The relative retention to r isopilocarpine, 0.76 1.0 for isopilocarpic acid lumes (about 40 μ L) of μ easure the responses for of pilocarpine (C₁₁H₁₆N₀) formula:

 (r_u/r_s)

ular weights of pilocapit he concentration, in mg Standard preparation, a carpine obtained from the aration, respectively.

m

ains not less than 85, percent of the labele \hat{v}_2). It is sterile.

ngle-dose containers, in

P Pilocarpine RS. carpine Nitrate RS. rgin of the Ocular Sys cular System, extract 101 in a small capped w porate the methanol exte in film: the IR absorpti at the same wavelength arpine RS.

eets the requirements

Ocular Systems in suit and suspend each from attach a tag identifying ibe containing 27.0 mL ottom of the tube and of the tube. Put the tu 1 which the temperature tubes with a horizon by of about 35 cycles urs, remove the assemb e them in similar to Determine the amount ijusting the volume to? es, by measuring the h of maximum absorb otometer, against saling absorbance of a Stand ride RS having a known of saline TS. Calculate ition taken by the formu

1s)27C,

ular weights of pilocal vely, A_U and A_s are the Standard solution , in µg per mL, of t lard solution. Calculate s by adding the pilocarp 168 hours.

from each Ocular Sys ed conforms to Accept irug release range for t more than 120.0% of

Buffer solution, Mobile phase, Standard preparation, System Buffer preparation, and Chromatographic system-Proceed as meeted in the Assay under Pilocarpine.

Assay preparation—Select not less than 10 Ocular Systems. Cut System into 4 pieces, transfer quantitatively to a 500-mL tempting the flask, and rinse all cutting utensils with 20 to 30 mL of thanol into the flask. Make additional rinses of the utensils with and the flasks to stand for 30 minutes, sonicate for about 15 how the hardware to volume, and mix. Transfer an aliquot of supernatant, equivalent to 6 mg of pilocarpine to a 200-mL numetric flask, dilute with water to volume, mix, and filter.

Procedure-Proceed as directed for Procedure in the Assay under mocarpine. Calculate the quantity, in mg, of Pilocarpine. Calculate quantity, in mg, of Pilocarpine in each ocular system taken by the hmula:

 $(208.26/271.27)(10/V)(C/N)(r_v/r_s),$

which 208.26 and 271.27 are the molecular weights of pilocarpine d pilocarpine nitrate, respectively, V is the volume, in mL, of the mematant taken (see Assay preparation), C is the concentration, in per mL, of USP Pilocarpine Nitrate RS in the Standard reparation, N is the number of Ocular Systems taken, and r_U and are the peak responses for pilocarpine obtained from the Assay eparation and the Standard preparation, respectively.

Pilocarpine Hydrochloride

H₁₆N₂O₂ · HCl 244.72

Margos 1001 277.72 M)-Furance, 3-ethyldihydro-4-[(1-methyl-1*H*-imidazol-5-yl)methyl]-, monohydrochloride, (3*S-cis*)-. hearpine monohydrochloride [54-71-7].

Pilocarpine Hydrochloride contains not less than 98.5 ercent and not more than 101.0 percent of $_{11}H_{16}N_2O_2 \cdot HCl$, calculated on the dried basis.

ekaging and storage-Preserve in tight, light-resistant containers. P Reference standards (11)-USP Pilocarpine Hydrochloride

tification-

À: Infrared Absorption (197M).

A solution (1 in 20) responds to the tests for Chloride (191). ting range (741): between 199° and 205°, but the range ween beginning and end of melting does not exceed 3°. **this rotation** (781S): between +88.5° and +91.5°. **Text solution**: 20 mg per mL, in water.

on drying (731)—Dry it at 105° for 2 hours: it loses not more 130% of its weight.

dily carbonizable substances (271)—Dissolve 250 mg in 5 mL sulfuric acid TS: the solution has no more color than Matching id B.

dinary impurities (466)-

let solution: dehydrated alcohol. mandard solution: dehydrated alcohol. huant: a mixture of hexanes, dehydrated alcohol, and ammoin hydroxide (70:30:1). Isualization: 17.

limits: not more than 1%.

alkaloids-Dissolve 200 mg in 20 mL of water, and divide the tion into two portions. To one portion add a few drops of 6 N monium hydroxide, and to the other add a few drops of potassium mate TS: no turbidity is produced in either solution.

y-Dissolve about 500 mg of Pilocarpine Hydrochloride, multiply weighed, in a mixture of 20 mL of glacial acetic acid 10 mL of mercuric acetate TS, warming slightly to effect tion. Cool the solution to room temperature, add 2 drops of violet TS, and titrate with 0.1 N perchloric acid VS. Perform a determination, and make any necessary correction. Each mL of perchloric acid is equivalent to 24.47 mg of $C_{11}H_{16}N_2O_2 \cdot HCl$.

Pilocarpine Hydrochloride Ophthalmic Solution

» Pilocarpine Hydrochloride Ophthalmic Solution is a sterile, buffered, aqueous solution of Pilocarpine Hydrochloride. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of C11H16N2O2 · HCl. It may contain suitable antimicrobial agents and stabilizers, and suitable additives to increase its viscosity.

Packaging and storage-Preserve in tight containers.

USP Reference standards (11)-USP Pilocarpine Hydrochloride 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. Sterility (71): meets the requirements.

pH (791): between 3.5 and 5.5.

Assav

Mobile phase—Mix 300 mL of a 1 in 50 solution of ammonium hydroxide in isopropyl alcohol and 700 mL of *n*-hexane. Filter through a 0.5-µm filter before using.

Standard preparation—Using an accurately weighed quantity of USP Pilocarpine Hydrochloride RS, prepare a solution having a

known concentration of about 1.6 mg per mL. Assay preparation—Transfer an accurately measured volume of Ophthalmic Solution, equivalent to about 80 mg of pilocarpine hydrochloride, to a 50-mL volumetric flask. Dilute with methanol to volume, and mix.

Chromatographic system (see Chromatography (621))—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 25-cm column that contains packing L3. The flow rate is about 2 mL per minute. Chromatograph three replicate injections of the Standard preparation, and record the peak responses as directed for Procedure: the relative standard deviation is not more than 2.0%.

Procedure-Separately inject equal volumes (about 10 µL) of the Standard preparation and the Assay preparation into the chromat-Summary properties of a suitable microsyringe or sampling valve, record the chromatograms, and measure the responses for the major peaks. The retention time is about 16 minutes for pilocarpine hydrochloride. Calculate the quantity, in mg, of $C_{11}H_{16}N_2O_2 \cdot HCl$ in each mL of the Ophthalmic Solution taken by the formula:

$50(C/V)(r_v/r_s),$

in which C is the concentration, in mg per mL, of USP Pilocarpine Hydrochloride RS in the Standard preparation, V is the volume, in mL, of Ophthalmic Solution taken, and r_{U} and r_{s} are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.

Pilocarpine Nitrate

C₁₁H₁₆N₂O₂ HNO₃ 271.27 2(3H)-Furanone, 3-ethyldihydro-4-[(1-methyl-1H-imidazol-5-

» Pilocarpine Nitrate contains not less than 98.5 percent and not more than 101.0 percent of $C_{11}H_{16}N_2O_2 \cdot NO_3$, calculated on the dried basis.

Packaging and storage-Preserve in tight, light-resistant containers. USP Reference standards (11)-USP Pilocarpine Nitrate RS. Identification-

A: Infrared Absorption (197K).

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1562 **Pilocarpine** | Official Monographs

B: Mix a solution (1 in 10) with an equal volume of ferrous sulfate TS, and superimpose the mixture upon 5 mL of sulfuric acid contained in a test tube: the zone of contact becomes brown.

Melting range (741): between 171° and 176°, with decomposition, but the range between beginning and end of melting does not exceed

Specific rotation (781S): between +79.5° and +82.5°. Test solution: 20 mg per mL, in water.

Loss on drying (731)—Dry it at 105° for 2 hours: it loses not more than 2.0% of its weight.

Readily carbonizable substances (271)-Dissolve 100 mg in 5 mL of sulfuric acid TS: the solution has no more color than Matching Fluid A.

Chloride—To 5 mL of a solution (1 in 50), acidified with nitric acid, add a few drops of silver nitrate TS: no opalescence is produced immediately.

Other alkaloids—Dissolve 200 mg in 20 mL of water, and divide the solution into two portions. To one portion add a few drops of 6 N ammonium hydroxide and to the other add a few drops of potassium dichromate TS: no turbidity is produced in either solution.

Assay-Dissolve about 600 mg of Pilocarpine Nitrate, accurately weighed, in 30 mL of glacial acetic acid, warming slightly to effect solution. Cool to room temperature, and titrate with 0.1 N perchloric acid VS, determining the endpoint potentiometrically. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 27.13 mg of C11H16N2O2 · NO3.

Pilocarpine Nitrate Ophthalmic Solution

» Pilocarpine Nitrate Ophthalmic Solution is a sterile, buffered, aqueous solution of Pilocarpine Nitrate. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{11}H_{16}N_2O_2 \cdot HNO_3$. It may contain suitable antimicrobial agents and stabilizers, and suitable additives to increase its viscosity.

Packaging and storage-Preserve in tight, light-resistant containers. USP Reference standards (11)-USP Pilocarpine Nitrate RS. Identification-

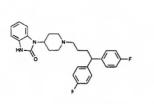
A: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation obtained as directed in the Assay

B: It responds to Identification test B under Pilocarpine Nitrate. Sterility (71): meets the requirements.

pH (791): between 4.0 and 5.5.

Assay-Proceed with Ophthalmic Solution as directed in the Assay under Pilocarpine Hydrochloride Ophthalmic Solution, except to read pilocarpine nitrate instead of pilocarpine hydrochloride throughout and to calculate the quantity, in mg, of $C_{11}H_{16}N_2O_2$ · HNO₃ in each mL of the Ophthalmic Solution taken by the formula given therein.

Pimozide



C28H29F2N3O 461.55

2H-Benzimidazol-2-one, 1-[1-[4,4-bis(4-fluorophenyl)buty] piperidinyl]-1,3-dihydro-

1-[1-[4,4-Bis(p-fluorophenyl)butyl]-4-piperidyl]-2-benzimida none [2062-78-4]

» Pimozide contains not less than 98.0 percent and more than 102.0 percent of C₂₈H₂₉F₂N₃O, calculated the dried basis.

Packaging and storage-Preserve in tight, light-resistant contain USP Reference standards (11)-USP Pimozide RS. Identification-

- Infrared Absorption (197K). Ultraviolet Absorption (197U)— A: B:
- Solution:
- 35 μg per mL. 0.1 N hydrochloric acid in methanol (1 in 10). Medium:

Melting range, Class I (741): between 216° and 220°. Loss on drying (731)—Dry it in vacuum at 80° for 4 hours: in not more than 0.5% of its weight.

Residue on ignition (281): not more than 0.2%, a 2-g portion platinum crucible being used for the test.

Heavy metals, Method II (231): 0.002%.

Ordinary impurities (466)

Test solution: chloroform. Standard solution: chloroform.

Eluant: a mixture of cyclohexane and acetone (1:1).

Visualization: 1, then 17. Limit—The total of any ordinary impurities observed does exceed 1.0%.

Organic volatile impurities, Method V (467): meets the real ments.

Solvent-Use dimethyl sulfoxide.

Assay-Dissolve about 320 mg of Pimozide, accurately weigh 40 mL of glacial acetic acid. Titrate with 0.1 N perchloric acid determining the endpoint potentiometrically. Perform a determination, and make any necessary correction. Each m 0.1 N perchloric acid is equivalent to 46.16 mg of C28H29F2N30

Pimozide Tablets

» Pimozide Tablets contain not less than 90.0 per and not more than 110.0 percent of the labeled amount $C_{28}H_{29}F_2N_3O.$

Packaging and storage-Preserve in tight, light-resistant con USP Reference standards(11)-USP Pimozide RS. Identification-The retention time of the major peak chromatogram of the Assay preparation corresponds to that a Standard preparation, both relative to the internal standard obtained in the Assay. SP 28

USP 28

olution, Procedure 1 Medium: 0.01 N hyd Apparatus 2: 50 rpm Time: 30 minutes. Sundard preparation-s, accurately weighed, of lactic acid. Heat or hot water, and shake. (not water, and shake. (nute the solution quantain a solution having me as that of the s solution).

Procedure—Transfer a table container, and ce ematant, estimated ming complete disso al volume of the Stand container add 20 mL roform. Shake each nutes, and centrifuge. transfer the chloro nine the amount of he chloroform layers ol *indard preparation*, in : probance at about 277 n Tolerances-Not less t H₂,F₂N₃O is dissolved i ormity of dosage uni Procedure for content ui 5.0 mL of 0.1 N hyd ns for 30 minutes. A chanical means for 20 n methanol to obtain a s of pimozide per mI mine the absorbance Pimozide RS in the sa out 40 µg per mL in 1 bout 40 µg por 1277 nm ture of 0.1 N hydrocl Calculate the quant by the formula:

0

which T is the labeled qu concentration, in µg ard solution, D is the solution from the Ta et and the extent of dilu solution from the Table V-[NOTE-Protect all onium acetate solu te in 100 mL of water, obile phase—Prepare mitrile and Ammoniu nents if necessary (se (621)).

mal standard solutio mixture of methanol on having a concentration and and preparation—T curately weighed, to a al standard solution, drofuran (1:1) to vol preparation-Weig Transfer an accura nt to about 25 mg of mL of Internal stand ol and tetrahydrofurat minutes. Dilute with 1:1) to volume, and ay preparation.

matographic system chromatograph is equ \times 25-cm column th out 2 mL per minute ard preparation, an edure: the relative sta

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Polymyxin B Sulfate and Bacitracin Zinc Topical Powder

» Polymyxin B Sulfate and Bacitracin Zinc Topical Powder contains not less than 90.0 percent and not more than 130.0 percent of the labeled amounts of polymyxin B and bacitracin.

Packaging and storage-Preserve in well-closed containers.

USP Reference standards (11)-USP Polymyxin B Sulfate RS. USP Bacitracin Zinc RS.

Microbial limits-Collect aseptically in a suitable container about 1 g from not less than 5 containers, dissolve in 500 mL of Fluid A, filter through a membrane filter as directed for Membrane Filtration under Test for Sterility of the Product to be Examined under Sterility Tests (71), except to place the filter on the surface of Soybean-Casein Digest Agar Medium in a Petri dish, incubate for 7 days at 30° to 35°, and count the number of colonies on the filter. Similarly prepare a second specimen, except to incubate at 20° to 25°. Not more than 20 colonies are observed from the two specimens. It meets also the requirements of the tests for absence of *Staphylococcus aureus* and *Pseudomonas aeruginosa* under *Microbial Limit Tests* $\langle 61 \rangle$.

Water, Method I (921): not more than 7.0%.

Assay for polymyxin B-Proceed as directed for polymyxin B under Antibiotics—Microbial Assays (81), using an accurately weighed portion of Topical Powder, equivalent to about 5000 USP Polymyxin B Units, shaken with 20 mL of water in a suitable volumetric flask. Dilute with Buffer No. 6 to volume, and mix. Dilute an accurately measured volume of the solution so obtained quantitatively with Buffer No. 6 to obtain a Test Dilution having a concentration of polymyxin B assumed to be equal to the median dose level of the Standard.

Assay for bacitracin—Proceed as directed for bacitracin under Antibiotics—Microbial Assays (81), using an accurately weighed portion of Topical Powder, equivalent to about 800 USP Bacitracin Units, added to a 100-mL volumetric flask, dilute with 0.01 N hydrochloric acid to volume, and mix. Dilute this solution quantitatively with Buffer No. 1 to obtain a Test Dilution having a concentration assumed to be equal to the median dose level of the Standard. In preparing each test dilution of the Standard, add additional hydrochloric acid to each to obtain the same concentration of hydrochloric acid as in the Test Dilution.

Polymyxin B Sulfate and Hydrocortisone Otic Solution

» Polymyxin B Sulfate and Hydrocortisone Otic Solution is a sterile solution containing not less than 90.0 percent and not more than 130.0 percent of the labeled amount of polymyxin B, and not less than 90.0 percent and not more than 110.0 percent of the labeled amount of hydrocortisone ($C_{21}H_{30}O_5$). It may contain one or more suitable buffers and preservatives.

NOTE-Where Polymyxin B Sulfate and Hydrocortisone Otic Solution is prescribed without reference to the quantity of polymyxin B or hydrocortisone contained therein, a product containing 10,000 Polymyxin B Units and 5 mg of hydrocortisone per mL shall be dispensed.

Packaging and storage-Preserve in tight, light-resistant containers. USP Reference standards (11)-USP Polymyxin B Sulfate RS. USP Hydrocortisone RS.

Sterility (71): meets the requirements.

pH (791): between 3.0 and 5.0.

Assay for polymyxin—Proceed with Otic Solution as directed und Assay for polymy an— rocced with the solution as uncerted under Antibiotics—Microbial Assays (81), using an accurately measure volume of Otic Solution diluted quantitatively with Buffer No. 6 yield a Test Dilution having a concentration assumed to be equal to the median dose level of the Standard. 12

Assay for hydrocortisone-

Mobile phase—Prepare a suitable solution of about 500 volumes a methanol, 500 volumes of water, and 1 volume of glacial acetic acid such that the retention time of hydrocortisone is between 6 and 16 minutes

Standard preparation—Dissolve a suitable quantity of Us Hydrocortisone RS, accurately weighed, in a mixture of methano and water (1:1) to obtain a solution having a known concentration of about 0.15 mg per mL.

Assay preparation-Transfer an accurately measured volume Otic Solution, equivalent to about 15 mg of hydrocortisone, to a 100 mL volumetric flask, dilute with a mixture of methanol and y (1:1) to volume, and mix.

Chromatographic system (see Chromatography (621))—The chromatograph is equipped with a 254-nm detector and a 4-nm 30-cm column that contains packing L1. The flow rate is about 2 m per minute. Chromatograph five replicate injections of the Stand preparation, and record the peak responses as directed for *Proceeding* the relative standard deviation is not more than 2.0%.

Procedure-Separately inject equal volumes (about 10 µL) of Standard preparation and the Assay preparation into the chron ograph by means of a suitable microsyringe or sampling va adjusting the specimen size and other operating parameters such the the peak obtained from the Standard preparation is about 0.6 fu scale. Record the chromatograms, and measure the responses for major peaks. Calculate the quantity, in mg, of $C_{21}H_{30}O_5$ in each mL the Otic Solution taken by the formula:

$(100C/V)(H_u/H_s),$

in which C is the concentration, in mg per mL, of US Hydrocortisone RS in the *Standard preparation*, V is the volume in mL, of the portion of Otic Solution taken, and H_{u} and H_{s} are peak responses obtained from the Assay preparation and Standard preparation, respectively.

Polymyxin B Sulfate and Trimethoprim **Ophthalmic Solution**

» Polymyxin B Sulfate and Trimethoprim Ophthalm Solution is a sterile, isotonic, aqueous solution Polymyxin B Sulfate and Trimethoprim Sulfate or Polymyxin B Sulfate and Trimethoprim that has been solubilized with Sulfuric Acid. It contains not less the 90.0 percent and not more than 130.0 percent of the labeled amount of polymyxin B and the equivalent of m less than 90.0 percent and not more than 110.0 percent the labeled amount of trimethoprim (C14H18N4O3). contains one or more preservatives.

Packaging and storage—Preserve in tight, light-resistant contain and store at controlled room temperature.

Labeling-Label it to indicate that it is to be stored at 15° to 25 protected from light.

USP Reference standards (11)-USP Polymyxin B Sulfate RS. US Trimethoprim RS.

Identification-

A: It meets the requirements for polymyxin B under Thin-Loy Chromatographic Identification Test (201BNP).

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

say for polymyxin E

dymyxin B assumed say for trimethopri

terility (71)—It meet imbrane Filtration u tamined.

hume of Ophthalmic

h Buffer No. 6, to ob

between 4

H (791):

Diluent—Prepare a etonitrile (870:130). Mobile phase—Dissc a mixture of water a dium hydroxide or 0. hution through a filter take adjustments if romatography (621) Standard preparation SP Trimethoprim RS i entration of about Assay preparationhthalmic Solution, ec 5-mL volumetric flask Chromatographic sy muid chromatograph i 9-mm × 30-cm colun out 1.5 mL per minut d record the peak resp for is not more than tak; and the relative station one than 2.0%.

Procedure-Separatel ndard preparation a and preparation a maph, record the chron ajor peaks. Calculat $i_{4}H_{14}N_4O_3$) in each m mula:

which C is the concen in the Standard p othalmic Solution tak \mathbf{I} r_s are the trimethop y preparation and t

olyvinyl Alco

民(0) nol, homopolymer. I alcohol polymer

olyvinyl Alcoho resented by the fe

which the averag 0. It is prepare olysis of polyvi entipoises, at 20 vinyl Alcohol i ent and not more label.

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lution as directed unit n accurately measure y with *Buffer No. 6* assumed to be equal

of about 500 volumes te of glacial acetic acid te is between 6 and 1

ble quantity of US a mixture of methanic known concentration

y measured volume y ydrocortisone, to a 10 of methanol and was

ography (621))tetector and a 4-mm flow rate is about 2 m flow rate is about 2 m ections of the Standar directed for Procedur an 2.0%. es (about 10 μ L) of th ation into the chrome ge or sampling van ng parameters such the ation is about 0.6 ful re the responses for the C₂₁H₃₀O₃ in each mLo

ng per mL, of US ation, V is the volume , and H_U and H_S are the preparation and the

'rimethoprim

hoprim Ophthalmi lucous solution of prim Sulfate or of prim that has been ntains not less that 30.0 percent of the he equivalent of m ian 110.0 percent of m (C₁₄H₁₈N₄O₃).

ight-resistant container

be stored at 15° to 25

myxin B Sulfate RS. US

rxin B under *Thin-Lap* NP). ethoprim peak in the presponds to that in the as obtained in the Ass while (71)—It meets the requirements when tested as directed for mbrane Filtration under Test for Sterility of the Product to be knnined.

(791): between 4.0 and 6.2.

Figure 1 For the second seco

lessy for trimethoprim-

Diluent-Prepare a mixture of 0.01 N hydrochloric acid and monitrile (870:130).

Mobile phase—Dissolve 1.65 g of ethanesulfonic acid in 1000 mL a mixture of water and acetonitrile (870:130). Adjust with 10 N dium hydroxide or 0.1 N hydrochloric acid to a pH of 3.5. Pass this huton through a filter having a 0.5-µm or finer porosity, and degas. Take adjustments if necessary (see System Suitability under memoraperaphy (621)).

Standard preparation—Dissolve an accurately weighed quantity of Standard preparation—Dissolve an accurately weighed quantity of Trimethoprim RS in *Diluent* to obtain a solution having a known ancentration of about 0.04 mg per mL.

Assay preparation—Transfer an accurately measured volume of phthalmic Solution, equivalent to about 1 mg of trimethoprim, to a x_mL volumetric flask, dilute with *Diluent* to volume, and mix. *Chromatographic system* (see *Chromatography* (621))—The aud chromatograph is equipped with a 254-nm detector and a $y_{-mm} \times 30$ -cm column that contains packing L11. The flow rate is bout 1.5 mL per minute. Chromatograph the *Standard preparation*, d record the peak responses as directed for *Procedure:* the tailing for is not more than 1.5, when calculated at 10% height of the ak; and the relative standard deviation for replicate injections is not three than 2.0%.

Procedure—Separately inject equal volumes (about 10 μ L) of the indard preparation and the Assay preparation into the chromathaph, record the chromatograms, and measure the responses for the ajor peaks. Calculate the quantity, in mg, of trimethoprim $G_{\rm H_{10}}N_{\rm s}O_{\rm s}$) in each mL of the Ophthalmic Solution taken by the mula:

$25(C/V)(r_u/r_s),$

which C is the concentration, in mg per mL, of USP Trimethoprim **B** in the Standard preparation; V is the volume, in mL, of the standard preparation is the standard preparation; and r_U and r_s are the trimethoprim peak area responses obtained from the large preparation and the Standard preparation, respectively.

olyvinyl Alcohol



H.O), henol, homopolymer. nyl alcohol polymer [9002-89-5].

Polyvinyl Alcohol is a water-soluble synthetic resin, presented by the formula:

$(C_2H_4O)_{,,}$

which the average value of n lies between 500 and 000. It is prepared by 85 percent to 89 percent transition of the prepared by 85 percent viscosity, centipoises, at 20°, of a solution containing 4 g of lyvinyl Alcohol in each 100 g is not less than 85.0 areant and not more than 115.0 percent of that stated on a label.

Packaging and storage—Preserve in well-closed containers.

Viscosity—After determining the Loss on drying, weigh a quantity of undried Polyvinyl Alcohol, equivalent to 6.00 g on the dried basis. Over a period of seconds, transfer the test specimen with continuous slow stirring to about 140 mL of water contained in a suitable tared flask. When the specimen is well-wetted, increase the rate of stirring, avoiding mixing in excess air. Heat the mixture to 90°, and maintain the temperature at 90° for about 5 minutes. Discontinue heating, and continue stirring for 1 hour. Add water to make the mixture weigh 150 g. Resume stirring to obtain a homogenous solution. Filter the solution through a tared 100-mesh screen into a 250-mL conical flask, cool to about 15°, mix, and proceed as directed under Viscosity (911).

pH $\langle 791 \rangle$: between 5.0 and 8.0, in a solution (1 in 25).

Loss on drying (731)—Dry it at 110° to constant weight: it loses not more than 5.0% of its weight.

Residue on ignition (281): not more than 2.0%.

Water-insoluble substances—Wash the tared 100-mesh screen used in the test for *Viscosity* with two 25-mL portions of water, and dry at 110° for 1 hour: not more than 6.4 mg of water-insoluble substances is found (0.1%).

Organic volatile impurities, *Method I* $\langle 467 \rangle$: meets the requirements.

Degree of hydrolysis-

Procedure—Transfer about 1 g of Polyvinyl Alcohol, previously dried at 110° to constant weight and accurately weighed, to a widemouth, 250-mL conical flask fitted by means of a suitable glass joint to a reflux condenser. Add 35 mL of dilute methanol (3 in 5), and mix gently to assure complete wetting of the solid. Add 3 drops of phenolphthalein TS, and add 0.2 N hydrochloric acid or 0.2 N sodium hydroxide, if necessary, to neutralize. Add 25.0 mL of 0.2 N sodium hydroxide VS, and reflux gently on a hot plate for 1 hour. Wash the condenser with 10 mL of water, collecting the washings in the flask, cool, and titrate with 0.2 N hydrochloric acid VS. Concomitantly perform a blank determination in the same manner, using the same quantity of 0.2 N sodium hydroxide VS.

Calculation of saponification value—Calculate the saponification value by the formula:

[(B - A)N56.11]/W,

in which B and A are the volumes, in mL, of 0.2 N hydrochloric acid VS consumed in the titration of the blank and the test preparation, respectively, N is the exact normality of the hydrochloric acid solution, W is the weight, in g, of the portion of Polyvinyl Alcohol taken, and 56.11 is the molecular weight of potassium hydroxide.

solution, m is the weight, in g, of the portion of Polyvinyl Alcohol taken, and 56.11 is the molecular weight of potassium hydroxide. *Calculation of degree of hydrolysis*—Calculate the degree of hydrolysis, expressed as percentage of hydrolysis of polyvinyl acetate, by the formula:

100 - [7.84S/(100 - 0.075S)],

in which S is the saponification value of the Polyvinyl Alcohol taken: between 85% and 89% is found.

Sulfurated Potash

Thiosulfuric acid, dipotassium salt, mixture with potassium sulfide (K₂S₂). Dipotassium thiosulfate mixture with potassium sulfide (K₂S₂)

Dipotassium thiosulfate mixture with potassium sulfide (K₂S_x) [39365-88-3].

» Sulfurated Potash is a mixture composed chiefly of potassium polysulfides and potassium thiosulfate. It contains not less than 12.8 percent of sulfur (S) in combination as sulfide.

Packaging and storage—Preserve in tight containers. Containers from which it is to be taken for immediate use in compounding prescriptions contain not more than 120 g. **Identification**—

A: To a 1 in 10 solution add an excess of 6N acetic acid: hydrogen sulfide is evolved, and sulfur is precipitated.

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Im Phosphate

,17-dihydroxy-21-(phosphong

,4-diene-3,20-dione 21-(disa

osphate contains not less ore than 102.0 percent n the dried basis.

e in tight containers. -USP Prednisolone RS.

reparation obtained as direct D-mL volumetric flask, mix w stion prepared as directed in e chloride. Insert the stopper, tle inversion (about once even sthylene chloride layer through the filtrate to dryness: the read on test A under Prednisolone. 1 of about 20 mg of it respo Phosphate (191). 1 +95° and +102°

a mixture of pH 7.0 phospi

: (9:1). n a solution (1 in 100).

han 6.5%.

Dissolve 143.3 mg of da 2PO4, in water to make 1000 alent of 0.10 mg of phosph

g of ammonium molybda

) mg of p-methylaminophe of sodium bisulfite, mix mL.

g of Prednisolone Sodi ixture of 10 mL of water a 25-mL volumetric flask of Phosphate reagent A to 25 mL, mix, and allow ites. Similarly and conc ising 5.0 mL of Stand ; of the substance under t es of both solutions in l iotometer, using water as 1 is not more than that of hosphate (PO4).

st specimen being used. : of Prednisolone Sod to make 25.0 mL. Pipe 50-mL tube, add 25.0 mix by gentle shaking de layer is clear (about the methylene chlor uitable spectrophotome culate the quantity, in isolone Sodium Phosph rbance of the untr nisolone RS obtained

of boric acid and 500 1 21 mL of 1N sod hloride, dilute with

g is found (1.0%).

r 250 mg of alka lask, dissolve by add and mix. Prepare

ndard preparation-Dissolve a suitable, accurately weighed tity of USP Prednisolone RS in methylene chloride, and dilute ntitatively and stepwise with methylene chloride to obtain a having a known concentration of about 16 µg per mL. Pipet biom having a known concentration of about physic per min. I per mL of the solution into a glass-stoppered, 100-mL cylinder, and 1.0 mL of Alkaline phosphatase solution and 1.0 mL of water. how to stand, with occasional gentle inversion, for 2 hours. Issay preparation—Dissolve about 100 mg of Prednisolone dium Phosphate, accurately weighed, in water that has been dive the methylene chloride to make 500 mL and mix Binet

mated with methylene chloride, to make 50.0 mL, and mix. Pipet mL of this solution into a 125-mL separator, and shake with two mL portions of water-washed methylene chloride, discarding the hylene chloride layers.

Procedure—Pipet 1 mL of the Assay preparation into a glass-oppered, 100-mL cylinder, add 1.0 mL of Alkaline phosphatase wition and about 50 mL of methylene chloride, insert the stopper, allow to stand, with occasional gentle inversion (about once ry 15 minutes), for 2 hours. Add methylene chloride to volume, and allow to stand until the methylene chloride layer is clear four 20 minutes). Concomitantly and without delay, determine the borbances of the methylene chloride solution obtained from the may preparation and the Standard preparation at 241 nm, with a mable spectrophotometer, using methylene chloride as the blank. chalate the quantity, in mg, of $C_2(H_2)N_2O_4P$ in the portion of reduisolone Sodium Phosphate taken by the formula:

 $1.344[5C(A_u/A_s)]$

which 1.344 is the ratio of the molecular weight of prednisolone redum phosphate to that of prednisolone, C is the concentration, in germL, of USP Prednisolone RS in the *Standard preparation*, and und A_{c} are the absorbances of the solution from the and A_s are the absorbances of the solution from the Assay eparation and the Standard preparation, respectively.

Prednisolone Sodium Phosphate Injection

Prednisolone Sodium Phosphate Injection is a sterile Bution of Prednisolone Sodium Phosphate in Water for rection. It contains not less than 90.0 percent and not ore than 110.0 percent of the labeled amount of rednisolone phosphate (C21H29O8P), present as the sodium salt.

chaging and storage—Preserve in single-dose or in multiple-dose trainers, preferably of Type I glass, protected from light.

P Reference standards (11)-USP Prednisolone RS. USP

Dissolv Dissolve 65 mg of phenylhydrazine hydrochloride in 100 mL thute sulfuric acid (3 in 5), add 5 mL of isopropyl alcohol, and Heat 5 mL of this solution with 1 mL of Assay preparation the das directed in the Assay) at 70° for 2 hours: a yellow color

esphate. terial endotoxins (85)—It contains not more than 5.0 USP totoxin Units per mg of prednisolone phosphate.

(791): between 7.0 and 8.0.

ticulate matter (788): meets the requirements under smallne injections.

requirements—It meets the requirements under Injections

H 9 buffer with magnesium—Prepare as directed in the Assay Prednisolone Sodium Phosphate. Ruline phosphatase solution—Prepare as directed in the Assay Prednisolone Sodium Phosphate.

Mandard preparation—river-misolone Sodium Phosphate. indard preparation-Prepare as directed in the Assay under

usop preparation—Pipet a volume of Injection, equivalent to u 100 mg of prednisolone phosphate, into a separator containing u of write With the photon with two 10 mL particular of of water. Wash the solution with two 10-mL portions of

methylene chloride, and discard the washings. Transfer the aqueous layer to a 50-mL volumetric flask, dilute with water to volume, and mix.

Procedure--Proceed as directed for Procedure in the Assay under Prednisolone Sodium Phosphate. Calculate the quantity, in mg, of $C_{21}H_{29}O_8P$ in each mL of the Injection taken by the formula:

$6.11(C/V)(A_U/A_s),$

in which C is the concentration, in μg per mL, of USP Prednisolone RS in the *Standard preparation*, V is the volume, in mL, of Injection taken, and A_U and A_S are the absorbances of the solution from the Assay preparation and the Standard preparation, respectively.

Prednisolone Sodium Phosphate Ophthalmic Solution

» Prednisolone Sodium Phosphate Ophthalmic Solution is a sterile solution of Prednisolone Sodium Phosphate in a buffered, aqueous medium. It contains not less than 90.0 percent and not more than 115.0 percent of the labeled amount of prednisolone phosphate (C21H29O8P), present as the disodium salt.

Packaging and storage-Preserve in tight, light-resistant containers. USP Reference standards (11)-USP Prednisolone RS

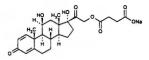
Identification-It responds to Identification test A under Prednisolone Sodium Phosphate and to Identification test A under Prednisolone Sodium Phosphate Injection.

Sterility (71): meets the requirements.

pH (791): between 6.2 and 8.2.

Assay-Proceed with Ophthalmic Solution as directed in the Assay under Prednisolone Sodium Phosphate Injection.

Prednisolone Sodium Succinate for Injection



C24H31NaO8 482.50

Pregna-1,4-diene-3,20-dione, 21-(3-carboxy-1-oxopropoxy)-11,17dihydroxy-, monosodium salt, (11β) -

11β,17,21-Trihydroxypregna-1,4-diene-3,20-dione 21-(sodium suc-cinate) [1715-33-9].

» Prednisolone Sodium Succinate for Injection is sterile prednisolone sodium succinate prepared from Prednisolone Hemisuccinate with the aid of Sodium Hydroxide or Sodium Carbonate. It contains the equivalent of not less than 90.0 percent and not more than 110.0 percent of the labeled amount of prednisolone $(C_{21}\hat{H}_{28}O_5)$. It contains suitable buffers.

Packaging and storage-Preserve in Containers for Sterile Solids as described under Injections (1).

USP Reference standards (11)-USP Prednisolone Hemisuccinate RS. USP Endotoxin RS.

Constituted solution-At the time of use, it meets the requirements for Constituted Solutions under Injections (1).

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between the least resolved peaks is not less than 1.2; and the relative standard deviation for replicate injections of the Standard solution is not more than 6.0% for each component or, if the Assay is performed concomitantly, the relative standard deviation for the propantheline bromide peak in the replicate injections of the Standard solution is not more than 2.0%.

For the control of the standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of xanthanoic acid, xanthone, and propantheline bromide related compound A greater than or equal to 0.1% in the portion of Tablets taken by the formula:

$100C/C_{x}(r_{v}/r_{s}),$

in which C is the concentration, in µg, of xanthanoic acid, xanthone, or propantheline bromide related compound A per mL of the *Standard solution*; C_x is the theoretical concentration, in µg per mL, of Propantheline Bromide in the Test solution; and r_{ij} and r_s are the related compound peak responses obtained from the Test solution and the Standard solution, respectively: not more than 4.0% of propantheline bromide related compound A and 1.0% each of xanthone and xanthanoic acid are found. Assa

pH 3.5 buffer solution and Mobile phase-Prepare as directed for

Related compounds under Propantheline Bromide. Standard preparation—Dissolve an accurately weighed quantity of USP Propantheline Bromide RS in Mobile phase to obtain a solution having a known concentration of about 0.3 mg per mL.

Assay preparation—Weigh and finely powder not less than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to 15 mg of propantheline bromide, to a 50-mL volumetric flask, dissolve in Mobile phase, dilute with Mobile phase to volume, mix, and filter.

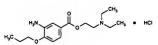
Chromatographic system (see Chromatography (621))—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 25-cm column that contains packing L7. The flow rate is about 2.0 mL per minute. Chromatograph the Standard preparation, and record peak responses as directed for *Procedure*: the relative standard deviation for replicate injections is not more than 2.0%. *Procedure*—Separately inject equal volumes (about 50 µL) of the

Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the peak responses. alculate the quantity, in mg, of C23H30BrNO3 in the portion of Tablets taken by the formula:

$50C(r_u/r_s),$

in which C is the concentration, in mg per mL, of USP Propantheline Bromide RS in the *Standard preparation*, and r_U and r_s are the peak responses due to Propantheline Bromide obtained from the *Assay* preparation and the Standard preparation, respectively.

Proparacaine Hydrochloride



C16H26N2O3 · HCl 330.85

Benzoic acid, 3-amino-4-propoxy-, 2-(diethylamino)ethyl ester,

monohydrochloride.
2-(Diethylamino)ethyl 3-amino-4-propoxybenzoate monohydro-chloride [5875-06-9].

» Proparacaine Hydrochloride contains not less than 97.0 percent and not more than 103.0 percent of $C_{16}H_{26}N_2O_3 \cdot HCl$, calculated on the dried basis.

Packaging and storage-Preserve in well-closed containers. USP Reference standard (11)-USP Proparacaine Hydrochlori RS

Identification-

A: It meets the requirements under Identification-Organ Nitrogenous Bases (181).

B: Dissolve 50 mg, accurately weighed, in water to make 250 mL, and mix. Pipet 10 mL of this solution into a 100-mL volument flask, add 2 mL of 10 percent, pH 6.0 phosphate buffer (see Buf Solutions in the section Reagents, Indicators, and Solutions), water to volume, and mix: the UV absorption spectrum of the solution exhibits maxima and minima at the same wavelengths as that of similar solution of USP Proparacaine Hydrochloride RS, concorr tantly measured, and the respective absorptivities, calculated on the dried basis, at the wavelength of maximum absorbance at about 30 nm do not differ by more than 3.0%.

C: A solution (1 in 50) responds to the tests for Chloride (19) the procedure for alkaloidal hydrochlorides being used Melting range (741): between 178° and 185°, but the ran

between beginning and end of melting does not exceed 2°. Loss on drying (731)-Dry it at 105° for 3 hours: it loses not m than 0.5% of its weight.

Residue on ignition (281): not more than 0.15%. Ordinary impurities (466)

Test solution: methanol. Standard solution: methanol.

Eluant: a mixture of butyl alcohol, water, and glacial acetic (5:3:1).

Visualization: 1; 17.

Assay-Place 250 mg of Proparacaine Hydrochloride, accura weighed, in a 250-mL conical flask, add 80 mL of a 1 in 20 solution of acetic anhydride in glacial acetic acid, and heat on a steam bath 10 minutes. Cool to room temperature, add 10 mL of mercuric acet TS and 1 or 2 drops of crystal violet TS, and titrate with 0.1 perchloric acid VS to a blue-green endpoint. Perform a blue determination, and make any necessary correction. Each mL of 0.1 perchloric acid is equivalent to 33.09 mg of $C_{16}H_{26}N_2O_3 \cdot HCl$.

Proparacaine Hydrochloride Ophthalm Solution

» Proparacaine Hydrochloride Ophthalmic Solution sterile, aqueous solution of Proparacaine Hydrochlorid It contains not less than 95.0 percent and not more the 110.0 percent of the labeled amount $C_{16}H_{26}N_2O_3 \cdot HCl.$

Packaging and storage-Preserve in tight, light-resistant contain Labeling-Label it to indicate that it is to be stored in a refrige after the container is opened.

USP Reference standards (11)-USP Proparacaine Hydrochlor RS

Identification-To 1 mL of Ophthalmic Solution in a test tube at mL of dilute hydrochloric acid (1 in 100), mix, and cool in an ice in the first state of the sta for 2 minutes. Add 2 drops of sodium nitrite solution (1 in 10), and cool again for 2 minutes. Add 1 mL of a solution prepared dissolving 200 mg of 2-naphthol in 10 mL of 1 N sodium hydron a scarlet-red precipitate is formed. Add 5 mL of acetone: precipitate does not dissolve.

Sterility (71): meets the requirements.

pH (791): between 3.5 and 6.0.

Assay— pH 7.5 buffer—Dissolve 6.8 g of monobasic potassium phose in 1000 mL of water, add 5 mL of triethylamine, and adjust with potassium hydroxide to a pH of 7.5. Filter through a filter have

porosity of 0.5 µm or finer, and degas. Mobile phase—Prepare a mixture of pH 7.5 buffer and acetom (60:40). Make adjustments if necessary (see System Suitability Chromatography (621)).

USP 2

standard preparatio prochloride RS, acc solve in and dilute w this stock solution to se to volume, and r Assay preparationrochloride, to a 10 to volume, and r Chromatographic s id chromatograph mm × 15-cm colu flow rate is about lard preparation, cedure: the tailing iency is not less t ndard deviation for 1 Procedure-[NOTE-licated.] Separately andard preparation a raph, record the chroi jor peaks. Calculate in mL of the Ophtha

which C is the conce drochloride RS in th of Ophthalmic Solution indard preparation, r

ropofol

H₁₈O 178.27 iol, 2,6-bis(1-methy Diisopropylphenol

Propofol contains pre than 102.0 per

kaging and storage and storageween 15° and 30°. being—The labeling ich the article complie

Reference standar Propofol Resolution

ification, Infrared fractive index (831):

ited compounds-[1 infacturing process, formed in conjuncti Found A, Limit of p by Test 1 procedure found B Test 2 and the st 1 ST 1-

Propofol Resolution epwise if necessary, netration of about 10 indard solution-Dis ropofol RS in metha

Slayback Exhibit 1055, Page 65 of 78 Slayback v. Eye Therapies - IPR2022-00142

USP

ell-closed containers. roparacaine Hydrochlon

er Identification-Organ

ed, in water to make 250 i into a 100-mL volume tors, and Solutions), on spectrum of the solu e wavelengths as that of drochloride RS, concor ptivities, calculated on f n absorbance at about 3

e tests for Chloride (19) s being used. and 185°, but the m es not exceed 2°. 3 hours: it loses not me

in 0.15%

ter, and glacial acetic

lydrochloride, accurate mL of a 1 in 20 solution d heat on a steam bath 10 mL of mercuric ace S, and titrate with 0.1 point. Perform a bl ection. Each mL of 0.1 $f C_{16}H_{26}N_2O_3 \cdot HCl.$

de Ophthalmi

halmic Solution is aine Hydrochlorid t and not more the led amount d

ight-resistant conta e stored in a refrigera

aracaine Hydrochlor

ition in a test tube a , and cool in an ice b solution (1 in 10), s a solution prepared 1 N sodium hydrox 5 mL of acetone:

ic potassium phosphine, and adjust with 5 rough a filter have

buffer and aceto ystem Suitability un

gandard preparation—Transfer about 25 mg of USP Proparacaine mochloride RS, accurately weighed, to a 25-mL volumetric flask, olve in and dilute with water to volume, and mix. Transfer 5.0 mL solve in and unue with water to volume, and mix. Transfer 5.0 mL this stock solution to a 50-mL volumetric flask, dilute with Mobile for to volume, and mix. [NOTE—Use this solution within 6 hours.] *Issay preparation*—Transfer an accurately measured volume of thalmic Solution, equivalent to about 10 mg of proparacaine thochloride, to a 100-mL volumetric flask, dilute with Mobile for to volume, and mix. [NOTE—Use this solution within 6 hours.] Chromatographic system (see Chromatography (621))-The id chromatograph is equipped with a 270-nm detector and a mm \times 15-cm column that contains 5-µm spherical packing L10. frow rate is about 1.5 mL per minute. Chromatograph the *indard preparation*, and record the peak responses as directed for *incedure:* the tailing factor is not more than 1.5, the column iciency is not less than 3000 theoretical plates, and the relative

Indency is not less than 3000 theoremcal plates, and the relative indard deviation for replicate injections is not more than 2.0%. *Procedure*—[NOTE—Use peak areas where peak responses are licated.] Separately inject equal volumes (about 10 μ L) of the indard preparation and the Assay preparation into the chromat-raph, record the chromatograms, and measure the responses for the jor peaks. Calculate the quantity, in mg, of C₁₆H₃₆N₂O₃·HCl in the mL of the Ophthalmic Solution taken by the formula:

$100(C/V)(r_{u}/r_{s}),$

which C is the concentration, in mg per mL, of USP Proparacaine which orde RS in the *Standard preparation*, V is the volume, in L of Ophthalmic Solution taken, and r_{U} and r_{s} are the proparacaine at responses obtained from the *Assay preparation* and the undard preparation, respectively.

ropofol

H₁₈O 178.27 mol, 2,6-bis(1-methylethyl) Diisopropylphenol [2078-54-8].

Propofol contains not less than 98.0 percent and not ore than 102.0 percent of $C_{12}H_{18}O_{12}$.

the storage — Preserve in tight, light-resistant containers for an atmosphere of inert gas. Store at 25°, excursions permitted tween 15° and 30°.

being—The labeling indicates the *Related compounds* test with uch the article complies.

PReference standards (11)—USP Propofol RS. USP Propofol dated Compound A RS. USP Propofol Related Compound B RS. P Propofol Resolution RS. USP Propofol for System Suitability

atification, Infrared Absorption (197F).

fractive index (831): between 1.5125 and 1.5145 at 20°.

ated compounds—[NOTE—On the basis of knowledge of the nufacturing process, either (1) Related compounds Test 1 is formed in conjunction with the Limit of propofol related apound A, Limit of propofol related compound B Test 1, and ay Test 1 procedures; or (2) Related compounds Test 2 is formed in conjunction with the Limit of propofol related pound B Test 2 and the Assay Test 2 procedures.] ound B Test 2 and the Assay Test 2 procedures.]

Resolution solution—Dissolve an accurately weighed quantity of Propofol Resolution RS in methanol, and dilute quantitatively, stepwise if necessary, with methanol to obtain a solution having a centration of about 100 mg per mL.

andard solution—Dissolve an accurately weighed quantity of Propofol RS in methanol, and dilute quantitatively, and stepwise

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if necessary, with methanol to obtain a solution having a concentration of about 0.1 mg per mL

Test solution- Transfer about 1000 mg of Propofol, accurately weighed, to a 10-mL volumetric flask, dissolve in and dilute with methanol to volume, and mix.

Chromatographic system (see Chromatography (621))—Proceed as directed under Assay Test 1, except to chromatograph the Standard solution six times and chromatograph the Resolution solution: the relative retention time is about 0.18 for 2,6-diisopropylphenyl isopropylether, 1.0 for propofol, and about 1.1 for 2-isopropyl-6-npropylphenol; the resolution, R, between propofol and 2-isopropyl-6n-propylphenol is not less than 2. Chromatograph the *Standard* solution six times, and record the peak responses as directed for *Procedure:* the column efficiency determined from the propofol peak is not less than 5000 theoretical plates; and the relative standard deviation for replicate injections is not more than 3.5%

Procedure—Separately inject equal volumes (about 1.0 μ L) of the Resolution solution, the Standard solution, and the Test solution into the chromatograph, record the chromatograms, and measure all the peak responses. Calculate the percentage of each impurity in the portion of Propofol taken by the formula:

$0.1(r_{1}/r_{2})$

in which r_i is the peak response for each impurity obtained from the Test solution; and rs is the peak response for propofol obtained from the Standard solution: not more than 0.1% of 2,6-diisopropylphenyl isopropylether is found; not more than 0.1% of each other individual impurity is found; and not more than 0.3% of total impurities is found.

TEST

Mobile phase-Prepare as directed in Assay Test 2.

System suitability solution 1—Transfer 5 μ L of USP Propofol RS and 15 μ L of USP Propofol Related Compound B RS to a 50-mL volumetric flask, dissolve in and dilute with hexane to volume, and mix

System suitability solution 2—Dissolve 1 mL of USP Propofol for System Suitability RS with hexane to make 10 mL. Test solution—Transfer about 1000 mg of Propofol, accurately

weighed, to a 10-mL volumetric flask, dissolve in and dilute with hexane to volume, and mix.

Reference solution—Dilute 1 mL of the Test solution with hexane to 100 mL, and mix. Dilute 1 mL of this solution with hexane to 10 mL, and mix.

Chromatographic system (see Chromatography (621))—Proceed as directed in Assay Test 2. Chromatograph System suitability solution I and System suitability solution 2, and record the peak responses as directed for *Procedure*: the relative retention times are about 0.8 for propofol related compound B from *System suitability solution* 1, 0.5 for 2-(1-methylethoxy)-1,3-bis(1-methylethylbenzene), 1.0 for propofol, and 5.0 for propofol related compound A from System suitability solution 2; the resolution, R, between propofol related compound B and propofol is at least 4.0.

compound B and proposed is at least 4.0. *Procedure*—Separately inject a volume (about 10 μ L) of the *Test solution* and the *Reference solution* into the chromatograph, record the chromatogram, and measure all peak responses. Calculate the percentage of each impurity in the portion of Propofol taken by the formula:

$0.1(r_i/r_s)(1/F),$

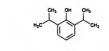
in which r_i is the peak response for each impurity obtained from the Test solution; r_s is the peak response for propofol obtained from the Reference solution; and F is the response factor. F is 0.2 for 2,6disopropylphenylisopropyl ether and 4.0 for propofol related compound A: not more than 0.2% of 2-(1-methylethoxy)-1,3-bis(1-methylethylbenzene) is found; not more than 0.2% of 2,6diisopropylphenylisopropyl ether is found; not more than 0.01% of propofol related compound A is found; not more than 0.05% of each other individual impurity is found; and not more than 0.3% of total impurities is found

Limit of propofol related compound A—[NOTE—This test is to be performed in conjunction with *Related compounds Test 1.*] *Mobile phase*—Prepare a filtered and degassed mixture of

acetonitrile, water, and methanol (50:40:10).

Standard solution-Prepare a solution in methanol containing 20 ug per mL of USP Propofol Related Compound A RS.

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d evaporate the solution residue in 0.5 mL de and 15 mL of etc nt the solvent, dry in ne solvent no longer disk: the IR absorpt e dispersion, previous ima only at the sto n of USP Scopolam ter.

ew drops of chlorine rm: the latter assume

 $1d -26^\circ$. > 50 mg of anhydre<math>r. on (1 in 20). ges (see *Loss on dry* 105° for an additional eight. m 100 mg. tion (1 in 100) add 0. S: the solution is

tion (1 in 20) add a fer

bidity is produced. A portion of the solution d.

 $\langle 7 \rangle$: meets the require

plarnine Hydrobronid of glacial acetic acida ightly to effect solution 2 drops of crystal via 1 VS. Perform a blan sction. Each mL of 0.4 $^{\circ}C_{17}H_{21}NO_4 \cdot HBr.$

le Injection

jection is a ster omide in Water 0.0 percent and in labeled amount

-resistant, single-dose e I glass. polamine Hydrobrom

ivalent to about 3 magnator, dilute with with monium hydroxide, 50 mL of ether to hrough a 25- \times 250of glass wool at the earth that previously oric acid saturated with pass 25 mL of wa ard. Elute with 100 mE ate in a suitable receresidue in 1 mL of alcost est A under Scopolam porate the solution of

• TS: a yellowish w slightly soluble in terial endotoxins (85)—It contains not more than 555.0 USP soloxin Units per mg of scopolamine hydrobromide. (791): between 3.5 and 6.5.

requirements—It meets the requirements under Injections

 $_{\rm H}^{\rm Y-0}$ Buffer—Dissolve 34.8 g of dibasic potassium phosphate in $_{\rm ML}$ of water, and adjust with 3 N hydrochloric acid or 1 N sodium troxide, as necessary, to a pH of 9.0, determined electrometrically, mix.

mernal standard solution—Transfer about 25 mg of homatropine arobromide to a 50-mL volumetric flask, dissolve in and dilute water to volume, and mix. Prepare fresh daily. Sandard stock solution—Transfer about 10 mg of 100 g

wall to votatily, and min. I repare near daily. Sandard stock solution—Transfer about 10 mg of USP Scopoline Hydrobromide RS, accurately weighed, to a 100-mL metric flask, dissolve in and dilute with water to volume, and Prepare fresh daily.

Standard preparation—Pipet 10 mL of the Standard stock solution a separator, add 2.0 mL of *Internal standard solution* and 5.0 mL H = 0.0 Buffer, and carefully adjust the solution with 1 N sodium roxide to a pH of 9.0, avoiding any excess. Immediately extract the two 10-mL portions of methylene chloride, filter the methylene bride extracts through 1 g of anhydrous sodium sulfate supported a small cotton plug in a funnel into a 50-mL beaker, and evaporate the nitrogen to approximately 2.0 mL. Issay solution—Transfer an accurately measured volume of

tsay solution—Transfer an accurately measured volume of ection, equivalent to about 10 mg of scopolamine hydrobromide, 100-mL volumetric flask. Dilute with water to volume, and mix. Assay preparation—Pipet 10 mL of the Assay solution into a parator, and proceed as directed for Standard preparation, mining with "add 2.0 mL of Internal standard solution." Chromatographic system (see Chromatography (621))—The gas

Enromatographic system (see Chromatography $\langle 621 \rangle$)—The gas imatograph contains a 2-mm × 1.8-m glass column packed with liquid phase G3 on support S1AB. The carrier gas is nitrogen, wing at a rate of 25 mL per minute. The column temperature is intained at 225°. Chromatograph the *Standard preparation*, and and the peak responses as directed for *Procedure:* the resolution for, *R*, between homatropine and scopolamine is not less than 5; balling factor is not more than 2.0; and the relative standard pration for replicate injections is not more than 2.0%.

ration for replicate injections is not more than 2.0%. Procedure—Separately inject equal volumes (about 1 μ L) of the indard preparation and the Assay preparation into the chromatinph, record the chromatograms, and measure the peak areas. Isulate the ratio, A_{U_1} of the area of the scopolamine hydrobromide if to the area of the internal standard peak in the chromatogram in the Assay preparation, and similarly calculate the ratio, A_S , in "chromatogram from the Standard preparation. Calculate the inity, in mg, of scopolamine hydrobromide H₁NO₄ · HBr · 3H₂O) in the volume of Injection taken by the inula:

$1.141 W(A_u/A_s),$

which 1.141 is the ratio of the molecular weight of scopolamine probromide trihydrate to that of anhydrous scopolamine hydromide; W is the weight, in mg, of USP Scopolamine Hydrobromide in the Standard preparation; and A_U and A_S are as calculated

copolamine Hydrobromide Ophthalmic

Scopolamine Hydrobromide Ophthalmic Ointment is polamine Hydrobromide in a suitable ophthalmic ment base. It contains not less than 90.0 percent and more than 110.0 percent of the labeled amount of $rH_{21}NO_4$ · HBr · 3H₂O. It is sterile.

aging and storage—Preserve in collapsible ophthalmic oint-

Reference standards (11)-USP Scopolamine Hydrobromide

Identification-

A: Transfer a portion of Ophthalmic Ointment, equivalent to about 50 mg of scopolamine hydrobromide, to a suitable separator, and dissolve in 25 mL of ether. Add 25 mL of 0.01 N hydrochloric acid, shake vigorously, allow the layers to separate, and discard the organic phase. Proceed as directed under *Identification—Organic Nitrogenous Bases* (181), beginning with "In a second separator dissolve 50 mg."

B: Transfer about 5 g of Ophthalmic Ointment to a separator, dissolve in 50 mL of ether, and extract with 20 mL of water: the extracted solution so obtained responds to the tests for *Bromide* $\langle 191 \rangle$.

Sterility (71): meets the requirements.

Metal particles—It meets the requirements of the test for Metal Particles in Ophthalmic Ointments (751).

Assay—Proceed with Ophthalmic Ointment as directed in the Assay under Scopolamine Hydrobromide Injection, but to prepare the Assay solution, weigh accurately a portion of Ophthalmic Ointment equivalent to about 10 mg of scopolamine hydrobromide into a separator containing 50 mL of ether, shake to dissolve, extract with three 25-mL portions of 0.2 N sulfuric acid, collect the acid extracts in a 100-mL volumetric flask, dilute with 0.2 N sulfuric acid to volume, and mix. Calculate the quantity, in mg, of C₁₇H₂₁NO₄ · HBr · 3H₂O in the portion of Ophthalmic Ointment taken by the formula given therein.

Scopolamine Hydrobromide Ophthalmic Solution

» Scopolamine Hydrobromide Ophthalmic Solution is a sterile, buffered, aqueous solution of Scopolamine Hydrobromide. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{17}H_{21}NO_4 \cdot HBr \cdot 3H_2O$. It may contain suitable antimicrobial agents and stabilizers, and may contain suitable additives for the purpose of increasing its viscosity.

Packaging and storage-Preserve in tight containers.

USP Reference standards (11)—USP Scopolamine Hydrobromide RS.

Identification-

A: A volume of Ophthalmic Solution, equivalent to about 3 mg of scopolamine hydrobromide, responds to *Identification* test A under Scopolamine Hydrobromide Injection.

B: Add to the Ophthalmic Solution silver nitrate TS: a yellowish white precipitate, insoluble in nitric acid but slightly soluble in 6 N ammonium hydroxide, is formed.

Sterility (71): meets the requirements.

pH (791): between 4.0 and 6.0.

Assay—Transfer an accurately measured volume of Ophthalmic Solution, equivalent to about 10 mg of scopolamine hydrobromide, to a 100-mL volumetric flask, dilute with water to volume, and mix. Using this as the Assay solution, proceed as directed in the Assay under Scopolamine Hydrobromide Injection. Calculate the quantity, in mg, of $C_{17}H_{21}NO_4$ ·HBr·3H₂O in the volume of Ophthalmic Solution taken by the formula given therein.

Scopolamine Hydrobromide Tablets

» Scopolamine Hydrobromide Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{17}H_{21}NO_4 \cdot HBr \cdot 3H_2O$.

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Silver Nitrate Ophthalmic Solution

» Silver Nitrate Ophthalmic Solution is a solution of Silver Nitrate in a water medium. It contains not less than 0.95 percent and not more than 1.05 percent of AgNO₃. The solution may be buffered by the addition of Sodium Acetate.

Packaging and storage-Preserve it protected from light, in inert, collapsible capsules or in other suitable single-dose containers. Clarity and color of solution-It is clear and colorless.

Identification-It responds to the tests for Silver (191) and for

Nitrate (191) Sterility (71): meets the requirements.

pH (791): between 4.5 and 6.0.

Assay-Place 5 mL of Ophthalmic Solution, accurately measured, in a conical flask, dilute with 20 mL of water, add 1 mL of nitric acid and 1 mL of ferric ammonium sulfate TS, and titrate with 0.02 N ammonium thiocyanate VS. Each mL of 0.02 N ammonium thiocyanate is equivalent to 3.397 mg of AgNO3.

Toughened Silver Nitrate

» Toughened Silver Nitrate contains not less than 94.5 percent of AgNO₃, the remainder consisting of silver chloride (AgCl).

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

A solution (1 in 50) responds to the tests for Silver (191). B: Mix a solution (1 in 10) in a test tube with 1 drop of diphenylamine TS, then carefully superimpose it upon sulfuric acid: a deep blue color appears at the zone of contact.

Copper-A solution (1 in 10) shows no trace of blue coloration when treated with an excess of 6 N ammonium hydroxide.

Assay-Add about 700 mg of Toughened Silver Nitrate, accurately weighed, to 50 mL of water, and when the silver nitrate has dissolved, filter the solution. Thoroughly wash the filter and sediment with water, add 2 mL of nitric acid and 2 mL of ferric ammonium sulfate TS to the combined filtrate and washings, and titrate with 0.1 N ammonium thiocyanate VS. Each mL of 0.1 N ammonium thiocyanate is equivalent to 16.99 mg of AgNO₃.

Simethicone

Simethicone

a-(Trimethylsilyl)-ω-methylpoly[oxy(dimethylsilylene)], mixture with silicon dioxide [8050-81-5].

» Simethicone is a mixture of fully methylated linear siloxane polymers containing repeating units of the formula [-(CH₃)₂SiO-], stabilized with trimethylsiloxy end-blocking units of the formula [(CH₃)₃ SiO-], and silicon dioxide. It contains not less than 90.5 percent and not more than 99.0 percent of polydimethylsiloxan $([-(CH_3)_2SiO_-]_{,})$, and not less than 4.0 percent and not more than 7.0 percent of silicon dioxide.

Packaging and storage-Preserve in tight containers. USP Reference standards (11)-USP Polydimethylsiloxane R USP Simethicone RS.

Identification, Infrared Absorption (197S)-

Test solution-Prepare as directed for Assay preparation in Assay.

Standard solution-Prepare as directed for Standard preparation in the Assay.

Cell size: 0.5 mm.

Defoaming activity--Foaming solution--Dissolve 1g of octoxynol 9 in 100 mL water

Test preparation—Transfer 200 mg of Simethicone to a 60-m bottle, add 50 mL of tertiary butyl alcohol, cap the bottle, and shi vigorously. [NOTE—Warm slightly, if necessary, to effect solution]

Procedure—[NOTE—For each test, employ a clean, unused, 25 mL glass jar.] Add, dropwise, 500 μL of the *Test preparation* to clean, unused, cylindrical 250-mL glass jar, fitted with a 50-mm carbon control of the test preparation of test pre in an upright position on a wrist-action shaker. Employing a radius 13.3 ± 0.4 cm (measured from center of shaft to center of both shake for 10 seconds through an arc of 10 degrees at a frequency 300 ± 30 strokes per minute. Record the time required for the fo to collapse. The time, in seconds, for foam collapse is determined the instant the first portion of foam-free liquid surface appear measured from the end of the shaking period. The defoaming activity time does not exceed 15 seconds.

Loss on heating—Heat about 15 g, accurately weighed, in an operated vessel having a diameter of 5.5 ± 0.5 cm and a wall height 2.5 ± 1.0 cm at 200° in a circulating air oven for 4 hours, and allo to come to room temperature in a desiccator before weighing: it loss not more than 18.0% of its weight.

Heavy metals-Mix 1.0 g of Simethicone with 10 mL of chlorof and dilute with the same solvent to 20 mL. Add 1.0 mL of a fresh prepared 0.002% solution of dithizone in chloroform, 0.5 mL water, and 0.5 mL of a mixture of 1 volume of ammonia TS and volumes of a 0.2% solution of hydroxylamine hydrochlorid Concomitantly prepare a Standard solution as follows: to 20 mL chloroform add 10 mL of a freshly prepared 0.002% solution dithizone in chloroform, 0.5 mL of *Standard Lead Solution* (Heavy Metals (231)) (containing 10 µg of lead per mL) and 0.5 mL a mixture of 1 volume of ammonia TS and 9 volumes of a 02 solution of hydroxylaria solution of hydroxylamine hydrochloride. Immediately shake by solutions vigorously for 1 minute. Any red color in the test solution not more intense than that in the Standard solution (5 µg per g). Organic volatile impurities, Method IV (467): meets the requ ments

Content of silicon dioxide-Transfer 3.00 g of Simethicone screw-capped bottle, add 10.0 mL of *n*-hexane, cap, and mix shaking (*Test solution*). Prepare a *Standard solution* by similar treating a 3.00-g portion of USP Simethicone RS. Prepare Dimethicone preparation by similarly treating a 3.00-g portion dimethicone preparation by similarly treating a 3.00-g portion spectrophotometer and 0.1-mm cells, determine the absorber spectra of well-mixed portions of the Test solution, the Standard solution, and the Dimethicone preparation between 7 and 9 using n-hexane as the blank. Determine the absorbances of the solution, the Standard solution, and the Dimethicone preparation the wavelength of minimum absorbance at about 8.2 µm observe the spectrum obtained from the Dimethicone preparation. Cale

TSP 28 USP 28

be percentage of silic

which C is the desi simethicone RS, A_U is absorbance of the Dime the Standard solutio Assay-Transfer about round, narrow-mouth f toluene, and swirl to id (2 in 5), close the b a suitable rate (e.g., a f 38 ± 2 mm). Trans emove about 5 mL of rew-capped test tube Close the tube with ngorously, and centrifu reparation) is obtained reating a 25.0-mL porti S in toluene having a repare a procedural bla concomitantly determin is at the wavelength c IR spectrophotomet lculate the quantity, ken by the formula:

which C is the colydimethylsiloxane R are the absorbances aration, respectivel

Simethicone C

Simethicone Cap ethylsiloxane ([-((ercent and not mo. mount of simethica

ackaging and storage SP Reference standau entification-Capsule nethicone.

sintegration (701):

niformity of dosage u foaming activity—In foaming activity under psule contents equiva say--[NOTE--Perform spules. The mean of the suffer 1 Capsule to a re-suffer add about 20 mL (the frequent swirling, up to here a suffer a suffer a suffer a suffer a to here a suffer a suffer a suffer a suffer a to here a suffer a suffer a suffer a suffer a to here a suffer a suff toluene, accurately r ount of simethicone in having an inert line anic (toluene) layer to the sulfate, agitate the to settle. If neces ation (Assay prepara larly treating a solu one having a known

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CP 28

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gle-dose glass or place of Type I or Type II glass molar concentration e less than 100 mL for direct injection but ively may state the tot

lotoxin RS.

r Sodium (191) and

not more than 0.5 US nount of sodium chlorid , and not more than 3 beled amount of sodie nd 24.3%

uirements.

1 water to 45 mL, and m.

a volume of Injection in a suitable vessel 20 mL, add 2 mL of nL. Proceed as direct tion (10 µg of Pb) in t Preparation: the limit loride.

ements under Injection

alent to about 90 mg ater, if necessary, to b of glacial acetic acid, 7 'S. Titrate, with shakin point. Each mL of 0.1 JaCl.

oride Injection

njection is a sterile oride in Water f ore suitable antim an 0.85 percent

Chloride Injection particular medicing diluted.

le-dose or multiple-dos ferably of Type I or Type

and proportion(s) of to include the statem ipital letters, on the last d in a contrasting col t may be placed proi NOT FOR INHALATION

P Reference standards (11)-USP Endotoxin RS. USP Methylaben RS. USP Propylparaben RS.

mimicrobial agent(s)-It meets the requirements under Antimibial Preservatives—Effectiveness (51), and meets the labeled bial preservatives—Effectiveness (51), and meets the labeled im for content of the antimicrobial agent(s) as determined by the thed set forth under Antimicrobial Agents-Content (341), except use the following procedure when methylparaben and propylparben are used as the antimicrobial agents.

Mobile phase-Prepare a filtered and degassed mixture of Mobile phase—repare a filtered and degassed mixture of the phase in the phase of t

SP Methylparaben RS and USP Propylparaben RS in methanol, and but a solution having known concentrations of about 1.2 and 0.12 ing per mL, respectively. Pipet 5 mL of this solution into a 50-mL momentic flask, add by ninet 30 mL of this solution into a 50-mL ute quantitatively, and stepwise if necessary, with methanol to metric flask, add by pipet 30 mL of methanol, dilute with water to nume, and mix.

Test preparation-Pipet 1 mL of Injection into a 10-mL volumetric sk add by pipet 7 mL of methanol, dilute with water to volume, nd mix.

Chromatographic system (see Chromatography (621))—The fauid chromatograph is equipped with a 254-nm detector and a 4-m \times 30-cm column that contains packing L1. The flow rate is The first of the second secon

Procedure—Separately inject equal volumes (about $12 \ \mu$ L) of the bandard preparation and the Test preparation into the chromato-raph by means of a suitable microsyringe or sampling valve, busting the specimen size and other operating parameters such that the peak obtained with the *Standard preparation* is about 0.7 full the check obtained with the *Standard preparation* is about 0.7 full the Record the chromatograms, and measure the height of the esks, at identical retention times, obtained with the Test preparation and the Standard preparation, and calculate the concentration in mg and calculate the concentration in mg mL, in the portion of methylparaben or propylparaben taken by formula:

$C(H_u/H_s),$

which C is the concentration, in mg per mL, of USP Methylparaben The standard preparation, in the standard preparation; and H_U and H_S are the peak heights obtained from the Test preparation and the Standard preparation, respectively.

acterial endotoxins (85)—It contains not more than 1.0 USP Endotoxin Unit per mL

rarticulate matter (788): meets the requirements for smallvolume injections.

Other requirements—It responds to the *Identification* test and meets be requirements for *pH*, *Iron*, *Heavy metals*, and *Assay* under *Sodium Choride Injection*. It meets also the requirements under *Injections* (1).

Sodium Chloride Irrigation

Sodium Chloride Irrigation is Sodium Chloride hjection that has been suitably packaged, and it contains to antimicrobial agents. It contains not less than 95.0 percent and not more than 105.0 percent of the labeled mount of NaCl.

eckaging and storage-Preserve in single-dose glass or plastic ners. Glass containers are preferably of Type I or Type II glass. container may be designed to empty rapidly and may contain a plane of more than 1 liter.

being The designation "not for injection" appears prominently

Reference standards(11)-USP Endotoxin RS.

utification—It responds to the tests for *Sodium* (191) and for *boride* (191).

Bacterial endotoxins (85)-It contains not more than 0.5 USP Endotoxin Unit per mL.

Sterility (71): meets the requirements

Other requirements-It meets the requirements for pH, Iron, Heavy metals, and Assay under Sodium Chloride Injection.

Sodium Chloride Ophthalmic Ointment

» Sodium Chloride Ophthalmic Ointment is Sodium Chloride in a suitable ophthalmic ointment base. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of NaCl. It is sterile.

Packaging and storage-Preserve in collapsible ophthalmic ointment tube

Identification—Transfer a quantity of Ophthalmic Ointment, equivalent to about 200 mg of sodium chloride, to a separator containing about 25 mL of ether, and extract with 5 mL of water: the aqueous extract so obtained responds to the tests for Sodium (191), and for Chloride (191).

Sterility (71): meets the requirements.

Minimum fill (755): meets the requirements.

Metal particles (751): meets the requirements. Assay-Transfer an accurately weighed quantity of Ophthalmic Ointment, equivalent to about 100 mg of sodium chloride, to a separator containing about 50 mL of ether, and extract with four 20-

mL portions of water. Combine the aqueous extracts in a conical flask, evaporate to a volume of about 10 mL, and add 10 mL of glacial acetic acid, 75 mL of methanol, and 0.5 mL of eosin Y TS. Tirrate, with shaking, with 0.1 N silver nitrate VS to a pink endpoint. Each mL of 0.1 N silver nitrate is equivalent to 5.844 mg of NaCl.

Sodium Chloride Inhalation Solution

» Sodium Chloride Inhalation Solution is a sterile solution of Sodium Chloride in water purified by distillation or by reverse osmosis and rendered sterile. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of NaCl. It contains no antimicrobial agents or other added substances.

Packaging and storage-Preserve in single-dose containers.

Identification-It responds to the test for Sodium (191) and for Chloride (191).

Sterility (71): meets the requirements.

pH (791): between 4.5 and 7.0.

Assay-Pipet a volume of Inhalation Solution, equivalent to about 90 mg of sodium chloride, into a conical flask, and add 10 mL of glacial acetic acid, 75 mL of methanol, and 0.5 mL of eosin Y TS. Tirrate, with shaking, with 0.1 N silver nitrate VS to a pink endpoint. Each mL of 0.1 N silver nitrate is equivalent to 5.844 mg of NaCl.

Sodium Chloride Ophthalmic Solution

» Sodium Chloride Ophthalmic Solution is a sterile solution of Sodium Chloride. It contains not less than 90.0 percent and not more than 110.0 percent of the

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1782 **Sodium** | Official Monographs

labeled amount of sodium chloride. It may contain suitable antimicrobial and stabilizing agents. It contains a buffer.

Packaging and storage-Preserve in tight containers.

Identification-Heat a portion of Ophthalmic Solution to boiling, and filter while hot. After cooling, the filtrate responds to the tests for Sodium (191) and for Chloride (191). Sterility (71): meets the requirements.

pH (791): between 6.0 and 8.0.

Assay-Transfer an accurately measured volume of Ophthalmic Solution, equivalent to about 90 mg of sodium chloride, to a conical flask, and add 10 mL of glacial acetic acid, 75 mL of methanol, and 0.5 mL of eosin Y TS. Titrate, with shaking, with 0.1 N silver nitrate VS to a pink endpoint. Each mL of 0.1 N silver nitrate is equivalent to 5.844 mg of NaCl.

Sodium Chloride Tablets

» Sodium Chloride Tablets contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of NaCl.

Packaging and storage-Preserve in well-closed containers.

Identification-A filtered extract of Tablets responds to the tests for Sodium (191) and for Chloride (191).

Disintegration (701): 30 minutes.

Uniformity of dosage units (905): meet the requirements. Iodide or bromide-Digest 2.0 g of powdered Tablets with 25 mL of warm alcohol for 3 hours, cool, and filter. Evaporate the filtrate to dryness, dissolve the residue in 5 mL of water, filter if necessary, and add 1 mL of chloroform. Cautiously introduce, dropwise, with constant agitation, 5 drops of dilute chlorine TS (1 in 3): the chloroform does not acquire a violet, yellow, or orange color.

Barium-Digest 4.0 g of powdered Tablets with 20 mL of water, filter, and divide the solution into two equal portions. To one portion add 2 mL of 2 N sulfuric acid and to the other add 2 mL of water: the solutions are equally clear after standing for 2 hours.

Calcium and magnesium-Digest 1 g of powdered Tablets with 50 mL of water, and filter. Add 4 mL of 6 N ammonium hydroxide to the filtrate, and divide the mixture into two equal portions. Treat one portion with 1 mL of ammonium oxalate TS and the other portion with 1 mL of dibasic sodium phosphate TS: neither mixture becomes turbid within 5 minutes.

Assay—Dissolve a counted number of not less than 20 Tablets in about 100 mL of water, filter into a 500-mL volumetric flask, and wash the original container and the filter with 100 mL of water in divided portions, adding the washings to the original filtrate. Dilute with water to volume. Pipet a volume of the solution, equivalent to about 90 mg of sodium chloride, to a conical flask, and add 10 mL of glacial acetic acid, 75 mL of methanol, and 0.5 mL of eosin Y TS. Titrate, with shaking, with 0.1 N silver nitrate VS to a pink endpoint. Each mL of 0.1 N silver nitrate is equivalent to 5.844 mg of NaCl.

Sodium Chloride Tablets for Solution

» Sodium Chloride Tablets for Solution are composed of Sodium Chloride in compressed form, containing no added substance. Sodium Chloride Tablets for Solution contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of NaCl.

Other requirements-The Sodium Chloride Tablets for Solution respond to the Identification test and meet the requirements for Packaging and storage, Iodide or bromide, Barium, Calcium and magnesium, Disintegration, Uniformity of dosage units, and Assay under Sodium Chloride Tablets.

Sodium Chloride and Dextrose Tablets

» Sodium Chloride and Dextrose Tablets contain not less than 92.5 percent and not more than 107.5 percent of the labeled amount of sodium chloride (NaCl) and of dextrose ($C_6H_{12}O_6 \cdot H_2O$).

Packaging and storage-Preserve in well-closed containers. Identification-

A: A filtered solution of Tablets responds to the flame test for Sodium (191) and to the test for Chloride (191).

B: Add a few drops of the filtered solution tablets to 5 mL of hot alkaline cupric tartrate TS: a copious red precipitate of cuprous oxide is formed.

Disintegration (701): 30 minutes.

Uniformity of dosage units (905): meet the requirements. Assay for sodium chloride—Transfer 20.0 mL of the solute prepared for the Assay for dextrose to a 100-mL volumetric final dilute with water to volume, mix, and proceed as directed in the Asso under Sodium Chloride Tablets, beginning with "Pipet a volume of the solution.

Assay for dextrose-Dissolve not less than 10 Tablets, contain from 2 to 5g of dextrose, in about 75 mL of water in a 100-n volumetric flask, add several drops of 6N ammonium hydroxid dibite with water to volume and min A6-20 dilute with water to volume, and mix. After 30 minutes, filter through a dry filter, and determine the angular rotation in a 200-mm tube 35°, retaining the excess of the solution for the Assay for soda chloride. The observed rotation in degrees, multiplied by 1.042 represents the weight, in g, of $C_6H_{12}O_6 \cdot H_2O$ in the specimen take

Sodium Citrate

C6H5Na3O7 (anhydrous) 258.07 1,2,3-Propanetricarboxylic acid, 2-hydroxy-, trisodium salt. Trisodium citrate (anhydrous) [68-04-2]. Trisodium citrate dihydrate 294.10 [6132-04-3].

» Sodium Citrate is anhydrous or contains two molect of water of hydration. It contains not less than 9 percent and not more than 100.5 percent of C6H5Na calculated on the anhydrous basis.

Packaging and storage-Preserve in tight containers. Labeling-Label it to indicate whether it is anhydrous or hydr Identification-

A: A solution (1 in 20) responds to the tests for Sodium and for Citrate (191).

B: Upon ignition, it yields an alkaline residue which effer when treated with 3 N hydrochloric acid.

Alkalinity-A solution of 1.0 g in 20 mL of water is alkal litmus paper, but after the addition of 0.20 mL of 0.10 N sulfur no pink color is produced by 1 drop of phenolphthalein TS. Water, Method III (921)—Dry it at 180° for 18 hours: the anh form loses not more than 1.0%, and the hydrous form between and 13.0%, of its weight.

USP 28 EP 28

rtrate--To a solution sium acetate TS and with a glass rod: no c wy metals (231)-Di drous sodium citrate i ion. Transfer 12 mL marison tube (Test Pre-mon to a second 50-mL dard Lead Solution (dard Lead Solution and marison tube (Standard cedure, omitting the dilu -Transfer about 350 by—Transfer about 350 100° for 18 hours and ac 100 mL of glacial acetic : a with 0.1 N perchloric atiometrically. Perform a ary correction. Each ml 602 mg of C₆H₅Na₃O₇.

dium Citrate and lution

odium Citrate and Ci tion of Sodium Citrate ous medium. It contain 2.23 g and not more the less than 6.11 g and no 1₅O₇), equivalent to not 10.5 g of sodiu $Na_3O_7 \cdot 2H_2O$; and no than 7.02 g of ci $0_7 \cdot H_2O$).

ing and storage-Preserve fication-

It meets the requirements of Add 2 mL of 15% potassiun m, boil, and cool. Add 4 mL o precipitate is formed (presen To 2 mL of a dilution of Oral cobaltinitrite TS: a yello tely (absence of potassium). It meets the requirements of th of Oral Solution and 20 mL o mhydride being used.

DRAL SOLUTION PACKAGED IN e requirements.

DRAL SOLUTION PACKAGED IN M e requirements. 1):

between 4.0 and 4.4. or sodium-

ium stock solution, Sodium sto and Standard preparation-Pre m and potassium under Tricitra preparation-Transfer an accu tion, equivalent to about 1 g of se volumetric flask, dilute with w 50 μ L of this solution to a 10-n im diluent solution to volume, a -Using a suitable flame pho Lithium diluent solution, con me emission readings for the Sta paration at the wavelength of ma

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1842 Suprofen | Official Monographs

Assay preparation-Transfer about 50 mg of Suprofen, accurately weighed, to a 50-mL volumetric flask, dilute with methanol to volume, and mix. Transfer 5.0 mL of this solution to a 25-mL volumetric flask, dilute with Buffer solution to volume, and mix. Transfer 2.0 mL of this solution to a 25-mL volumetric flask, dilute with Buffer solution to volume, and mix.

Chromatographic system-The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about 2 mL per minute. Chromatograph the *Standard preparation*, and record the peak responses as directed for Procedure: the column efficiency determined from the analyte peak is not less than 500 theoretical plates, the tailing factor for the peak is not more than 2.0, and the relative standard deviation for replicate injections is not more than 2%.

Procedure—[NOTE—Use peak areas where peak responses are indicated.] 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. Calculate the quantity, in mg, of $C_{14}H_{12}O_3S$ in the portion of Suprofen taken by the formula:

$3125C(r_u/r_s),$

in which C is the concentration, in mg per mL, of USP Suprofen RS in the Standard preparation, and r_U and r_s are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.

Suprofen Ophthalmic Solution

» Suprofen Ophthalmic Solution is a sterile, buffered, aqueous solution of Suprofen adjusted to a suitable tonicity. It contains a suitable antimicrobial preservative. It contains not less than 90.0 percent and not more than 115.0 percent of the labeled amount of $C_{14}H_{12}O_3S$.

Packaging and storage-Preserve in tight containers.

USP Reference standards (11)-USP Suprofen 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. Sterility (71): meets the requirements when tested as directed for Membrane Filtration under Test for Sterility of the Product to be Examined.

pH (791): between 6.5 and 8.0.

Assay

Buffer solution, Mobile phase, Standard preparation, and Chromatographic system—Proceed as directed in the Assay under Suprofen.

Assay preparation-Transfer an accurately measured volume of Ophthalmic Solution, equivalent to about 20 mg of suprofen, to a 100-mL volumetric flask. Dilute with Buffer solution to volume, and mix. Transfer 2.0 mL of this solution to a 25-mL volumetric flask, dilute with *Buffer solution* to volume, and mix.

Procedure-Proceed as directed in the Assay under Suprofen. Calculate the quantity, in mg, of C14H12O3S in each mL of the Ophthalmic Solution taken by the formula:

$1250(C/V)(r_U/r_s),$

in which C is the concentration, in mg per mL, of USP Suprofen RS in the Standard preparation, V is the volume, in mL, of Ophthalmic Solution taken, and r_{U} and r_{s} are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.

Absorbable Surgical Suture

» Absorbable Surgical Suture is a sterile, flexible strand prepared from collagen derived from healthy mammais. or from a synthetic polymer. Suture prepared from synthetic polymer may be in either monofilament or multifilament form. It is capable of being absorbed by living mammalian tissue, but may be treated to modify its resistance to absorption. Its diameter and tensile strength correspond to the size designation indicated on the label, within the limits prescribed herein. It may be modified with respect to body or texture. It may be impregnated or treated with a suitable coating, softening, or antimicrobial agent. It may be colored by a color additive approved by the FDA. The collagen suture is designated as either *Plain Suture* or *Chromic Suture*. Both types consist of processed strands of collagen, but Chromic Suture is processed by physical or chemical means so as to provide greater resistance to absorption in living mammalian tissue.

Packaging and storage-Preserve dry or in fluid, in containers (packets) so designed that sterility is maintained until the container opened. A number of such containers may be placed in a box.

Labeling-The label of each individual container (packet) of Sutu indicates the size, length, type of Suture, kind of needle (if a needle is included), number of sutures (if multiple), lot number, and name of the manufacturer or distributor. If removable needles are used, the labeling so indicates. Suture size is designated by the metric size (gauge number) and the corresponding USP size. The label of the **box** indicates also the address of the manufacturer, packer, or distributed

and the composition of any packaging fluids used. NOTE—If the Suture is packaged with a fluid, make the require measurements for the first four of the following tests within 2 minute after removing it from the fluid.

Length-Determine the length of Suture without stretching: length of each strand is not less than 95.0% of the length stated on the

Diameter-Determine the diameter of 10 strands of Suture directed under Sutures-Diameter (861).

Collagen suture-The average diameter, and not fewer than 20, of the 30 measurements on the 10-strand sample are within the limits of average diameter prescribed in *Table 1* for the respective size. Not of the individual measurements is less than the midpoint of the ra for the next smaller size or more than the midpoint of the range for next larger size.

Synthetic suture-The average diameter of the strands be measured is within the tolerances prescribed in Table 2 for respective size. None of the observed measurements is less than midpoint of the range for the next smaller size or more than midpoint of the range for the next larger size.

Tensile strength—Determine the tensile strength on not fewer the 10 strands of Suture as directed for Surgical Sutures under Tens Strength (881).

Collagen suture-The tensile strength, determined as the mini strength for each individual strand tested, and calculated as average strength from any one lot, is as set forth in Table 1. If more than one strand fails to meet the limit on individual stranger repeat the test with not forme that are the limit on individual stranger repeat the test with not fewer than 20 additional strands: requirements of the test are met if none of the additional strands f below the limit on individual strands, and if the average strength of the strands tested does not fall below the stated limit in Table 1.3

Synthetic suture-The minimum tensile strength of each size synthetic suture, calculated as the average strength from any one is as set forth in Table 2.

Needle attachment-Suture on which eyeless needles are s meets the requirements under Sutures-Needle Attachment (871)

Sterility (71): meets the requirements.

Extractable color (if Suture is dyed)-Prepare the Ma Solution that corresponds to the extractable color of the Sutur

USP 28

03.	P Size Mi 12-0	II.
	11-0	
	10-0	
	9-0	
	8-0	
	7-0	
	6-0	
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tensile strength of th

ning the Colorim ble 3, and adding w der Solutions in the composition of the

Tab

for of Suture Cot Extractable Ch Color) llow-brown n-blue plet

Slayback Exhibit 1055, Page 71 of 78 Slayback v. Eye Therapies - IPR2022-00142

USP

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8

atography (621)) 305-nm detector and ing L1. The flow rate Resolution solution, ure: the relative retent .0 for tetracaine; and the k and the tetracaine pe andard preparation, an ure: the relative standard e than 2.0%. imes (about 5 µL) of ration into the chrome leasure the areas for of tetracaine hydrochi : Injection taken by the

mL, of USP Tetracai tion; V is the volume, tetracaine peak response ne Standard preparation

for Injection

jection contains not han 110.0 percenter ine hydrochloride

iners for Sterile Solids f Type I glass. dotoxin RS. USP Tetre

g portion dissolves in vield a colorless solu

it meets the requirement 1).

asurement of absorbance

st B under Tetracaine

tot more than 0.7 USE :hloride.

meets the requirement

ted in the Assay under tion. of one container, with the add water to volume, valent to about 1 mg a netric flask, add 5 mL a mL of Buffer No. 6, 1 d Other Solutions under ater to volume, and min dure in the Assay, except ssay preparation. $D_2 \cdot HCl$ in each container

portion used in the *Te t preparation*, and *C* and

(791): between 5.0 and 6.0, in a solution (1 in 100).

(791): between 5.0 and 6.0, in a solution (1 in 100). **ter**, Method I (921): not more than 2.0%. **ridue on ignition**—Weigh accurately about 500 mg, transfer to a ter, and dissolve in 10 mL of methanol. Filter through paper viously washed with methanol, collecting the filtrate in an ignited tard crucible and washing the beaker and the filter paper with 25 to 30 mL of methanol. Evaporate with the aid of heat and a ment of air to dryness, and proceed as directed under Residue on ment of air to dryness, and proceed as directed under *Residue on* minon (281), beginning with "Heat, gently at first." Not more than 1% of residue is found.

Terracaine Hydrochloride for Injection in water to obtain a test humon containing 50 mg per mL, and proceed as directed in the test Chromatographic purity under Tetracaine, beginning with prepare a Standard solution."

ther requirements-It meets the requirements for Sterility Tests (1) and Labeling under Injections (1).

ssay Standard preparation--Prepare as directed in the Assay under macaine Hydrochloride in Dextrose Injection.

Assay preparation—Transfer to a tared 20-mL beaker the contents a sufficient number of containers of Tetracaine Hydrochloride for frection to yield about 100 mg of tetracaine hydrochloride. Weigh mediately, and transfer with the aid of water to a 500-mL fumetic flask. Add water to volume, and mix. Transfer 5.0 mL to a 0-mL volumetric flask, add 5 mL of dilute hydrochloric acid (1 in (0) and 10 mL of Buffer No. 6, 10 percent, pH 6.0 (see Phosphate f_{m} (81)) then add water to volume and mix fers (81)), then add water to volume, and mix.

Procedure-Concomitantly determine the absorbances of the The absorbance of the Standard preparation at the wavelength of maximum absorbance at about 310 nm, with a suitable performance for the portion of C₁₃H₂₄N₂O₂. HCl in the portion of Tetracaine Hydrochloride religion taken by the formula:

 $10C(A_U/A_s),$

which C is the concentration, in μ g per mL, of USP Tetracaine adorchloride RS in the *Standard preparation*, and A_U and A_s are the sorbances of the Assay preparation and the Standard preparation, spectively.

Fetracaine Hydrochloride Ophthalmic Solution

Tetracaine Hydrochloride Ophthalmic Solution is a terile, aqueous solution of Tetracaine Hydrochloride. It potains not less than 90.0 percent and not more than 10.0 percent of the labeled amount of $H_{24}H_{24}N_2O_2$. HCl. It may contain suitable antimicrobial ind thickening agents.

ckaging and storage-Preserve in tight, light-resistant containers. being Label it to indicate that the Ophthalmic Solution is not to used if it contains crystals, or if it is cloudy or discolored.

Reference standards (11)-USP Tetracaine Hydrochloride

itification-Add 5 mL of Ophthalmic Solution to 5 mL of water a test tube, then add 1 mL of potassium thiocyanate solution (1 in a crystalline precipitate is formed. Recrystallize the precipitate m water, and dry at 80° for 2 hours: the crystals so obtained melt ween 130° and 132°

rility (71): meets the requirements.

(791): between 3.7 and 6.0.

Mobile phase—Prepare 0.01 M of dibasic ammonium phosphate in the state of the state of the solution and acetonitrile the solution and degassed mixture of this solution and acetonitrile the solution of the solution and acetonitrile 30) Make adjustments if necessary (see System Suitability Chromatography (621)).

Standard preparation-Dissolve an accurately weighed quantity of USP Tetracaine Hydrochloride RS in water to obtain a solution having a known concentration of about 0.1 mg per mL.

Assay preparation-Transfer an accurately measured volume of Ophthalmic Solution, equivalent to about 10 mg of tetracaine hydrochloride, to a 100-mL volumetric flask, dilute with water to volume, and mix.

Chromatographic system (see Chromatography (621))- The liquid chromatograph is equipped with a 280-nm detector and a 4.6-nm × 25-cm column containing packing L10. The flow rate is about 2 mL per minute. Chromatograph the Standard preparation, and record the peak responses as directed for *Procedure:* the column efficiency is not less than 500 theoretical plates; the tailing factor for the analyte peak 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 10 μ L) 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 $C_{13}H_{24}N_2O_2 \cdot HCl$ in each mL of the Ophthalmic Solution taken by the formula:

$100(C/V)(r_u/r_s),$

in which C is the concentration, in mg per mL, of USP Tetracaine Hydrochloride RS in the *Standard preparation*, V is the volume, in mL, of Ophthalmic Solution taken; and r_u and r_s are the tetracaine peak responses obtained from the Assay preparation and the Standard preparation, respectively.

Tetracaine Hydrochloride Topical Solution

» Tetracaine Hydrochloride Topical Solution is an aqueous solution of Tetracaine Hydrochloride. It contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of C15H24N2O2 · HCl. It contains a suitable antimicrobial agent.

Packaging and storage-Preserve in tight, light-resistant containers. Labeling-Label it to indicate that the Topical Solution is not to be used if it contains crystals, or if it is cloudy or discolored. USP Reference standards (11)-USP Tetracaine Hydrochloride

Identification-

RS

A: Ultraviolet Absorption (197U) -Solutions: solutions of the Topical Solution employed for measurement of absorbance in the Assay.

B: It responds to the tests for Chloride (191).

pH (791): between 4.5 and 6.0.

Assay-

Standard preparation—Prepare as directed in the Assay under Tetracaine Hydrochloride in Dextrose Injection.

Assay preparation—Using an accurately measured volume of Topical Solution, prepare as directed in the Assay under Tetracaine Hydrochloride in Dextrose Injection. Procedure—Proceed as directed for Procedure in the Assay under

Tetracaine Hydrochloride in Dextrose Injection. Calculate the quantity, in mg, of $C_{15}H_{24}N_2O_2$ HCl in the volume of Topical Solution taken by the formula:

$C(A_U/A_s),$

in which C is the concentration, in µg per mL, of USP Tetracaine Hydrochloride RS in the Standard preparation, and Au and As are the absorbances of the Assay preparation and the Standard preparation, respectively.

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ontains not less the 100.5 percent ied basis.

containers. ihydrozoline Hydroch

ulated on the dried ba

tests for Chloride (19 hours: it loses not m

0.1% i mL of water, and ad

I acetic acid, and w

oraying with hydro chromatographic p ts.] irozoline Hydrochlog nd dissolve in 60 m Add 5 mL of an nd 3 drops of quinals cid VS. Perform a bh ection. Each mL of 0, $f C_{13}H_{16}N_2 \cdot HCl.$

loride Nasal

Nasal Solution rochloride in w ontains not less th 110.0 percent of

containers. ahydrozoline Hydrod

im of the Nasal Solut tration of about 1 in 4 wavelengths as that ine Hydrochloride problal limits (61)—It meets the requirements of the tests for are of Staphylococcus aureus and Pseudomonas aeruginosa. (791): between 5.3 and 6.5.

Ordized nitroprusside reagent—Dissolve 1.0 g of sodium nitro-neyanide in water to make 10.0 mL (Solution A). Dissolve 1.0 g of assium ferricyanide in water to make 10.0 mL (Solution B). Set 1.0 mL each of Solution A and Solution B to a 100-mL metric flask, add 1 mL of sodium hydroxide solution (1 in 10), allow to stand until the solution changes to a light yellow color 20 to 30 minutes). Dilute with water to volume, and mix. Store refrigerator or keep in an ice bath, and use within 4 hours

Standard preparation—Dissolve a suitable quantity of USP rahydrozoline Hydrochloride RS, accurately weighed, in water, dilute quantitatively with water to obtain a solution having a wn concentration of about 100 µg per mL.

Assay preparation—Transfer an accurately measured volume of al Solution, equivalent to about 10 mg of tetrahydrozoline throchloride, to a 100-mL volumetric flask, dilute with water to tume, and mix.

Procedure-Transfer 5.0 mL each of the Standard preparation and Assay preparation to separate glass-stoppered test tubes. Piper 5 Lof water into a third tube to provide a blank. To each tube add 4.0 of Oxidized nitroprusside reagent, mix, and allow to stand at 30° 15 minutes. Concomitantly determine the absorbances of the tions in 1-cm cells at the wavelength of maximum absorbance at but 570 nm, with a suitable spectrophotometer, using the blank to the instrument. Calculate the quantity, in mg, of $C_{13}H_{16}N_2 \cdot HCl$ in the mL of the Nasal Solution taken by the formula:

 $0.1(C/V)(A_u/A_s),$

which C is the concentration, in μg per mL, of USP mhydrozoline Hydrochloride RS in the *Standard preparation*, V be volume in mL, of Nasal Solution taken, and A_{U} and A_{S} are the potentiation of the solutions from the Assay preparation and the indard preparation, respectively.

tetrahydrozoline Hydrochloride ophthalmic Solution

Tetrahydrozoline Hydrochloride Ophthalmic Solution a sterile, isotonic solution of Tetrahydrozoline drochloride in water. It contains not less than 90.0 cent and not more than 110.0 percent of the labeled ount of C₁₃H₁₆N₂ · HCl.

taging and storage-Preserve in tight containers.

Reference standards (11)—USP Tetrahydrozoline Hydrochlo-

ntification—The UV absorption spectrum of the Ophthalmic mion, diluted with dilute hydrochloric acid (1 in 100) to a contration of about 1 in 4000, exhibits maxima and minima at the wavelengths as that of a similar solution of USP Tetrahydro-te Hydrochloride RS, concomitantly measured. Hity (71): meets the requirements.

(791): between 5.8 and 6.5.

andard preparation—Dissolve a suitable quantity of USP andrdrozoline Hydrochloride RS, accurately weighed, in water, dilute quantitatively with water to obtain a solution having a

The quantitatively with water to obtain a solution having a reconcentration of about 500 μ g per mL. *Seedure*—Transfer 2.0 mL of *Standard preparation* to a 50-mL metric flask. Transfer an accurately measured volume of malmic Solution, equivalent to about 1 mg of tetrahydrozoline Schloride, to a second 50-mL flask, and transfer 2 mL of water to at 50-mL volumetric flask to provide a blank. To each flask add at . of homoschool blue solution (1 in 1000), dilute of bromophenol blue sodium salt solution (1 in 1000), dilute Ask with potassium biphthalate solution (1 in 1000), under Mask with potassium biphthalate solution (1 in 100) to volume, mix. Allow to stand for 20 minutes, and filter each mixture of a suitable filter paper (Whatman No. 42 or the equivalent)

that does not absorb the dye, discarding the first 15 mL of the filtrate. Transfer 20.0 mL of the subsequent filtrate to separate 125-mL separators, and extract each solution with four 20-mL portions of chloroform, filtering each extract through a pledget of glass wool into a 100-mL volumetric flask. Dilute the combined extracts from each solution with chloroform to volume, and mix. Concomitantly determine the absorbances of the solutions in 1-cm cells at the wavelength of maximum absorbance at about 415 nm, with a suitable spectrophotometer, using the blank to set the instrument. Calculate the quantity, in µg, of $C_{13}H_{16}N_2$ HCl in each mL of the Ophthalmic Solution taken by the formula:

$2(C/V)(A_U/A_s),$

in which C is the concentration, in μg per mL, of USP Tetrahydrozoline Hydrochloride RS in the Standard preparation, V is the volume, in mL, of Solution taken, and A_{ij} and A_{s} are the absorbances of the solutions from the Ophthalmic Solution and the Standard preparation, respectively.

Thalidomide

 (\pm) -N-(2,6-Dioxo-3-piperidyl)phthalimide. α -(N-Phthalimido)glutarimide [50-35-1] [50-35-1].

» Thalidomide contains not less than 98.0 percent and not more than 101.5 percent of C13H10N2O4, calculated on the anhydrous basis.

Packaging and storage—Preserve in tight containers, protected from light, at controlled room temperature.

USP Reference standards (11)-USP Thalidomide RS.

Identification, Infrared Absorption (197K).

Microbial limits (61): meets the requirements.

Water, Method Ic (921): not more than 0.5%.

Solvent: anhydrous dimethyl sulfoxide.

Heavy metals, Method II (231): 0.002%.

Chromatographic purity— Solution A—Prepare a filtered and degassed mixture of water, acetonitrile, and phosphoric acid (95:5:0.1).

Solution B—Prepare a filtered and degassed mixture of water, acetonitrile, and phosphoric acid (85:15:0.1).

Diluent-Prepare a mixture of water, acetonitrile, and phosphoric acid (50:50:0.1).

Mobile phase-Use variable mixtures of Solution A and Solution B

as directed for Chromatographic system. Make adjustments if necessary (see System Suitability under Chromatography (621)). Phthalic acid stock solution—Transfer about 100 mg of phthalic acid to a 100-mL volumetric flask, dissolve in a mixture of acetonitrile and water (80:5), and dilute with acetonitrile to volume. Mix, and dilute quantitatively, and stepwise if necessary, with acetonitrile to obtain a solution having a concentration of about

0.1 mg per mL. Standard stock solution—Dissolve, with the aid of sonication, an accurately weighed quantity of USP Thalidomide RS in acetonitrile to obtain a solution having a known concentration of about 1 mg per mL

Standard solution—Pipet 2.0 mL of the Standard stock solution and 2.0 mL of the Phthalic acid stock solution into a 100-mL volumetric flask, dilute with Diluent to volume, and mix. Pipet 10.0 mL of this solution into a 100-mL volumetric flask, add 10.0 mL of phosphoric acid solution (1 in 100), dilute with water to volume, and mix to obtain a solution having a known concentration of about 0.0002 mg of phthalic acid per mL.

Slayback Exhibit 1055, Page 73 of 78 Slayback v. Eye Therapies - IPR2022-00142 stepwise with methanol to obtain Standard solutions having the following compositions:

Standard solution	Concentration (µg RS per mL)	Percentage (%, for comparison with test specimen)
A	200	0.4
В	100	0.2
С	50	0.1

Separately apply 10-µL portions of the solutions to a suitable thinlayer 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 a solvent system consisting of a mixture of chloroform, methanol, and ammonium hydroxide (80:20:1) until the solvent front has moved about threefourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Expose the plate to iodine vapors for 2 hours, and locate the spots on the plate by examination under short-wavelength UV light. Compare the intensities of any secondary spots observed in the chromatogram of the test solution, excluding the origin spot due to the maleate anion, with those of the principal spots in the chromatograms of the Standard solutions: no secondary spot is more intense than the principal spot obtained from Standard solution A (0.4%), and the sum of the intensities of all secondary spots, from Standard solution C, does not exceed 1.0%.

Organic volatile impurities, Method I (467): meets the requirements.

-Dissolve about 800 mg of Timolol Maleate, accurately Assavweighed, in about 90 mL of glacial acetic acid, and titrate with 0.1 N perchloric acid VS, determining the endpoint potentiometrically, using a platinum electrode and a sleeve-type calomel electrode containing 0.1 N lithium perchlorate in acetic anhydride (see Titrimetry (541)). Perform a blank determination, and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 43.25 mg of $C_{13}H_{24}N_4O_3S \cdot C_4H_4O_4$.

Timolol Maleate Ophthalmic Solution

» Timolol Maleate Ophthalmic Solution is a sterile, aqueous solution of Timolol Maleate. It contains an amount of C13H24N4O3S · C4H4O4 equivalent to not less than 90.0 percent and not more than 110.0 percent of the labeled amount of timolol (C13H24N4O3S).

Packaging and storage-Preserve in tight, light-resistant containers. USP Reference standards (11)-USP Timolol Maleate RS.

Identification-Dilute a suitable quantity of Ophthalmic Solution with water to obtain a solution having a concentration of about 20 μ g of timolol per mL: the UV absorption spectrum of the solution so obtained exhibits maxima and minima at the same wavelengths as that of a similar preparation of USP Timolol Maleate RS, concomitantly measured.

Sterility (71): meets the requirements.

pH (791): between 6.5 and 7.5.

Assa

pH 2.8 phosphate buffer-Dissolve 11.1 g of monobasic sodium phosphate in 1000 mL of water, adjust with phosphoric acid to a pH of 2.8 ± 0.05 , filter, and degas.

Diluent-Prepare a mixture of acetonitrile and pH 2.8 phosphate buffer (2:1).

Mobile phase-Prepare a mixture of pH 2.8 phosphate buffer and methanol (65:35). Make adjustments if necessary (see System Suitability under Chromatography (621)). [NOTE-Minimize the time the Reference Standard, the Ophthalmic Solution, the standard stock solution, the Standard preparation, and the Assay preparation are exposed to direct light.]

USP 2 28

Standard preparation—Transfer about 34 mg of USP Timole abile phase—Prepare Maleate RS, accurately weighed, to a 25-mL volumetric flast 8 phosphate buffer dissolve in and dilute with water to volume, and mix. Transfer 5.0 m and ard preparation of this stock solution to a 50-mL volumetric flask, add 15 mL or ate RS, accurately v of this stock solution to a 50-mL volumetric flask, add 15 mL Diluent, dilute with water to volume, and mix. L of 0.05 M monol

Assay preparation-Transfer an accurately measured volume of Ophthalmic Solution, equivalent to about 5 mg of timolol, to a 50-ml volumetric flask, add 15 mL of *Diluent*, dilute with water to volume and mix.

and mix. Chromatographic system (see Chromatography (621))—The relatent to about 10 m liquid chromatograph is equipped with a 295-nm detector and a add 10 mL of 0.0 4.6-mm \times 15-cm column that contains 5-µm packing L1. The malent to about 20 mL of 0.0 column temperature is maintained at 40°, and the flow rate is about 20 mL of water, ε 1.2 mL per minute. Chromatograph the Standard preparation, and me, and mix. record the peak responses as directed for Procedure: the tailing factor bromatographic sy is not more than 2.0, the column efficiency is not less than 3600 m \times 30-cm colum injections is not more than 2.0%. injections is not more than 2.0%.

Procedure-Separately inject equal volumes (about 10 µL) of the Standard preparation and the Assay preparation into the chromat-ograph, record the chromatograms, and measure the peak area responses for the major peaks. Calculate the quantity, in mg, of timolol (C13H24N4O3S) in each mL of Ophthalmic Solution taken by the formula:

$(316.43/432.49)(50C/V)(r_u/r_s),$

in which 316.43 and 432.49 are the molecular weights of timolol and timolol maleate, respectively, C is the concentration, in mg per mL, of USP Timolol Maleate RS in the Standard preparation, V is the volume, in mL, of Ophthalmic Solution taken, and r_u and r_s are the peak area responses of the timolol peaks obtained from the Assay preparation and the Standard preparation, respectively.

Timolol Maleate Tablets

» Timolol Maleate Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of C13H24N4O3S · C4H4O4.

Packaging and storage-Preserve in well-closed containers. USP Reference standards (11)-USP Timolol Maleate RS. Identification-Transfer a portion of powdered Tablets, equivalent to about 30 mg of timolol maleate, to a 50-mL volumetric flask, add about 2 mL of 0.1 N hydrochloric acid, and shake gently. Add about 30 mL of methanol, agitate for 20 minutes, add methanol to volume, mix, and centrifuge. Similarly prepare a Standard solution containing 0.6 mg of USP Timolol Maleate RS per mL. Separately apply 10 µL of the test solution and 10 µL of the Standard solution to a thin-layer chromatographic plate (see Chromatography (621)) coated with a 0.25-mm layer of chromatographic silica gel mixture. Develop the chromatogram using a solvent system consisting of a mixture of chloroform, methanol, and ammonium hydroxide (80:20:1) until the solvent front has moved about three-fourths of the length of the plate. Air-dry, and examine under short-wavelength UV light: the Rr values of the principal spots obtained from the test solution correspond to those obtained from the Standard solution.

Dissolution, Procedure for a Pooled Sample (711)-Medium: 0.1 N hydrochloric acid; 500 mL.

Apparatus 1: 100 rpm.

Time: 20 minutes. Procedure—Determine the amount of timolol maleate in solution in filtered portions of the solution under test, in comparison with a Standard solution having a known concentration of USP Timolol Maleate RS in the same medium, employing the procedure set forth in the Assay, making any necessary modifications.

Tolerances—Not less than 80% (Q) of the labeled amount of timolol maleate ($C_{13}H_{24}N_4O_3S \cdot C_4H_4O_4$) is dissolved in 20 minutes. Uniformity of dosage units (905): meet the requirements. Assa

pH 2.8 phosphate buffer-Transfer 22.08 g of monobasic sodiu phosphate to a 2-liter volumetric flask, dilute with water to volume adjust with phosphoric acid to a pH of 2.8 \pm 0.05, and filter.

ard is dissolved, ad to volume, and mi say preparation-V Transfer an ac ste t 1.8 mL per minut

Standard preparatic Procedure: the relat the tailing factor fc Procedure—Separate mdard preparation a aph by means of a su chromatograms, an ulate the quantity, Tablets taken by the

which C is the con leate RS in the Sta. ponses obtained for the Standard prep

imolol Male lydrochloro1

Timolol Male ontain not less 10.0 percent of $C_{17}\tilde{H}_{28}N_4O_7$ $C_7H_8CIN_3O_4S_2$).

ickaging and sto intainers.

SP Reference sta hydrochlorothiazide RS

Identification-Tra b about 20 mg of containing about 5 Centrifuge. Separate Maleate RS and US standard solutions Separately apply 3 solution to a thin-la (621)) coated with Mixture. Develop Multiple of a miniput of a mini ouths of the lengt avelength UV lig rom the Standard solution.

Medium: 0.1 N Apparatus 2: Time: 20 mini Procedure-D hH₂₄N₄O₃S · C₄H e: Prepare a S

Slayback Exhibit 1055, Page 74 of 78 Slayback v. Eye Therapies - IPR2022-00142 of a mixture of methanol in

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t, Tris(hydroxy-ion, Resolution directed in the

shed portion a tobramycin, to: ir 20- to 25-)-mL volumetri

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irements.

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rid to a pH of 6.0. Dilute with water to obtain a solution having a

ind to a prior of o. Drute with water to obtain a solution having a mown concentration of about 1.1 mg per mL. System suitability solution 1—Dilute the System suitability stock putton quantitatively, and stepwise if necessary, with water to obtain solution having a known concentration of about 0.22 mg per mL. System suitability solution 2—Heat a portion of the System iability stock solution in a suitable sealed glass container at 100° for 8 to 9 hours. Cool to room temperature, and dilute with water to obtain a solution having a known concentration of about 0.22 mg per

шİ Standard solution-Prepare a solution of about 55 mg of USP Tobramycin RS, accurately weighed, in a 50-mL volumetric flask. Dissolve in water, add 1.0 mL of 1.0 N sulfuric acid, dilute with water by volume, and mix. Dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a concentration of $1.10 \ \mu g$ of ubramycin per mL.

Test solution-Transfer an accurately measured volume of Inhalation Solution, equivalent to about 240 mg of tobramycin, to a 90-mL volumetric flask, dilute with water to volume, and mix. Dilute antitatively, and stepwise if necessary, with water to obtain a lution having a concentration of 192 µg of tobramycin per mL.

Derivatization procedure-[NOTE-Heat all solutions at the same emperature and for the same duration as indicated. Move all flasks to and from the 60° constant-temperature bath at the same time.] To separate 50-mL flasks transfer 15.0 mL of *System suitability solution* 1, 15.0 mL of System suitability solution 2, 15.0 mL of Standard solution, 15.0 mL of Test solution, and 15.0 mL of Blank solution. To each flask, add 10 mL of 2,4-Dinitrofluorobenzene reagent and 10 mL of Tris(hydroxymethyl)aminomethane reagent, shake, and insert the stopper. Place the flasks in a constant-temperature bath at $60 \pm 2^{\circ}$, and heat for 50 ± 5 minutes. Remove the flasks from the bath, and allow to stand for 10 minutes. Add acetonitrile to about 2 mL below the 50-mL mark, allow to cool to room temperature, dilute with acetonitrile to volume, and mix. Allow the solutions to stand for 16 hours. The solutions thus obtained are Derivatized system suitability solution 1, Derivatized system suitability solution 2, the Berivatized standard solution, the Derivatized test solution, and the Derivatized blank solution.

Chromatographic system (see Chromatography (621))—The liquid chromatograph is equipped with a 365-nm detector and a 4.6-mm × 25-cm column that contains packing L11. The flow rate is about 1.2 mL per minute. The chromatograph is programmed as follows.

1 1 1 1				
, polyethylens, over-wrapped	Time (minutes)	Solution A (%)	Solution B (%)	Elution
S. USP Tobra	0 0-14	79 79→66	$\begin{array}{c} 21\\ 21 \rightarrow 34 \end{array}$	equilibration linear gradient
tion determined	14-25 25-35	66→30 30	$34 \rightarrow 70$	linear gradient isocratic
than 60 USP	35-40 40-50	$30 \rightarrow 20$ $20 \rightarrow 5$	70→80 80→95	linear gradient
.1 .				

Chromatograph Derivatized system suitability solution 2, and record the peak responses as directed for Procedure: the capacity factor, k', determined from tobramycin is not less than 15.5. Chromatograph Derivatized system suitability solution 1, and use the chromatogram to locate the degradation peaks from comparison to Derivalized system suitability solution 2 (deoxystreptamine kanosaminide and Bebramine will increase in response in Derivatized system suitability solution 2 when viewed at a 0-10 mAbs unit or 0-5 mV unit full scale). Record the peak responses as directed for Procedure: the Tative retention times are about 0.36 for an impurity, 0.66 for ecxystreptamine kanosaminide, 0.94 for nebramine, 0.96 for nd 200 mOsmol kanamycin B, and 1.00 for tobramycin. The resolution, R, between the nebramine and kanamycin peaks is not less than 1.0. The relative xture of water andard deviation for replicate injections of the Derivatized standard tolution is not more than 2.0%.

Procedure-Separately inject equal volumes (about 45 µL) of perivatized system suitability solution 1, Derivatized system uitability solution 2, the Derivatized standard solution, the Derivatized test solution, and the Derivatized blank solution, record the chromatograms, and measure the peak responses, disregarding my peak corresponding to those obtained from the *Derivatized blank* solution. Relative retention times of 0.36, 0.66, and 0.94 from those found at the derivatized test solution. For unknown peak determinations,

test solution that correspond to those in the chromatogram of Derivatized system suitability solution I. Calculate the percentage of each impurity in relation to the tobramycin content of the Inhalation Solution taken by the formula:

in which r_i is the peak area of any impurity obtained from the *Derivatized test solution*; and r_s is the peak area for tobramycin obtained from the *Derivatized standard solution*: not more than 0.25% of the impurity noted at a relative retention time of 0.36 is found; not more than 0.3% of deoxystreptamine kanosaminide is found; not more than 0.4% of nebramine is found; not more than 0.1% of any unknown impurity is found; not more than 0.2% of total unknown impurities is found; and not more than 1.0% of total impurities is found.

Content of sodium chloride-Pipet 25 mL of Inhalation Solution into a suitable container. Add between 70 and 100 mL of water. Add 10 mL of an acidic gelatin solution, prepared by dissolving 2 g of gelatin and 50 mL of nitric acid in 1000 mL of water. Titrate potentiometrically with 0.1 N silver nitrate VS using a suitable silver electrode: not less than 90.0% and not more than 110.0% of the labeled amount of sodium chloride is found.

Other requirements-It meets the requirements for the Identification tests under Tobramycin.

Assay

Mobile phase, 2,4-Dinitrofluorobenzene reagent, Tris(hydroxymethyl)aminomethane reagent, Standard preparation, Derivatization procedure, Resolution solution, and Chromatographic system— Proceed as directed in the Assay under Tobramycin.

Assay preparation-Transfer an accurately measured volume of Inhalation Solution to a suitable volumetric flask, and quantitatively dilute with water to obtain a solution having a concentration of about

192 µg of tobramycin per mL. Procedure—Proceed as directed in the Assay under Tobramycin. Calculate the quantity, in mg, of tobramycin $(C_{18}H_{37}N_5O_9)$ in each mL of Inhalation Solution taken by the formula:

$(CE)(L/D)(r_U/r_s),$

in which C, E, r_U , and r_s are as defined therein; L is the labeled quantity, in mg, of tobramycin per mL in the Inhalation Solution taken; and D is the concentration, in μg per mL, of tobramycin in the Assay preparation.

Tobramycin Ophthalmic Solution

» Tobramycin Ophthalmic Solution contains the equivalent of not less than 90.0 percent and not more than 120.0 percent of the labeled amount of tobramycin $(C_{18}H_{37}N_5O_9)$. It may contain one or more suitable buffers, dispersants, preservatives, and tonicity agents.

Packaging and storage—Preserve in tight containers, and avoid exposure to excessive heat.

USP Reference standards (11)-USP Tobramycin RS.

Identification-

A: Prepare a Standard solution of USP Tobramycin RS containing 3 mg per mL. Separately apply 6 μ L of Ophthalmic Solution, 6 μ L of the Standard solution, and 6 μ L of a mixture Solution, 6 μ L of the Standard solution, and 6 μ L of a mixture consisting of equal volumes of the two solutions to a thin-layer chromatographic plate (see *Chromatography* (621)) coated with a 0.25-mm layer of chromatographic silica gel mixture. Proceed as directed for *Identification* test A under *Tobramycin*, beginning with "Direct the plate in a suitable chromatographic chamber." The 'Place the plate in a suitable chromatographic chamber.' specified results are obtained.

B: The retention time of the major peak for tobramycin in the chromatogram of the Derivatized assay preparation corresponds to that in the chromatogram of the Derivatized standard preparation, as obtained in the Assay.

Sterility (71)-It meets the requirements when tested as directed for Membrane Filtration under Test for Sterility of the Product to be Examined.

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1942 **Tobramycin** | Official Monographs

pH (791): between 7.0 and 8.0.

Assa

Mobile phase, 2,4-Dinitrofluorobenzene reagent, Tris(hydroxymethyl)aminomethane reagent, and Resolution solution-Prepare as directed in the Assay under Tobramycin.

Standard preparation-Transfer about 33 mg of USP Tobramycin RS, accurately weighed, to a 50-mL volumetric flask, add 20 mL of water and 1 mL of 1 N sulfuric acid, and swirl to dissolve. Dilute with water to volume, and mix. Transfer 10.0 mL of this solution to a second 50-mL volumetric flask, dilute with water to volume, and mix. This solution contains about 0.132 mg of USP Tobramycin RS per mL.

Assay preparation-Transfer an accurately measured volume of Ophthalmic Solution, equivalent to about 6 mg of tobramycin, to a 50-mL volumetric flask, dilute with water to volume, and mix.

Derivatization procedure-Proceed as directed in the Assay under Tobramycin, except to use 5.0 mL each of the Standard preparation and the Assay preparation, instead of 4.0 mL of each.

Chromatographic system—Proceed as directed in the Assay under Tobramycin, except to use a 4-mm × 15-cm column and to maintain the column temperature at 40°.

Procedure-Proceed as directed in the Assay under Tobramycin. Calculate the quantity, in mg, of tobramycin ($C_{18}H_{37}N_5O_9$) in each mL of the Ophthalmic Solution taken by the formula:

 $0.05(CE/V)(r_{ll}/r_{s}),$

in which V is the volume, in mL, of Ophthalmic Solution taken to prepare the Assay preparation; and the other terms are as defined therein.

Tobramycin and Dexamethasone Ophthalmic Ointment

» Tobramycin and Dexamethasone Ophthalmic Ointment contains not less than 90.0 percent and not more than 120.0 percent of the labeled amount of tobramycin (C18H37N5O9), and not less than 90.0 percent and not more than 110.0 percent of the labeled amount of dexamethasone $(C_{22}H_{29}FO_5)$.

Packaging and storage-Preserve in collapsible ophthalmic ointment tubes

USP Reference standards (11)-USP Dexamethasone RS. USP Tobramycin RS.

Identification-

A: To 1 g of Ophthalmic Ointment in a test tube add 2 mL of chloroform, and shake to dissolve. Add 0.5 mL of sodium sulfate solution (1 in 10), shake vigorously, and centrifuge: the clear supernatant aqueous liquid meets the requirements for Identification test A under Tobramycin. [NOTE-If, after centrifuging, an oily film remains on top of the supernatant aqueous liquid, transfer the supernatant aqueous liquid to a second test tube, and wash it with 2 mL of chloroform.]

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

Sterility (71)-It meets the requirements when tested as directed for Membrane Filtration under Test for Sterility of the Product to be Examined.

Minimum fill (755): meets the requirements.

Water, Method I (921): not more than 1.0%, 20 mL of a mixture of toluene and methanol (7:3) being used in place of methanol in the titration vessel.

Metal particles (751): meets the requirements.

Assay for tobramycin-

Mobile phase, 2,4-Dinitrofluorobenzene reagent, Tris(hydroxymethyl)aminomethane reagent, Standard preparation, Resolution solution, and Chromatographic system-Proceed as directed in the Assay under Tobramycin

USP USP 28

Assay preparation—Transfer an accurately weighed portion **Tobramycin a** Ophthalmic Ointment, equivalent to about 4.5 mg of tobramycin, to phthalmic Si separator, add 50 mL of ether, and extract with four 20- to 25-10 phthalmic Si portions of water. Combine the water extracts in a 100-mL volume

flask, dilute with water to volume, and mix.

Derivatization procedure-Proceed as directed in the Assay unity Tobramycin and] Tobramycin, except to use 15.0 mL of Assay preparation instead with is a sterile aq

Procedure—Proceed as directed in the Assay under Tobramyca Calculate the quantity of tobramycin ($C_{18}H_{37}N_5O_9$), in mg, in the count of tobramyca portion of Ophthalmic Ointment taken by the formula: 0.0 percent and r

$$(4/150)(CE)(r_u/r_s),$$

in which the terms are as defined therein.

Assay for dexamethasone-Diluent-Prepare a mixture of methanol and water (750:250). Mobile phase-Prepare a suitable mixture of methanol and water

: 45), pass through a suitable filter having a 1-µm or finer porosity and degas. Make adjustments if necessary (see System Suitability

and degas. Marc adjustments in increasing (act 2) in footium sulfate, disp under Chromatography (621)). Standard preparation—Dissolve an accurately weighed quantity of prematant meets the USP Dexamethasone RS in *Diluent* to obtain a stock solution having for any cit. B: The retention tin a known concentration of about 0.2 mg per mL. Transfer 15.0 mL of B: The retention tin

this stock solution to a separator containing about 50 mL of *n*-hexane promatogram of the A and shake. Allow the layers to separate, and drain the lower phase promatogram of the S_L into a 50-mL volumetric flask. Repeat the extraction with two 15-mL dexamethasone. portions of Diluent, combining the lower phase from each extraction serility (71)-It meets

in the same 50-mL volumetric flask. Dilute with Diluent to volume Membrane Filtration u and mix. This solution contains about 0.06 mg of USP Dexameth framined. asone RS per mL.

Resolution solution—Prepare a stock solution of chlorobutanol and USP Dexamethasone RS in *Diluent* containing about 1 mg of anhydrous chlorobutanol and 0.2 mg of USP Dexamethasone RS per mL. Proceed as directed for Standard preparation beginning with "Transfer 15.0 mL of this stock solution to a separator." The solution so obtained contains about 0.3 mg of anhydrous chlorobutanol and 0.06 mg of USP Dexamethasone RS per mL.

Assay preparation-Transfer an accurately weighed quantity of Ophthalmic Ointment, equivalent to about 3 mg of dexamethasone, a separator containing about 50 mL of n-hexane, and shake. Add 15 mL of Diluent, and shake. Allow the layers to separate, and drain the lower phase into a 50-mL volumetric flask. Repeat the extraction with two 15-mL portions of *Diluent*, combining the lower phase from each extraction in the same 50-mL volumetric flask. Dilute with *Diluent* to

volume, mix, and centrifuge. Use the clear solution. Chromatographic system (see Chromatography (621))-The liquid chromatograph is equipped with a 206-nm detector and an 8.0-mm \times 10-cm column that contains packing L1. The flow rate is about 3 mL per minute. Chromatograph the Resolution solution, and measure the peak responses as directed for Procedure: the relative retention times are about 0.7 for chlorobutanol and 1.0 for dexamethasone; and the resolution, R, between chlorobutanol and dexamethasone is not less than 1.8. Chromatograph the Standard preparation, and measure the peak responses as directed for Procedure: the tailing factor is not more than 2; the column efficiency is not less than 350 theoretical plates; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure-Separately inject equal volumes (about 100 µL) of the Standard preparation and the Assay preparation into the chromate ograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of dexamethasone $(C_{22}H_{29}FO_5)$ in the portion of Ophthalmic Ointment taken by the formula:

$$50C(r_u/r_s)$$
,

in which C is the concentration, in mg per mL, of U_{set}^{SP} Dexamethasone RS in the *Standard preparation*; and r_{ij} and r_{s} are the dexamethasone peak responses obtained from the Assay preparation and the Standard preparation, respectively.

dentification-A: To 1 mL of Oph

abeled amount of (

hckaging and storage

SP Reference stand

bramycin RS

H (791): between 5.

say for tobramycin-Mobile phase, 2,4-1 whyl)aminomethane solution, and Chromatc say under Tobramyci. Assay preparationhthalmic Suspension 50-mL volumetric flag Derivatization proced bramycin, except to u 4.0 mL.

Procedure-Proceed aculate the quantity, tion of Ophthalmic !

which the terms are a w for dexamethas Mobile phase-Prepa 5:45), filter through : and degas. Make ac Chromatography Standard preparation me RS, accurately we methanol, dilute with of this solution to hanol to volume, an USP Dexamethasone Assay preparation-Mulalmic Suspension avalent to about 4 m dilute with metha Chromatographic sy d chromatograph i mm × 25-cm colur 1.5 mL per minut measure the peak re or for the analyte pea not less than 1400 ion for replicate is Pocedure-Separate dard preparation a ph, record the chror

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1998 **Tropicamide** | Official Monographs

pH (791): between 10.0 and 11.5, in a solution prepared as directed in the labeling.

Water, Method I (921)-Add 5 mL of glacial acetic acid prior to the titration: the content is not more than 1.0%.

Particulate matter (788): meets the requirements for smallvolume injections.

Potassium chloride content-

Potassium chorus content Standard solutions (1, 2, 3, 4, and 5) each containing 0.60 mEq of sodium (35 mg of sodium chloride) per liter, and to the solutions add, respectively, 0, 2, 4, 6, and 8-mg supplements of potassium, in the form of the chloride, per liter. If measured because of changes in the sensitivity of the photometer. necessary, because of changes in the sensitivity of the photometer, vary the levels of concentration of the potassium, keeping the ratios between solutions approximately as given. Standard graph—Set a suitable flame photometer for maximum

emittance at a wavelength of 766 nm to 767 nm. (The exact wavelength setting will vary slightly with the instrument.) Adjust the instrument to zero emittance with solution I. Then adjust the instrument to 100% emittance with solution 5. Read the percentage emittance of solutions 2, 3, and 4. Plot the observed emittance of solutions 2, 3, 4, and 5 as the ordinate and the concentration, in μg per mL, of potassium as the abscissa on arithmetic coordinate paper.

Procedure-Dissolve the entire contents of 1 container of Tromethamine for Injection in sufficient water, and dilute quantitatively and stepwise with water to obtain a solution containing about 4 µg of potassium per mL, or a quantity corresponding to the concentration of the Standard solutions. Adjust the instrument to zero emittance with solution 1 and to 100% emittance with solution 5. Read the percentage emittance of the test solution. By reference to the Standard graph, determine the concentration, in µg per mL, of potassium in the test solution, apply the dilution factor, and calculate the quantity, in mg, of potassium in the container of Tromethamine for Injection. Each mg of potassium is equivalent to 1.907 mg of potassium chloride (KCl).

Sodium chloride content-Proceed as directed under Potassium Sodium chloride content—Proceed as directed under *Potassium* chloride content, with the following modifications: (1) Prepare the *Standard solutions* to contain 0, 2, 4, 6, and 8 mg of sodium, in the form of the chloride, per 1000 mL, without added potassium; (2) prepare the *Standard graph* with the flame photometer set at 588 nm to 589 nm; and (3) under *Procedure* read "sodium" for "potassium" throughout. Each mg of sodium is equivalent to 2.542 mg of sodium chloride (NaCl).

Other requirements—It meets the requirements for Sterility Tests (71), Uniformity of Dosage Units (905), and Labeling under Injections (1).

Assay for tromethamine-Dissolve the entire contents of 1 container of Tromethamine for Injection in sufficient water, diluting with water to an accurately measured volume to obtain a solution containing about 36 mg of tromethamine per mL. Transfer to a beaker an accurately measured volume of the solution, equivalent to about 180 mg of tromethamine, dilute with water to about 100 mL, add bromocresol purple TS, and titrate with 0.1 N hydrochloric acid VS to a yellow endpoint. Each mL of 0.1 N hydrochloric acid is equivalent to 12.11 mg of C4H11NO3.

Tropicamide



C17H20N2O2 284.35

Benzeneacetamide, N-ethyl-α-(hydroxymethyl)-N-(4-pyridinyl-

methyl)-, (\pm) -. (\pm)-N-Ethyl-2-phenyl-N-(4-pyridylmethyl)hydracrylamide [1508-75-4].

» Tropicamide contains not less than 99.0 percent and not more than 101.0 percent of C₁₇H₂₀N₂O₂, calculated on the dried basis.

USP 28 USP 28

Infrared Absorption (197K). Ultraviolet Absorption (197U)— A:

R:

- Solution: 25 µg per mL. Medium: 3 N hydrochloric acid.
- Melting range, Class I (741): between 96° and 100°.

Loss on drying (731)—Dry about 500 mg, accurately weighed, in vacuum over phosphorus pentoxide at 80° for 4 hours: it loses not more than 0.5% of its weight.

Heavy metals, Method II (231): 0.002%.

Assay—Dissolve about 750 mg of Tropicamide, accurately weighed in 80 mL of glacial acetic acid, add 4 drops of crystal violet TS, and titrate with 0.1 N perchloric acid VS to a blue-green endpoint. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 28.44 mg of C12H20N2O2.

Tropicamide Ophthalmic Solution

» Tropicamide Ophthalmic Solution is a sterile, aqueous solution of Tropicamide. It contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of C₁₇H₂₀N₂O₂. It contains a suitable antimicrobial agent, and may contain suitable substances to increase its viscosity.

Packaging and storage-Preserve in tight containers, and avoid freezing.

USP Reference standards (11)-USP Tropicamide RS.

Identification-

A: Extract 10 mL of it with 25 mL of chloroform, filter the chloroform extract through dry, folded filter paper, and evaporate the filtrate to dryness: the residue so obtained responds to *Identification* test A under Tropicamide.

B: The UV absorption spectrum of the solution employed for measurement of absorbance in the Assay exhibits maxima and minima at the same wavelengths as that of a similar solution of USP Tropicamide RS, concomitantly measured.

Sterility $\langle 71 \rangle$: meets the requirements.

pH (791): between 4.0 and 5.8.

Assay-Transfer an accurately measured volume of Ophthalmic Solution, equivalent to about 30 mg of tropicamide, to a 100-ml volumetric flask, add water to volume, and mix. Transfer 10.0 mL this solution to a separator, add 2 mL of sodium carbonate solution (in 10), extract with four 20-mL portions of chloroform, and combine the extracts in a second separator. Wash the combined extracts with 25-mL portion of pH 6.5 phosphate buffer (see Buffer Solutions in section Reagents, Indicators, and Solutions), and transfer to anot separator. Wash the aqueous layer with 10 mL of chloroform, and it to the extracts. Extract the chloroform solution with four 20portions of dilute sulfuric acid (1 in 6), combine the acid extracts in 100-mL volumetric flask, and add the dilute acid to volume. Dissol an accurately weighed quantity of USP Tropicamide RS in dia sulfuric acid (1 in 6), and dilute quantitatively and stepwise with $a_{\rm S}$ same solvent to obtain a Standard solution having a know concentration of about 30 μ g per mL. Concomitantly determine the absorbances of both solutions in Lemma the neural and the absorbances of both solutions in 1-cm cells at the wavelength a maximum absorbance at about 253 nm, with a suitable spectrophy tometer, using dilute substrated of the other than the suitable spectrophy tometer, using dilute sulfaric acid (1 in 6) as the blank. Calculate quantity, in mg, of $C_{17}H_{20}N_2O_2$ in each mL of the Ophthalmic Solution taken by the formula: taken by the formula:

$(C/V)(A_U/A_s),$

in which C is the concentration, in μg per mL, of USP Tropical RS in the Standard solution, V is the volume, in mL, of Ophthal Solution relates and 4 an Solution taken, and A_y and A_s are the absorbances of the solution \mathbf{I} the Ophthalmic Solution and the Standard solution, respectively

ized from an e wurus Linné (] herein, it conta in each mg, ca than 90.0 perce labeled potency NOTE-Determ check the adj erforming the Reference Stan

Packaging and s aposure to excess **USP** Reference st Solubility test—A Units, is soluble in

Microbial limits absence of Staphy monella species

oss on drying (7 of more than 5.0% sidue on ignitio

mit of chymotry 0.067 M Phosph tassium phospha 73g of anhydrou L of solution. Mi lution with 61.1 popwise, if necess H of 7.0.

Substrate solutio r, suitable for us 067 M Phosphate ith additional pH ored in the froze wever, to freeze Crystallized Try tallized Trypsi: d to obtain a solu Procedure-Con pipped to main artment. Deter after the mea erature does n 1010 N hydrochlo cm cell. Place t ument so that t of Crystallized of the Substrate teter. [NOTE-Thi Substrate solut rbance at 30-see procedure on the bsorbance. If the 3 minutes, re entration. The first run in rate orbance change te portion of th a curve of absor activity causir the conditions Chymotrypsin 1

bich A_2 is the a bance straight-

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of ZnSO, into ison tube (A) uix, and allow r-comparison tandard Lead sium Cyanide nL of sodium to stand for 5 lution in tube 102%. t of 1.12 g-of uL volumetric onium sulfide hrough a dry 0 mL of the evaporate to

Zinc Sulfate, er. Add 5 mL 0.1 mL of disodium VS 05 M edetate

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in the Assa aken.

Tinc Sulfate Ophthalmic Solution

» Zinc Sulfate Ophthalmic Solution is a sterile solution of Zinc Sulfate in Water rendered isotonic by the addition of suitable salts. It contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $ZnSO_4$.

Packaging and storage-Preserve in tight containers.

Identification—It responds to the tests for Zinc (191) and for *Sulfate* (191).

sterility (71): meets the requirements..

pH $\langle 791 \rangle$: between 5.8 and 6.2; or, if it contains sodium citrate, between 7.2 and 7.8.

Assay—Pipet into a beaker a volume of Ophthalmic Solution, equivalent to about 25 mg of zinc sulfate. Add 1 mL of glacial acetic acid, and adjust by the dropwise addition of 6 N ammonium hydroxide to a pH of between 5.0 and 5.5. Add 1 drop of copper ethylenediaminetetraacetate solution [prepared by mixing 1 mL of cupric sulfate solution (1 in 40) and 1 mL of 0.1 M edetate disodium] and 3 drops of a 1 in 1000 solution of 1-(2-pyridylazo)-2-naphthol in anhydrous methanol, and titrate with 0.01 M edetate disodium VS. Each mL of 0.01 M edetate disodium is equivalent to 1.614 mg of ZnSO₄.

Add the following:

AZinc Sulfide Topical Suspension

(Monograph under this new title—to become official July 1, 2007) (Current monograph title is White Lotion)

» Prepare Zinc Sulfide Topical Suspension as follows:

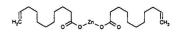
Zinc Sulfate	40 g 40 g
Purified Water, a sufficient quantity to make	1000 mL

Dissolve the Zinc Sulfate and the Sulfurated Potash separately, each in 450 mL of Purified Water, and filter each solution. Add the sulfurated potash solution slowly to the zinc sulfate solution with constant stirring. Then add the required amount of Purified Water, and mix.

NOTE-Prepare the Topical Suspension fresh, and shake it thoroughly before dispensing.

Packaging and storage—Dispense in tight containers. AUSP28 (Official July 1, 2007)

Zinc Undecylenate



 $C_{22}H_{38}O_4Zn$ 431.92 10-Undecenoic acid, zinc(2+) salt. Zinc 10-undecenoate [557-08-4].

» Zinc Undecylenate contains not less than 98.0 percent and not more than 102.0 percent of $C_{22}H_{38}O_4Zn$, calculated on the dried basis.

Packaging and storage—Preserve in well-closed containers. Identification—

A: Acidify about 5 g with 25 mL of 2 N sulfuric acid, add 20 mL of water, and extract in a separator with two 25-mL portions of ether. Evaporate the ether solution until the odor of ether no longer is perceptible. Add potassium permanganate TS dropwise to a 1-mL portion of this residue: the permanganate color is discharged.

B: A 3-mL portion of the residue of undecylenic acid obtained in *Identification* test A responds to *Identification* test B under *Undecylenic Acid.*

C: Dissolve about 100 mg in a mixture of 10 mL of water and 1 mL of ammonium hydroxide, and add a few drops of sodium sulfide TS: a white, flocculent precipitate of zinc sulfide is formed.

Loss on drying (731)—Dry it at 105° for 2 hours: it loses not more than 1.25% of its weight.

Alkalies and alkaline earths—Boil 1.50 g with a mixture of 50 mL of water and 10 mL of hydrochloric acid, filter while hot, and wash the separated acid with about 50 mL of hot water. Render the combined filtrate and washings alkaline with 6N ammonium hydroxide, add ammonium sulfide TS to precipitate the zinc completely, dilute with water to 200 mL, mix, and filter. To 100 mL of the clear filtrate add 0.5 mL of sulfuric acid, evaporate to dryness, and ignite over a low flame to constant weight: the weight of the residue does not exceed 7.5 mg (1.0%).

Assay—Boil 50.0 mL of 0.1 N sulfuric acid VS with about 1 g of Zinc Undecylenate, accurately weighed, for 10 minutes, or until the undecylenic acid layer is clear, adding water, as necessary, to maintain the original volume. Cool, and transfer the mixture, with the aid of water, to a 500-mL separator. Dilute with water to about 250 mL, and extract with two 100-mL portions of solvent hexane. Wash the combined extracts with water until the last washing is neutral to litmus, add the washings to the original water layer, and evaporate on a steam bath to about 100 mL. Cool, add 3 drops of methyl orange TS, and titrate the excess sulfuric acid with 0.1 N sodium hydroxide VS. Perform a blank determination (see *Residual Titrations* under *Titrimetry* (541)). Each mL of 0.1 N sulfuric acid is equivalent to 21.60 mg of $C_{22}H_{18}O_4Zn$.

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