Ophthalmic Ointment Monographs: Tobramycin and Dexamethasone Ophthalmic Ointment

Type of Posting	Revision Bulletin
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Expert Committee	Chemical Medicines Monographs 1 to 6
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015-2020 Council of Experts, the Chemical Medicines Expert Committees 1 to 6 has revised the monographs listed below. The purpose of the revision is to replace the requirement to comply with the entire content of the USP general chapter *Ophthalmic Products—Quality Tests* <771> with a requirement to comply only with the subsection for *Particulate and Foreign Matter* in *Ophthalmic Products—Quality Tests* <771>, and with the section for *Container Content* for those monographs where the requirement for Minimum Fill was deleted.

- Atropine Sulfate Ophthalmic Ointment
- Bacitracin Ophthalmic Ointment
- Bacitracin Zinc and Polymyxin B Sulfate Ophthalmic Ointment
- Bland Lubricating Ophthalmic Ointment
- Chloramphenicol and Polymyxin B Sulfate Ophthalmic Ointment
- Chloramphenicol Ophthalmic Ointment
- Chlortetracycline Hydrochloride Ophthalmic Ointment
- Ciprofloxacin Ophthalmic Ointment
- Dexamethasone Sodium Phosphate Ophthalmic Ointment
- Erythromycin Ophthalmic Ointment
- Gentamicin and Prednisolone Acetate Ophthalmic Ointment
- Gentamicin Sulfate Ophthalmic Ointment
- Hydrocortisone Acetate Ophthalmic Ointment
- Idoxuridine Ophthalmic Ointment
- Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Hydrocortisone Acetate Ophthalmic Ointment
- Neomycin and Polymyxin B Sulfates and Bacitracin Ophthalmic Ointment
- Neomycin and Polymyxin B Sulfates and Bacitracin Zinc Ophthalmic Ointment
- Neomycin and Polymyxin B Sulfates and Dexamethasone Ophthalmic Ointment
- Neomycin and Polymyxin B Sulfates Ophthalmic Ointment
- Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Hydrocortisone Ophthalmic Ointment
- Neomycin and Polymyxin B Sulfates, Bacitracin, and Hydrocortisone Acetate Ophthalmic Ointment
- Neomycin Sulfate and Dexamethasone Sodium Phosphate Ophthalmic Ointment
- Neomycin Sulfate Ophthalmic Ointment
- Oxytetracycline Hydrochloride and Polymyxin B Sulfate Ophthalmic Ointment
- Sodium Chloride Ophthalmic Ointment
- Sulfacetamide Sodium and Prednisolone Acetate Ophthalmic Ointment
- Sulfacetamide Sodium Ophthalmic Ointment
- Tetracycline Hydrochloride Ophthalmic Ointment
- c Ophthalmic Ointment
- Tobramycin Ophthalmic Ointment

The Revision Bulletins for the monographs listed above supersede the currently official version of these monographs. The Revision Bulletin will be incorporated in the First Supplement to USP 40–NF 35.

Should you have any questions, please contact Margareth R. C. Marques, M.Sc., Ph.D. (301-816-8106 or mrm@usp.org).

Tobramycin and Dexamethasone Ophthalmic Ointment

DEFINITION

Tobramycin and Dexamethasone Ophthalmic Ointment contains NLT 90.0% and NMT 120.0% of the labeled amount of tobramycin ($C_{18}H_{37}N_5O_9$), and NLT 90.0% and NMT 110.0% of the labeled amount of dexamethasone ($C_{22}H_{29}FO_5$).

IDENTIFICATION

Change to read:

- **A. THIN-LAYER CHROMATOGRAPHY**

  Solution A: 100 mg/mL of sodium sulfate in water

  Diluent: Butyl alcohol and pyridine (100:1)

  Standard solution: 6 mg/mL of USP Tobramycin RS in water

  Sample solution: To 1 g of Ophthalmic Ointment in a test tube add 2 mL of chloroform, and shake to dissolve. Add 0.5 mL of *Solution A*, shake vigorously, and centrifuge. Use the clear supernatant aqueous liquid. 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.

  Solution B: *Standard solution* and *Sample solution* (1:1)

  Chromatographic system

  ▲(See *Chromatography* ⟨621⟩*, Thin-Layer Chromatography*.)▲*USP39*

  Adsorbent: 0.25-mm layer of chromatographic silica gel mixture

  Application volume: 3 µL

  Developing solvent system: Methanol, chloroform, and ammonium hydroxide (60:25:30)

  Spray reagent: 10 mg/mL of ninhydrin in *Diluent*

  Analysis

  Samples: *Standard solution*, *Sample solution*, and *Solution B*

  Apply the *Standard solution*, the *Sample solution*, and *Solution B* to the plate. Place the plate in a suitable chromatographic chamber, and develop the chromatogram in the *Developing solvent system* until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the chamber, allow the solvent to evaporate, and heat the plate at 110° for 15 min. Immediately locate the spots on the plate by spraying it with *Spray reagent*.

  Acceptance criteria: Tobramycin appears as a pink spot, and the R_F values of the spots of the *Sample solution* and of *Solution B*, respectively, correspond to those of the *Standard solution*.

- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay* for *Dexamethasone*.

ASSAY

- **TOBRAMYCIN**

  Mobile phase: Dissolve 2.0 g of tris(hydroxymethyl)aminomethane in 800 mL of water. Add 20 mL of 1 N sulfuric acid, and dilute with acetonitrile to obtain 2000 mL of solution. Cool, and pass through a filter of 0.2-µm or finer pore size.

  Solution A: 10 mg/mL of 2,4-dinitrofluorobenzene in alcohol. This solution may be used for 5 days if refrigerated when not in use.

  Solution B: 15 mg/mL of tris(hydroxymethyl)aminomethane in water. This solution may be used for 1 month if refrigerated when not in use.

  Solution C: 3 mg/mL of tris(hydroxymethyl)aminomethane prepared as follows. Transfer 40 mL of *Solution B* to a 200-mL volumetric flask. Add dimethyl sulfoxide while mixing, and dilute with dimethyl sulfoxide to volume. Use this reagent within 4 h. If kept immersed in an ice-water bath below 10°, the reagent may be used for up to 8 h.

  Standard stock solution: 1.1 mg of USP Tobramycin RS prepared as follows. Transfer 55 mg of USP Tobramycin RS into a 50-mL volumetric flask. Add 1 mL of 1 N sulfuric acid and enough water to dissolve it, and dilute with water to volume.

  Standard solution: 0.22 mg/mL of USP Tobramycin RS from *Standard stock solution* in water

  Sample solution: Nominally 0.045 mg/mL of tobramycin from Ophthalmic Ointment in water prepared as follows. Transfer a portion of Ophthalmic Ointment containing nominally 4.5 mg of tobramycin to a separator. Add 50 mL of ether, and extract with four 20- to 25-mL portions of water. Combine the water extracts in a 100-mL volumetric flask, and dilute with water to volume.

  Derivatized standard solution, Derivatized sample solution, and Blank solution: Proceed as follows. Heat all solutions at the same temperature and for the same duration of time as indicated. Move all flasks to and from the 60° constant temperature bath at the same time.

  To separate 50-mL volumetric flasks transfer 4.0 mL of the *Standard solution*, 15.0 mL of the *Sample solution*, and 4.0 mL of water. To each flask add 10 mL of *Solution A* and 10 mL of *Solution C*, shake, and insert the stopper. Place the flasks in a constant temperature bath at 60 ± 2°, and heat for 50 ± 5 min. Remove the flasks from the bath, and allow to stand for 10 min. Add acetonitrile to about 2 mL below the 50-mL mark, allow to cool to room temperature, then dilute with acetonitrile to volume. The solutions thus obtained are the *Derivatized standard solution*, the *Derivatized sample solution*, and the *Blank solution*, respectively.

  System suitability stock solution: 0.24 mg/mL of *p*-naphtholbenzein in acetonitrile. Prepare freshly.

  System suitability solution: Transfer 2 mL of the *System suitability stock solution* to a 10-mL volumetric flask, dilute with *Derivatized standard solution* to volume, and use promptly.

  Chromatographic system

  (See *Chromatography* ⟨621⟩*, System Suitability*.)

  Mode: LC

  Detector: UV 365 nm

  Column: 3.9-mm × 30-cm; packing L1

  Flow rate: 1.2 mL/min

  Injection volume: 20 µL

  System suitability

  Samples: *Derivatized standard solution* and *System suitability solution*

  [NOTE—The relative retention times for *p*-naphtholbenzein and tobramycin are about 0.6 and 1.0, respectively.]

  Suitability requirements

  Resolution: NLT 4.0 between *p*-naphtholbenzein and tobramycin, *System suitability solution*

  Relative standard deviation: NMT 2.0%, *Derivatized standard solution*

  Analysis

  Samples: *Derivatized standard solution*, *Derivatized sample solution*, and *Blank solution*

  Use the *Blank solution* to identify the solvent and reagent peaks.

Calculate the percentage of the labeled amount of tobramycin ($C_{18}H_{37}N_5O_9$) in the portion of Ophthalmic Ointment taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times P \times F \times 100$$

r_U = peak area of tobramycin from the *Derivatized sample solution*
r_S = peak area of tobramycin from the *Derivatized standard solution*
C_S = concentration of USP Tobramycin RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of tobramycin in the *Sample solution* (mg/mL)
P = potency of tobramycin in USP Tobramycin RS (µg/mg)
F = conversion factor, 0.001 mg/µg

Acceptance criteria: 90.0%–120.0%

- **DEXAMETHASONE**

Mobile phase: Methanol and water (55:45)
Diluent: Methanol and water (75:25)
System suitability stock solution: 1 mg/mL of anhydrous chlorobutanol and 0.2 mg/mL of USP Dexamethasone RS in *Diluent*
System suitability solution: 0.3 mg/mL of anhydrous chlorobutanol and 0.06 mg/mL of USP Dexamethasone RS in *Diluent* prepared as follows. Transfer 15.0 mL of the *System suitability stock solution* to a separator containing about 50 mL of *n*-hexane, 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.
Standard stock solution: 0.2 mg/mL of USP Dexamethasone RS in *Diluent*
Standard solution: 0.06 mg/mL of USP Dexamethasone RS in *Diluent* prepared as follows. Transfer 15.0 mL of the *Standard stock solution* to a separator containing about 50 mL of *n*-hexane, 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.
Sample solution: Transfer a portion of Ophthalmic Ointment containing nominally 3 mg of dexamethasone to a separator containing 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⟩, *System Suitability*.)
Mode: LC
Detector: UV 206 nm
Column: 8.0-mm × 10-cm; packing L1
Flow rate: 3 mL/min
Injection volume: 100 µL
System suitability
Samples: *System suitability solution* and *Standard solution*
[NOTE—The relative retention times for chlorobutanol and dexamethasone are about 0.7 and 1.0, respectively.]
Suitability requirements
Resolution: NLT 1.8 between chlorobutanol and dexamethasone, *System suitability solution*
Tailing factor: NMT 2, *Standard solution*
Column efficiency: NLT 350 theoretical plates, *Standard solution*
Relative standard deviation: NMT 2.0%, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of dexamethasone ($C_{22}H_{29}FO_5$) in the portion of Ophthalmic Ointment taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times P \times 100$$

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Dexamethasone RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of dexamethasone in the *Sample solution* (mg/mL)
P = potency of dexamethasone in USP Dexamethasone RS (mg/mg)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Delete the following:

▲• **MINIMUM FILL** ⟨**755**⟩**:** Meets the requirements ▲*USP39*

SPECIFIC TESTS

Delete the following:

▲• **METAL PARTICLES IN OPHTHALMIC OINTMENTS** ⟨**751**⟩**:** Meets the requirements ▲*USP39*

Change to read:

• **STERILITY TESTS** ⟨**71**⟩**:** ▲Meets the requirements▲*USP39*

Delete the following:

▲• **WATER DETERMINATION,** *Method I* ⟨**921**⟩
Analysis: Use 20 mL of a mixture of toluene and methanol (7:3) in place of methanol in the titration vessel.
Acceptance criteria: NMT 1.0%
▲*USP39*

Change to read:

▲• **OTHER REQUIREMENTS:** It meets the requirements •for *Particulate and Foreign Matter* and *Container Contents*• (RB 1-Aug-2016) in *Ophthalmic Products—Quality Tests* ⟨771⟩, •*Drug Product Quality, Universal Tests, Particulate and Foreign Matter* and *Container Contents*.• (RB 1-Aug-2016)
▲*USP39*

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in collapsible ophthalmic ointment tubes.
• **USP REFERENCE STANDARDS** ⟨**11**⟩
USP Dexamethasone RS
USP Tobramycin RS