Mix *Solution A* and *Solution B.* To 25 mL of this stock solution add 50 g of tartaric acid and 250 mL of water, and mix.

Test preparation—Dissolve 57 mg of Doxapram Hydrochloride in 0.5 mL of 0.1 N sodium hydroxide, add 1.0 mL of chloroform, and shake.

Standard preparation A—Dissolve 57 mg of USP Doxapram Hydrochloride RS in 0.5 mL of 0.1 N sodium hydroxide, add 1.0 mL of chloroform, and shake.

Standard preparation B—Dissolve 11.4 mg of USP Doxapram Hydrochloride RS in 0.5 mL of 0.1 N sodium hydroxide, add 100 mL of chloroform, and shake.

Procedure—Apply 10-µL portions of the chloroform solutions obtained from the *Test preparation* and the *Standard preparations* to a suitable thin-layer chromatographic plate (see *Chromatography* ⟨621⟩) coated with a 0.25-mm layer of chromatographic silica gel mixture. Allow the spots to dr y, and develop the chromatogram in a chromatographic chamber lined with paper and equilibrated with a solvent system consisting of a mixture of isopropyl alcohol and 1 N ammonium hydroxide (4:1) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Spray the plate with *Dragendorff reagent* in order to visualize the spots: the R_F value of the principal spot obtained from the *Test preparation* corresponds to that obtained from *Standard preparation A*, and no spot, other than the principal spot, in the chromatogram of the *Test preparation* is larger or more intense than the principal spot obtained from *Standard preparation B* (0.2%).

Assay—Dissolve about 800 mg of Doxapram Hydrochloride, previously dried and accurately weighed, in 50 mL of glacial acetic acid, add 1 drop of cr ystal violet TS and 10 mL of mer curic acetate TS, and titrate with 0.1 N per chloric acid VS to a blue-green endpoint. Per form a blank determination, and make any necessary correction. Each mL of 0.1 N per chloric acid is equivalent to 41.50 mg of $C_{24}H_{30}N_2O_2 \cdot HCl$.

Doxapram Hydrochloride Injection

» Doxapram Hydrochloride Injection is a sterile solution of Doxapram Hydrochloride in W ater for Injection. It contains not less than 90.0 per cent and not more than 110.0 per cent of the labeled amount of $C_{24}H_{30}N_2O_2 \cdot HCl \cdot H_2O$.

Packaging and storage—Preserve in single-dose or in multiple-dose containers, preferably of T ype I glass.

USP Reference standards ⟨11⟩**—**
USP Doxapram Hydrochloride RS
USP Endotoxin RS

Identification—

A: The chromatogram obtained from the *Assay preparation* in the *Assay* exhibits a major peak for doxapram, the retention time of which corresponds to that of the doxapram peak in the chromatogram of the *Standard preparation*.

B: Transfer a volume of Injection, equivalent to about 50 mg of doxapram hydrochloride hydrate, to a separator containing 5 mL of water. Add 1 mL of a saturated solution of sodium chloride to the separator, insert the stopper, and mix. Add 5 mL of 2.5 N sodium hydroxide, and extract with three 15-mL portions of chloroform. Pass each extract through a pledget of glass wool, combine the filtrates in a 50-mL volumetric flask, dilute with chloroform to volume, and mix. Evaporate to dr yness about 5 mL of this solution. Dissolve the residue in 0.01 N sulfuric acid, dilute with the same solvent to 100 mL, and mix: the UV absorption spectrum of the solution so obtained exhibits maxima and minima at the same wavelengths as a solution similarly prepared, about 50 mg of USP Doxapram Hydrochloride RS, instead of Doxapram Hydrochloride Injection, being used.

Bacterial endotoxins ⟨85⟩**—**It contains not more than 3.3 USP Endotoxin Units per mg of doxapram hydrochloride.

pH ⟨791⟩: between 3.5 and 5.0.

Other requirements—It meets the requirements under *Injections* ⟨1⟩.

Assay—

Mobile phase—Dissolve 2.8 g of monobasic potassium phosphate in 1 L of water, adjust with 50% phosphoric acid or 1 N potassium hydroxide to a pH of 3.0 ± 0.1, and filter through a 0.5-µm or finer porosity filter. Prepare a suitable mixture of this solution and acetonitrile (65:35). Make adjustments if necessar y (see *System Suitability* under *Chromatography* ⟨621⟩).

Internal standard solution—Prepare a solution of diphenhydramine hydrochloride in water containing about 1.5 mg per mL.

Standard preparation—Dissolve an accurately weighed quantity of USP Doxapram Hydrochloride RS in water to obtain a solution having a known concentration of about 2 mg per mL. Transfer 5.0 mL of this solution and 5.0 mL of *Internal standard solution* to a 50-mL volumetric flask, dilute with water to volume, and mix.

Assay preparation—Transfer an accurately measured volume of Injection, equivalent to about 100 mg of doxapram hydrochloride monohydrate, to a 50-mL volumetric flask, dilute with water to volume, and mix. T ransfer 5.0 mL of this solution and 5.0 mL of *Internal standard solution* to a 50-mL volumetric flask, dilute with water to volume, and mix.

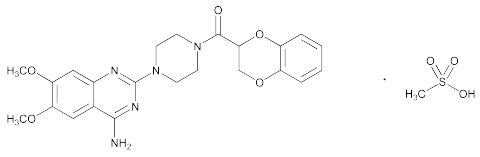
Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 225-nm detector and a 4.6-mm × 15-cm column containing 5- µm packing L10, and is maintained at 40 °. The flow rate is about 1.5 mL per minute. Chromatograph the *Standard preparation*, and record the responses as directed under *Procedure:* the relative retention times are about 1.0 for doxapram and 1.2 for diphenhydramine, the resolution, *R,* between the doxapram and diphenhydramine peaks is not less than 3.0; the tailing factor for the peaks is not more than 2.0, and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 5 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of doxapram hydrochloride hydrate ($C_{24}H_{30}N_2O_2 \cdot HCl \cdot H_2O$) in each mL of the Injection taken by the formula:

$$(432.98 / 414.98)(500C / V)(R_U / R_S)$$

in which 432.98 and 414.98 are the molecular weights of doxapram hydrochloride monohydrate and anhydrous doxapram hydrochloride, respectively, *C* is the concentration, in mg per mL, of USP Doxapram Hydrochloride RS in the *Standard preparation*, *V* is the volume, in mL, of Injection taken to prepare the *Assay preparation*, and R_U and R_S are the ratios of the peak responses of doxapram and diphenhydramine obtained from the *Assay preparation* and the *Standard preparation*, respectively.

Doxazosin Mesylate



$C_{23}H_{25}N_5O_5 \cdot CH_4O_3S$ 547.58

Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl]-, monomethanesulfonate.

1-(4-Amino-6,7-dimethoxy-2-quinazolinyl)-4-(1,4-benzodioxan-2-ylcarbonyl)piperazine monomethanesulfonate [77883-43-3].

» Doxazosin Mesylate contains not less than 98.0 percent and not more than 102.0 per cent of $C_{23}H_{25}N_5O_5 \cdot CH_4O_3S$, calculated on the dried basis.

Packaging and storage—Preserve in well-closed containers, and store below 30 °.

USP Reference standards ⟨11⟩**—**
USP Doxazosin Mesylate RS
USP Doxazosin Related Compound A RS
N-1,4-Benzodioxane-2-carbonyl piperazine.
$C_{13}H_{16}N_2O_3$ 248.28
USP Doxazosin Related Compound B RS
6,7-Dimethoxyquinazoline-2,4-dione.
$C_{10}H_{10}N_2O_4$ 222.20
USP Doxazosin Related Compound C RS
2-Chloro-4-amino-6,7-dimethoxyquinazoline.
$C_{10}H_{10}ClN_3O_2$ 239.66
USP Doxazosin Related Compound D RS
1,4-Benzodioxane-2-carboxylic acid.
$C_9H_8O_5$ 196.16
USP Doxazosin Related Compound E RS
2,4-Dichloro-6,7-dimethoxyquinazoline.
$C_{10}H_8Cl_2N_2O_2$ 259.09
USP Doxazosin Related Compound F RS
N,N'-Bis(1,4-benzodioxane-2-carbonyl)piperazine.
$C_{22}H_{22}N_2O_6$ 410.42
USP Terazosin Related Compound A RS
1-(4-Amino-6,7-dimethoxy-2-quinazolinyl)piperazine, dihydrochloride.
$C_{14}H_{19}N_5O_2 \cdot 2HCl$ 362.25
USP Terazosin Related Compound C RS
1,4-Bis(4-amino-6,7-dimethoxy-2-quinazolinyl)piperazine, dihydrochloride.
$C_{24}H_{28}N_8O_4 \cdot 2HCl$ 565.45

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

Loss on drying ⟨731⟩**—**Dry it in vacuum at 105 ° for 4 hours: it loses not more than 2.0% of its weight.

Residue on ignition ⟨281⟩**:** not more than 0.1%.

Heavy metals, *Method II* ⟨231⟩**:** 20 µg per g.

Related compounds—

Solvent A, Solvent D, Mobile phase, System suitability solution, and *Chromatographic system*—Proceed as directed in the *Assay.*

Solvent B—Use acetonitrile.

Solvent C— Use water.

Mobile phase—Use variable mixtures of *Solvent A, Solvent B,* and *Solvent C* as directed for *Chromatographic system* in the *Assay.* Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Dissolve accurately weighed quantities of USP Doxazosin Mesylate RS, USP Doxazosin Related Compound A RS, USP Doxazosin Related Compound B RS, USP Doxazosin Related Compound C RS, USP Doxazosin Related Compound D RS, USP Doxazosin Related Compound E RS, USP Doxazosin Related Compound F RS, USP Terazosin Related Compound A RS, and USP Terazosin Related Compound C RS in approximately 2 mL of *Solvent D;* and dilute quantitatively, and stepwise if necessary, with *Solvent C* and *Solvent D* to obtain a solution having a known concentration of 0.0015 mg per mL of each of the Reference Standards. The final ratio of *Solvent C* to *Solvent D* is maintained at 9:1. Sonicate briefly to dissolve completely.

Test solution—Dissolve an accurately weighed quantity of Doxazosin Mesylate in approximately 2 mL of *Solvent D,* and dilute with *Solvent C* and *Solvent D* to obtain a solution having a known concentration of 0.6 mg per mL. The final ratio of *Solvent C* to *Solvent D* is maintained at 9:1. Sonicate briefly to dissolve completely.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for all the peaks. Calculate the per centage of each impurity in the portion of Doxazosin Mesylate taken by the formula:

$$100(C_S / C_T)(r_i / r_S)$$

in which C_S is the concentration, in mg per mL, of each Reference Standard in the *Standard solution;* C_T is the concentration, in mg per mL, of Doxazosin Mesylate in the *Test solution;* r_i is the peak response for each individual impurity obtained from the *Test solution;* and r_S is the peak response for each individual impurity obtained from the *Standard solution:* not more than 0.3% of terazosin related compound A is found; not more than 0.25% of any other identified individual impurity is found; not more than 0.10% of any other unidentified impurity is found; and not more than 1.0% of total impurities is found. Calculate the percentages of doxazosin related compound G and doxazosin related compound H [NOTE—The doxazosin related compound G is the mesylate salt and has the same retention time as that of the terazosin related compound A. The doxazosin related compound H is the mesylate salt and has the same retention time as that of the doxazosin related compound C.] in the portion of Doxazosin Mesylate taken by the formula:

$$(100/F)(C_S / C_T)(r_i / r_S)$$

in which the response factor, F, is 0.735 for doxazosin related compound G and 0.769 for doxazosin related compound H; C_S is the concentration, in mg per mL, of USP Doxazosin Mesylate RS in the *Standard solution;* C_T is the concentration, in mg per mL, of Doxazosin Mesylate in the *Test solution;* r_i is the peak response of doxazosin related compound G or doxazosin related compound H in the *Test solution;* and r_S is the peak response of USP Doxazosin Mesylate RS in the *Standard solution.*

Assay—

Solvent A—Dissolve 5 g of phosphoric acid (84%–86%) in 100 mL of water.

Solvent B—Use acetonitrile.

Solvent C—Use water.

Solvent D—Prepare a mixture of 100 mL of *Solvent B* and 2 g of phosphoric acid (84%–86%).

Mobile phase—Use variable mixtures of degassed *Solvent A, Solvent B,* and *Solvent C,* as directed for *Chromatographic system.* Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Dissolve accurately weighed quantities of USP Doxazosin Related Compound A RS and USP Doxazosin Related Compound B RS in approximately 2.5 mL of *Solvent D.* Further dilute this solution quantitatively, and stepwise if necessary, with *Solvent C* and *Solvent D* to obtain a final solution having a known concentration of 12 µg per mL of each of the related compounds. The final ratio of *Solvent C* to *Solvent D* is maintained at 9:1. Sonicate briefly to dissolve completely.

Standard preparation—Dissolve an accurately weighed quantity of USP Doxazosin Mesylate RS in approximately 2 mL of *Solvent D,* and dilute with *Solvent C* and *Solvent D* to obtain a solution having a known concentration of 0.6 mg per mL. The final ratio of *Solvent C* to *Solvent D* is maintained at 9:1. Sonicate briefly to dissolve completely.

Assay preparation—Dissolve an accurately weighed quantity of Doxazosin Mesylate in approximately 2 mL of *Solvent D,* and dilute with *Solvent C* and *Solvent D* to obtain a solution having a concentration of 0.6 mg per mL, based on the labeled quantity of doxazosin mesylate. The final ratio of *Solvent C* to

Solvent D is maintained at 9:1. Sonicate briefly to dissolve completely.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 210-nm detector and a 4-mm × 25-cm column that contains 5- µm packing L1. The flow rate is about 0.8 mL per minute, and the column temperature is maintained at 35 °. The chromatograph is programmed as follows.

Time (min)	Solvent A (%)	Solvent B (%)	Solvent C (%)	Elution
0–10	20	10→22	70→58	linear gradient
10–35	20	22→50	58→30	linear gradient
35–40	20	50	30	equilibration

[NOTE—Between sample injections, the system is re-equilibrated for at least 7 minutes, or until a stable baseline is obtained, representing the starting composition.]

Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between doxazosin related compound A and doxazosin related compound B is not less than 4.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the doxazosin mesylate peaks. Calculate the percentage of $C_{23}H_{25}N_5O_5 \cdot CH_4O_3S$ in the portion of Doxazosin Mesylate taken by the formula:

$$100(C_S / C_T)(r_U / r_S)$$

in which C_S is the concentration, in mg per mL, of USP Doxazosin Mesylate RS in the *Standard preparation;* C_T is the concentration, in mg per mL, of Doxazosin Mesylate in the *Assay preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

Doxazosin Tablets

» Doxazosin Tablets contain an amount of doxazosin mesylate equivalent to not less than 90.0 percent and not more than 110.0 per cent of the labeled amount of doxazosin ($C_{23}H_{25}N_5O_5$).

Packaging and storage—Preserve in tight containers.

USP Reference standards ⟨11⟩**—**
USP Doxazosin Mesylate RS

Identification—The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

Dissolution ⟨711⟩—

Medium: 0.01 N hydrochloric acid; 900 mL.

Apparatus 2: 50 rpm.

Time: 30 minutes.

Procedure—Determine the amount of doxazosin mesylate ($C_{23}H_{25}N_5O_5 \cdot CH_4SO_3$) dissolved by employing UV absorption at the wavelength of maximum absorbance at about 246 nm on filtered portions of the solution under test, suitably diluted with *Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Doxazosin Mesylate RS in the same *Medium.*

Tolerances—Not less than 70% *(Q)* of the labeled amount of $C_{23}H_{25}N_5O_5 \cdot CH_4SO_3$ is dissolved in 30 minutes.

Uniformity of dosage units ⟨905⟩: meet the requirements.

Assay—

Buffer solution—Transfer 3.4 g of monobasic potassium phosphate into a 1-L flask, and add 800 mL of water and 4.0 mL of triethylamine to dissolve. Adjust with phosphoric acid to a pH of 4.5, and dilute with water to volume.

Mobile phase—Prepare a filtered and degassed mixture of methanol and *Buffer solution* (11 : 9). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩.)

Diluent: A mixture of methanol and 0.1 N hydrochloric acid (9 : 1).

Standard preparation—Dissolve an accurately weighed quantity of USP Doxazosin Mesylate RS in *Diluent,* and dilute quantitatively and stepwise if necessary, with *Diluent* to obtain a solution having a final concentration of about 49 µg per mL.

Chromatographic system (see Chromatography ⟨621⟩*)*—The liquid chromatograph is equipped with a 245-nm detector and a 4.6-mm × 25-cm column that contains 5- µm packing L1. The flow rate is about 1 mL per minute, and the column temperature is maintained at 40 °. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the capacity factor, k′, for doxazosin is not less than 2.0; the column efficiency is not less than 1000 theoretical plates; the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

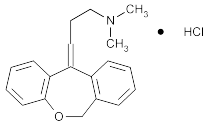
Assay preparation—Transfer 10 Tablets, whole or ground, into a 250-mL volumetric flask, add 10 mL of water, and sonicate until the Tablets are disintegrated. Add 150 mL of *Diluent,* sonicate for 30 minutes, dilute with *Diluent* to volume, and mix. Quantitatively dilute a portion of the supernatant with *Diluent* to obtain a solution having a concentration of about 0.04 mg of doxazosin per mL.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the doxazosin peaks. Calculate the quantity, in mg, of doxazosin ($C_{23}H_{25}N_5O_5$) in the portion of Tablets taken by the formula:

$$(451.48/547.58)CD(r_U / r_S)$$

in which 451.48 and 547.58 are the molecular weights of doxazosin and doxazosin mesylate, respectively; *C* is the concentration, in mg per mL, of USP Doxazosin Mesylate RS in the *Standard preparation; D* is the dilution volume, in mL, considering the initial 250-mL flask and any subsequent dilution used to prepare the *Assay preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

Doxepin Hydrochloride



$C_{19}H_{21}NO \cdot HCl$ 315.84

1-Propanamine, 3-dibenz[*b,e*]oxepin-11(6*H*)ylidene-*N,N*-dimethyl-, hydrochloride.

N,N-Dimethyldibenz[*b,e*]oxepin-$\Delta^{11(6H),\gamma}$-propylamine hydrochloride [1229-29-4; 4698-39-9((E)-isomer); 25127-31-5((Z)-isomer)].

» Doxepin Hydrochloride, an (*E*) and (*Z*) geometric isomer mixture, contains the equivalent of not less than 98.0 per cent and not more than 102.0 percent of doxepin hydrochloride ($C_{19}H_{21}NO \cdot$