverine citrate in 0.1 N hydrochloric acid (700 mcg./ml.); Beckman model DK-2A spectrophotometer.

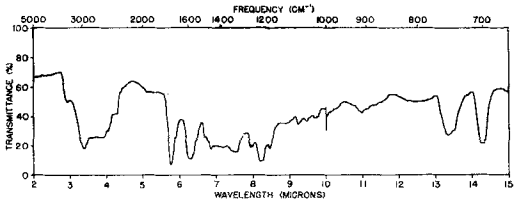

Fig. 2—Infrared spectrum of alverine citrate in potassium bromide disk (0.5%); Perkin-Elmer model 21 spectrophotometer, sodium chloride prism.

beaker. Wash the aqueous phase with 10 ml. of chloroform and filter as before into the beaker. Add methanolic methyl red T.S., and titrate with 0.1 *N* perchloric acid in dioxane. Perform a blank determination, and make any necessary correction. Each milliliter of 0.1 *N* perchloric acid is equivalent to 47.36 mg. of $C_{20}H_{27}N \cdot C_6H_8O_7$. The amount of alverine citrate 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.

Alverine citrate[1] is a non-narcotic, smooth-muscle antispasmodic which is approximately 3 times as potent as papaverine and with a longer duration of action. It is neither an anticholinergic nor a derivative of atropine and adverse reactions commonly associated with anticholinergics are not manifest.

Identity Tests—Alverine citrate may be identified by the preparation of an oxalate salt. The free base is isolated by extraction with ether from basic solution and is reacted with oxalic acid in aqueous solution to form the oxalate. The derivative when dried at 55° in vacuum melts between 139° and 142°.

Quantitative Tests—The nonaqueous titration of the extracted base with perchloric acid gave an average value of 100.4 ± 0.3%.[2] Alternatively, alverine citrate may be dissolved in glacial acetic acid and titrated directly with 0.1 *N* perchloric acid. With crystal violet indicator, the color change from blue to blue-green corresponds to the midpoint of the inflection obtained by simultaneous potentiometric measurement. Montequi *et al.* (1) have assayed alverine citrate by formation of a reineckate and subsequent bromometric determination. The method is reported to be accurate to within 1%. Titrimetric analyses of commercial tablets gave an average value of 97.3 ± 1.0%[2] of the labeled amount of alverine citrate.

REFERENCE

(1) Montequi, R., de Valderrama, E. F., and Collado, M. C., *Anales Real Acad. Farm.*, **30**, 281(1964); through *Chem. Abstr.*, **63**, 434(1965).

[1] Marketed as Spacolin by Philips Roxane Laboratories, Columbus, Ohio.

[2] Maximum deviation from the mean value.