Qualitative and Quantitative Tests for Doxapram Hydrochloride

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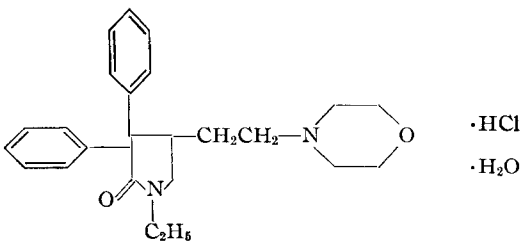
Provisional, unofficial monographs are developed by the Drug Standards Laboratory, in cooperation with the manufacturers of the drug concerned, for publication in the *Journal of Pharmaceutical Sciences*. The ready availability of this information affords discriminating medical and pharmaceutical practitioners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

1-ETHYL-4-(2-MORPHOLINOETHYL)-3,3-DIPHENYL-2-PYRROLIDINONE HYDROCHLORIDE HYDRATE; $C_{24}H_{30}N_2O_2 \cdot HCl \cdot H_2O$; mol. wt. 433.00. The structural formula of doxapram hydrochloride may be represented as



Physical Properties—Doxapram hydrochloride occurs as a white to off-white, odorless, crystalline powder and melts within a range of 2° between 217° and 221° (U.S.P., class I). It is sparingly soluble in water and in alcohol, soluble in chloroform, and practically insoluble in ether. The pH of a solution of doxapram hydrochloride in carbon dioxide-free water (1 in 100) is between 3.5 and 5.0.

Identity Tests—A 1 in 2500 solution of doxapram hydrochloride in water exhibits ultraviolet absorbance maxima at about 252 mμ, 258 mμ [absorptivity (a) about 1.1], and 264 mμ and absorbance minima at about 244 mμ, 254 mμ, and 262 mμ. The spectrum is shown in Fig. 1.

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

Purity Tests—Dry about 1 Gm. of doxapram hydrochloride, accurately weighed, at 105° for 2 hr.: it loses not more than 4.5% of its weight.

Char about 1 Gm. of doxapram hydrochloride, accurately weighed, in a tared platinum crucible, 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%.

Dissolve 1.0 Gm. of doxapram hydrochloride in 25 ml. of water by gentle warming, and cool: the heavy metals limit determined by U.S.P. method I is 20 p.p.m.

Assay—*Chloride*—Transfer about 300 mg. of doxapram hydrochloride, accurately weighed, to a 250-ml. iodine flask, and dissolve in 50 ml. of water. Add 25.0 ml. of 0.1 N silver nitrate, 3 ml. of nitric acid, 5 ml. of nitrobenzene, and 2 ml. of ferric ammonium sulfate T.S. Shake well, and titrate the excess silver nitrate with 0.1 N ammonium thiocyanate. Each milliliter of 0.1 N silver nitrate is equivalent to 3.545 mg. of chloride (Cl). The amount of chloride found is not less than 7.90% and not more than 8.30% of the weight of the sample taken.

Doxapram Hydrochloride—Transfer about 800 mg. of doxapram hydrochloride, accurately weighed, to a 200-ml. tall form beaker, add 50 ml. of glacial acetic acid, and stir until the sample is completely dissolved. Add 10 ml. of mercuric acetate T.S., 1 drop of crystal violet T.S., and titrate with 0.1 N perchloric acid to a blue-green end point. Perform a blank titration and make any necessary correction. Each milliliter of 0.1 N perchloric acid is equivalent to 43.30 mg. of $C_{24}H_{30}N_2O_2 \cdot HCl \cdot H_2O$. The amount of doxapram hydrochloride found is not less than 98.0% and not more than 100.5% of the weight of the sample taken.

DOSAGE FORMS OF DOXAPRAM HYDROCHLORIDE

Doxapram Hydrochloride Injection

Physical Properties—Doxapram hydrochloride injection is a sterile aqueous solution with chlorobutanol present as a preservative. The pH of the solution is between 3.5 and 5.0.

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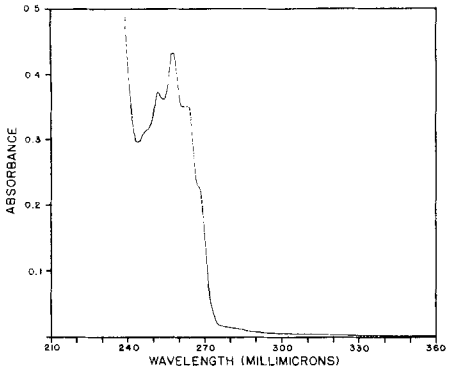

Fig. 1—Ultraviolet absorption spectrum of doxapram hydrochloride in water (400 mcg./ml.); Beckman model DK-2A spectrophotometer.

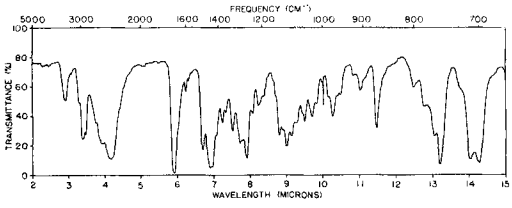

Fig. 2—Infrared spectrum of doxapram hydrochloride in potassium bromide disk (0.5%); Perkin-Elmer model 21 spectrophotometer, sodium chloride prism.

Identity Test—The solution prepared by dilution of the injection in the *Assay* exhibits absorbance maxima and minima at the same wavelengths as the doxapram hydrochloride standard solution.

Assay—Pipet a volume of doxapram hydrochloride injection, equivalent to 100 mg. of doxapram hydrochloride, into a 250-ml. volumetric flask, dilute to volume with water, and mix. Concomitantly determine the absorbance of this solution and of a standard solution of doxapram hydrochloride, in water, at a concentration of about 400 mcg./ml., in 1-cm. cells, at the maximum at about 258 mμ, with a suitable spectrophotometer, using water as the blank. Calculate the quantity, in milligrams, of $C_{24}H_{30}N_2O_2 \cdot HCl \cdot H_2O$ in each milliliter of injection, by the formula $0.25 \times (C/V) \times (A_u/A_s)$, in which C is the exact concentration of the standard solution, in micrograms per milliliter, V is the volume, in milliliters, of the injection taken, A_u is the absorbance of the sample solution, and A_s is the absorbance of the doxapram hydrochloride standard solution. The amount of doxapram hydrochloride found is not less than 95.0% and not more than 105.0% of the labeled amount.

DISCUSSION

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

Doxapram hydrochloride[1] is a respiratory stimulant which acts primarily to increase tidal volume and secondarily to increase respiratory rate. It is particularly effective following general anesthesia to prevent postanesthetic respiratory depression or hypoventilation.

Quantitative Methods—The assay for chloride determines the nonactive portion of the molecule but serves as a control on the purity of the bulk material. Analysis of doxapram hydrochloride by the indicator titration method gave an average value of 8.18 ± 0.09%[2] chloride (Cl). The calculated value for chloride content is 8.19%.

The nonaqueous titrimetric procedure for doxapram hydrochloride gave an average value of 99.4 ± 0.3%.[2] The indicator end point was determined by simultaneous indicator and potentiometric observation during the titration. The electrode system employed was glass *versus* calomel modified by replacement of the aqueous salt bridge with 0.02 *N* lithium chloride in glacial acetic acid.

Analysis of commercial doxapram hydrochloride injection by the spectrophotometric method gave an average value of 99.6 ± 0.5%[2] of the labeled amount of doxapram hydrochloride. This approach can be used for analysis of bulk doxapram hydrochloride provided suitable reference standard material is available for absorbance measurement.

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

[2] Maximum deviation from the mean value.