# Qualitative and Quantitative Tests for Oxymetazoline Hydrochloride

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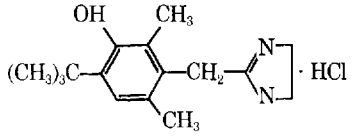
6-TERT-BUTYL-3-(2-IMIDAZOLIN-2-YLMETHYL)-2,4-DIMETHYL-PHENOL HYDROCHLORIDE; $C_{16}H_{24}N_2O \cdot HCl$; mol. wt. 296.84. The structural formula of oxymetazoline hydrochloride may be represented as



**Physical Properties.**—Oxymetazoline hydrochloride occurs as a white to nearly white, fine crystalline powder, m.p. about 300° dec., U.S.P. class I. It is soluble in water, freely soluble in alcohol, and insoluble in ether and in chloroform.

**Identity Tests.**—Dissolve about 2 mg. of oxymetazoline hydrochloride in 1 ml. of water, add 0.5 ml. of sodium nitroprusside solution (1 in 100), 2 drops of sodium hydroxide solution (15 in 100), mix, and allow to stand 10 min. Add 1 ml. of sodium bicarbonate solution (5 in 100) and allow to stand 10 min.: a violet color is produced.

A 1 in 20,000 solution of oxymetazoline hydrochloride in water exhibits an ultraviolet maximum at about 279 mμ [absorptivity ($a$) about 6.0] and a minimum at about 252 mμ. The spectrum is shown in Fig. 1.

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

Dissolve about 50 mg. of oxymetazoline hydrochloride in 3 ml. of water, add ammonia T.S. until basic, and filter. Acidify the filtrate with diluted nitric acid and add 1 ml. of silver nitrate T.S.: a white precipitate forms, which is insoluble in diluted nitric acid, but soluble in ammonia T.S. (presence of chloride).

**Purity Tests.**—Dry about 1 Gm. of oxymetazoline hydrochloride, accurately weighed, at 105° to con-

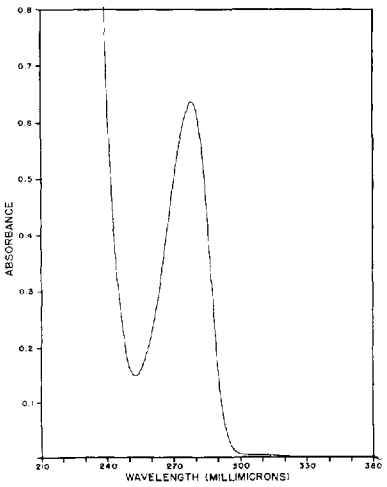



Fig. 1.—Ultraviolet absorption spectrum of oxymetazoline hydrochloride in water (100 mcg./ml.); Beckman model DK-2A spectrophotometer.

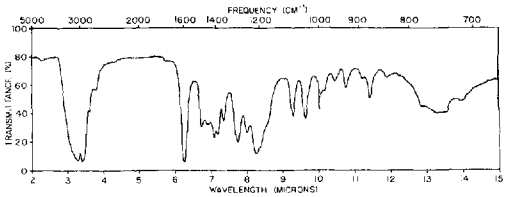



Fig. 2.—Infrared spectrum of oxymetazoline hydrochloride in potassium bromide disk (0.5%); Perkin-Elmer model 21 spectrophotometer, sodium chloride prism.

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stant weight (about 3 hr.): it loses not more than 0.5% of its weight.

Char about 1 Gm. of oxymetazoline hydrochloride, 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 oxymetazoline hydrochloride 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 I: the heavy metals limit for oxymetazoline hydrochloride is 10 p.p.m.

**Assay.**—Transfer about 500 mg. of oxymetazoline hydrochloride, accurately weighed, to a tall-form 200-ml. beaker and dissolve in 50 ml. of glacial acetic acid. Add 10 ml. of mercuric acetate T.S. and titrate potentiometrically with 0.1 *N* acetous perchloric acid. Alternatively, add 2 drops of crystal violet T.S. and titrate to an emerald-green end point.[1] Each milliliter of 0.1 *N* perchloric acid is equivalent to 29.68 mg. of $C_{16}H_{24}N_2O.HCl$. The amount of oxymetazoline hydrochloride found is not less than 98.5% and not more than 101.5%.

## DOSAGE FORMS OF OXYMETAZOLINE HYDROCHLORIDE

### Oxymetazoline Hydrochloride Nasal Solution

**Identity Tests.**—Transfer 2 ml. of oxymetazoline hydrochloride nasal solution to a test tube containing 2 ml. of alcohol, add 0.5 ml. of sodium nitroprusside solution (1 in 100), 2 drops of sodium hydroxide solution (15 in 100), mix, and allow to stand 10 min. Add 1 ml. of sodium bicarbonate solution (5 in 100), adjust the pH to about 8 with diluted hydrochloric acid, and allow to stand 10 min.: a violet color is produced.

**Assay.**—Transfer to a separator an accurately measured volume of oxymetazoline hydrochloride nasal solution equivalent to 5 mg. of oxymetazoline hydrochloride. Add 25 ml. of saturated sodium borate solution and extract with four 25-ml. portions of chloroform, combining the extracts in a 250-ml. separator. Extract the chloroform phase with two 20-ml. portions of 0.5 *N* hydrochloric acid, combine the acid extracts in a 100-ml. volumetric flask, dilute with the acid to volume, and mix. Concomitantly determine the absorbance of this solution and of a standard solution of oxymetazoline hydrochloride, in the same medium, at a concentration of about 50 mcg./ml., in 1-cm. cells, at the maximum at about 279 mμ, with a suitable spectrophotometer, using 0.5 *N* hydrochloric acid as the blank. Calculate the quantity, in mg., of $C_{16}H_{24}N_2O \cdot HCl$ in each ml. of the nasal solution taken, by the formula $0.1 \times (C/V) \times (A_u/A_s)$, in which $C$ is the exact concentration of the standard solution, in mcg./ml., $V$ is the volume, in ml., of the nasal solution taken, $A_u$ is the absorbance of the sample solution, and $A_s$ is the absorbance of the oxymetazoline hydrochloride standard solution. The amount of oxymetazoline hydrochloride found is not less than 95.0% and not more than 115.0% of the labeled amount.

## DISCUSSION

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

Oxymetazoline hydrochloride,[2] synthesized by Fruhstorfer and Mueller-Calgan (1), is a nasal decongestant for the treatment of a wide variety of allergic and infectious disorders, including rhinitis, nasopharyngitis, and sinusitis.

**Identity Tests.**—The absorbance maximum for oxymetazoline hydrochloride in water or acid solution is about 279 mμ. A bathochromic displacement, typical for phenols, is noted by an absorbance maximum at about 302 mμ in 0.5 *N* NaOH with a calculated absorptivity of about 15.3.

**Quantitative Methods.**—The potentiometric nonaqueous titration for oxymetazoline hydrochloride was conducted using glass *versus* calomel electrodes. The calomel electrode was modified by replacing the aqueous potassium chloride salt bridge with 0.02 *N* lithium chloride in glacial acetic acid. The indicator end point is sharp and corresponds to a 100–150-mv. break in the potentiometric titration curve obtained under identical conditions. An average value of 99.9 ± 0.4%[3] was obtained for oxymetazoline hydrochloride by this titrimetric method.

Analysis of commercial oxymetazoline hydrochloride nasal solution by the spectrophotometric method gave an average value of 110.7 ± 0.9%[3] of the labeled amount. The suitability of the procedure was verified by the quantitative recovery of a standard oxymetazoline hydrochloride solution carried through the extractive steps as included for the nasal solution.

## REFERENCE

(1) Fruhstorfer, W., and Mueller-Calgan, H., Ger. pat. 1,117,588 (November 23, 1961); through *Chem. Abstr.*, **57**, 4674(1962).

[1] If the indicator method is used, perform a blank titration and make any necessary correction.

[2] Marketed as Afrin by the Schering Corp., Bloomfield, N. J.

[3] Maximum deviation from the mean value.