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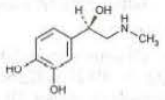
separator. Extract the chloroform solution with 50.0 mL of 0.1 N sulfuric acid. Filter the acid layer through paper, and dilute 5.0 mL of it with 0.1 N sulfuric acid to 100.0 mL.

Procedure—Proceed as directed for *Procedure* in the *Assay* under *Ephedrine Sulfate Capsules*. Calculate the quantity, in mg, of $(C_{10}H_{15}NO)_2 \cdot H_2SO_4$ in the portion of Syrup taken by the formula:

$$C(A_U / A_S),$$

in which C is the concentration, in µg per mL, of USP Ephedrine Sulfate RS in the *Standard preparation*, and A_U and A_S are the absorbances of the solutions from the *Assay preparation* and the *Standard preparation*, respectively.

Epinephrine



$C_9H_{13}NO_3$ 183.20
1,2-Benzenediol, 4-[1-hydroxy-2-(methylamino)ethyl]-, (*R*)-.
(–)-3,4-Dihydroxy-α-[(methylamino)methyl]benzyl alcohol
[*51-43-4*].

» Epinephrine contains not less than 97.0 percent and not more than 100.5 percent of $C_9H_{13}NO_3$, calculated on the dried basis.

Packaging and storage—Preserve in tight, light-resistant containers.

USP Reference standards ⟨11⟩—*USP Epinephrine Bitartrate RS*. *USP Norepinephrine Bitartrate RS*.

Identification—To 5 mL of pH 4.0 acid phthalate buffer (see *Buffer Solutions* in the section *Reagents, Indicators, and Solutions*) add 0.5 mL of a slightly acid solution of Epinephrine (1 in 1000) and 1.0 mL of 0.1 N iodine. Mix, and allow to stand for 5 minutes. Add 2 mL of sodium thiosulfate solution (1 in 40): a deep red color is produced.

Specific rotation ⟨781S⟩: between –50.0° and –53.5°.

Test solution: 20 mg per mL, in 0.6 N hydrochloric acid.

Loss on drying ⟨731⟩—Dry it in vacuum over silica gel for 18 hours: it loses not more than 2.0% of its own weight.

Residue on ignition ⟨281⟩: negligible, from 100 mg.

Limit of adrenalone—Its absorptivity (see *Spectrophotometry and Light-Scattering* ⟨851⟩) at 310 nm, determined in a solution in dilute hydrochloric acid (1 in 200) containing 2 mg per mL, is not more than 0.2.

Limit of norepinephrine—

Epinephrine standard solution—Dilute with methanol an accurately measured volume of a solution of USP Epinephrine Bitartrate RS in formic acid containing about 364 mg per mL to obtain a solution having a concentration of about 20 mg per mL.

Norepinephrine standard solution—Dilute with methanol an accurately measured volume of a solution of USP Norepinephrine Bitartrate RS in formic acid containing 16 mg per mL to obtain a solution having a known concentration of 1.6 mg per mL.

Test solution—Dissolve 200 mg of Epinephrine in 1.0 mL of formic acid, and dilute with methanol to 10.0 mL, and mix.

Procedure—Apply 5-µL portions of *Epinephrine standard solution*, *Norepinephrine standard solution*, and *Test solution* 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 dry, and develop the chromatogram in an unsaturated tank using a solvent system consisting of a mixture of *n*-butanol, water, and formic acid (7 : 2 : 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 in warm circulating air. Spray with Folin-Ciocalteu Phenol TS, followed by sodium carbonate solution (1 in 10): the R_f value of the principal spot obtained from the *Test solution* corresponds to that obtained from the *Epinephrine standard solution*. Any spot obtained from the *Test solution* is not larger nor more intense than the spot with the same R_f value obtained from the *Norepinephrine standard solution*, corresponding to not more than 4.0% of norepinephrine.

Assay—Dissolve about 300 mg of Epinephrine, accurately weighed, in 50 mL of glacial acetic acid TS, warming slightly if necessary to effect solution. Add crystal violet TS, and titrate with 0.1 N perchloric acid VS. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 18.32 mg of $C_9H_{13}NO_3$.

Epinephrine Inhalation Aerosol

» Epinephrine Inhalation Aerosol is a solution of Epinephrine in propellants and Alcohol prepared with the aid of mineral acid in a pressurized container. It contains not less than 90.0 percent and not more than 115.0 percent of the labeled amount of epinephrine ($C_9H_{13}NO_3$).

Packaging and storage—Preserve in small, nonreactive, light-resistant aerosol containers equipped with metered-dose valves and provided with oral inhalation actuators.

USP Reference standards ⟨11⟩—*USP Epinephrine Bitartrate RS*.

Identification—Place 10 mL of water in a small beaker, and deliver 2 sprays from the Inhalation Aerosol under the surface of the water, actuating the valve by pressing the tip against the bottom of the beaker. To 5 mL of the solution add 1 drop of dilute sulfuric acid (1 in 200), add 0.5 mL of 0.1 N iodine, allow to stand for 5 minutes, and add 1 mL of 0.1 N sodium thiosulfate: a red-brown color is produced.

Delivered dose uniformity over the entire contents: meets the requirements for *Metered-Dose Inhalers* under *Aerosols, Metered-Dose Inhalers, and Dry Powder Inhalers* ⟨601⟩.

PROCEDURE FOR DOSE UNIFORMITY—

Ferro-citrate solution and *Buffer solution*—Prepare as directed under *Epinephrine Assay* ⟨391⟩.

Standard preparation—Dissolve an accurately weighed quantity of USP Epinephrine Bitartrate RS in a freshly prepared sodium bisulfite solution (1 in 500), and dilute quantitatively and stepwise with the same sodium bisulfite solution as necessary to obtain a solution having a known concentration of about 18 µg per mL.

Test preparation—Discharge the minimum recommended dose into the sampling apparatus and detach the inhaler as directed. Rinse the apparatus (filter and interior) with four 5.0-mL portions of a freshly prepared sodium bisulfite solution (1 in 500), and transfer the resulting solutions quantitatively to a 50-mL centrifuge tube. Add 10 mL of chloroform, insert the stopper, shake vigorously for 1 minute, and centrifuge for 5 minutes. Use the clear supernatant as directed in the *Procedure*.

Procedure—Into three separate flasks, transfer the *Test preparation*, 20.0 mL of the *Standard preparation*, and 20.0 mL of water to provide the blank. To each flask add 100 µL of *Ferro-citrate solution* and 1.0 mL of *Buffer solution*, and mix. Concomitantly determine the absorbances with a suitable spectrophotometer, in 5-cm cells, of the solutions from the *Test preparation* and the *Standard preparation*, at the wavelength of maximum absorbance at about 530 nm, against the blank. Calculate the quantity, in µg, of $C_9H_{13}NO_3$ contained in the minimum dose taken by the formula:

$$(183.20 / 333.29)(20CN)(A_U / A_S),$$

in which C is the concentration, in µg per mL, of USP Epinephrine Bitartrate RS in the *Standard preparation; N* is the number of sprays discharged to obtain the minimum recommended dose; 183.20 and 333.29 are the molecular weights of epinephrine and epinephrine bitartrate, respectively; and A_U and A_S are the absorbances of the solutions from the *Test preparation* and the *Standard preparation*, respectively.

Assay—Weigh the Inhalation Aerosol, chill to a temperature below –30°, remove the valve by suitable means, and allow the Inhalation Aerosol to warm slowly to room temperature to expel the more volatile propellant fractions. Transfer the residues in the aerosol

container and valve to a 125-mL separator with the aid of six 5-mL portions of dilute sulfuric acid (1 in 1000), and extract the solution with three 25-mL portions of chloroform. Proceed as directed in the *Assay* under *Epinephrine Nasal Solution*, beginning with "Rinse the stopper and mouth of the separator," but use 10.0 mL instead of 5.0 mL of chloroform in the determination of the specific rotation. Dry the empty aerosol container and valve, weigh them, and determine the net weight of the Inhalation Aerosol. Calculate the quantity, in mg, of $C_9H_{13}NO_3$ in the Inhalation Aerosol taken by the formula:

$$(183.20/309.32)(W)(0.5 + 0.5R/93),$$

in which 183.20 and 309.32 are the molecular weights of epinephrine and triacetylepinephrine, respectively, and W is the weight, in mg, and R is the specific rotation (in degrees, without regard to the sign), of the isolated triacetylepinephrine.

Epinephrine Injection

» Epinephrine Injection is a sterile solution of Epinephrine in Water for Injection prepared with the aid of Hydrochloric Acid or other suitable buffers. It contains not less than 90.0 percent and not more than 115.0 percent of the labeled amount of $C_9H_{13}NO_3$.

Packaging and storage—Preserve in single-dose or in multiple-dose, light-resistant containers, preferably of Type I glass.

Labeling—The label indicates that the Injection is not to be used if its color is pinkish or darker than slightly yellow or if it contains a precipitate.

USP Reference standards ⟨11⟩—*USP Epinephrine Bitartrate RS. USP Endotoxin RS.*

Color and clarity—

Standard solution—Transfer 2.0 mL of 0.100 N iodine VS to a 500-mL volumetric flask, dilute with water to volume, and mix.

Procedure—Visually examine a portion of the Injection (*Test solution*) in a suitable clear glass test tube against a white background: it is not pinkish and it contains no precipitate. If any yellow color is observed in the *Test solution*, concomitantly determine the absorbances of the *Test solution* and the *Standard solution* in 1-cm cells with a suitable spectrophotometer set at 460 nm: the absorbance of the *Test solution* does not exceed that of the *Standard solution*.

Identification—It responds to the *Identification* test under *Epinephrine Nasal Solution*.

Bacterial endotoxins ⟨85⟩ It contains not more than 357.0 USP Endotoxin Units per mg of epinephrine.

pH ⟨791⟩: between 2.2 and 5.0.

Total acidity—Transfer 5.0 mL of Injection to a flask, add 10 mL of water, and titrate with 0.01 N sodium hydroxide VS to a pH of 7.40. Perform a blank determination, and make any necessary correction. Not more than 25.0 mL of 0.01 N sodium hydroxide is required.

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

Assay—

Mobile phase—To 1 liter of 0.05 M monobasic sodium phosphate add about 519 mg of sodium 1-octanesulfonate and about 45 mg of edetate disodium, and mix. Adjust by the dropwise addition of phosphoric acid, if necessary, to a pH of 3.8. Mix 85 volumes of this solution with 15 volumes of methanol. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Epinephrine Bitartrate RS in *Mobile phase*, and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.1 mg of epinephrine per mL.

Assay preparation—Transfer an accurately measured volume of Injection, equivalent to about 1 mg of epinephrine, to a 10-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

System suitability preparation—Dissolve 10 mg of dopamine

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 280-nm detector and a 4.6-mm × 15-cm column that contains packing L7. The flow rate is about 2 mL per minute. Chromatograph the *Standard preparation* and the *System suitability preparation*, and record the peak responses as directed under *Procedure:* the resolution, R, between the epinephrine and dopamine hydrochloride peaks is not less than 3.5, and the relative standard deviation for replicate injections is not more than 2.0%.

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 major peaks. The relative retention times are about 1.0 for epinephrine and 2.0 for dopamine hydrochloride. Calculate the quantity, in mg, of $C_9H_{13}NO_3$ in each mL of the Injection taken by the formula:

$$(183.20/333.29)(10)(C/V)(r_U/r_S),$$

in which 183.20 and 333.29 are the molecular weights of epinephrine and epinephrine bitartrate, respectively; C is the concentration, in mg per mL, of USP Epinephrine Bitartrate RS in the *Standard preparation*; V is the volume, in mL, of Injection taken; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively.

Epinephrine Inhalation Solution

» Epinephrine Inhalation Solution is a sterile solution of Epinephrine in Purified Water prepared with the aid of Hydrochloric Acid. It contains, in each 100 mL, not less than 0.9 g and not more than 1.15 g of $C_9H_{13}NO_3$.

Packaging and storage—Preserve in small, well-filled, tight, light-resistant containers.

Labeling—The label indicates that the Inhalation Solution is not to be used if its color is pinkish or darker than slightly yellow or if it contains a precipitate.

Color and clarity—Using the Inhalation Solution as the *Test solution*, proceed as directed for *Color and clarity* under *Epinephrine Injection*.

Identification—It meets the requirements for the *Identification* test under *Epinephrine Nasal Solution*.

Sterility ⟨71⟩: meets the requirements.

Assay—Pipet 10 mL of Inhalation Solution into a 125-mL separator, and extract the solution with two 10-mL portions of chloroform. Proceed as directed in the *Assay* under *Epinephrine Nasal Solution*, beginning with "Rinse the stopper and mouth of the separator," but use for the acetylation 1.05 g of sodium bicarbonate and 0.50 mL of acetic anhydride, and extract the acetylated product with six 15-mL portions of chloroform instead of the 25-mL portions specified therein, and use 15.0 mL of chloroform instead of 5.0 mL in the determination of the specific rotation.

Epinephrine Nasal Solution

» Epinephrine Nasal Solution is a solution of Epinephrine in Purified Water prepared with the aid of Hydrochloric Acid. It contains, in each 100 mL, not less than 90 mg and not more than 115 mg of $C_9H_{13}NO_3$.

Packaging and storage—Preserve in small, well-filled, tight, light-resistant containers.

Labeling—The label indicates that the Nasal Solution is not to be used if its color is pinkish or darker than slightly yellow or if it

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