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Ciprofloxacin and Dexamethasone Otic Suspension

DEFINITION

Ciprofloxacin and Dexamethasone Otic Suspension is a sterile, aqueous suspension containing ciprofloxacin hydrochloride and dexamethasone. It contains NLT 90.0% and NMT 110.0% of the labeled amount of ciprofloxacin ($C_{17}H_{18}FN_3O_3$) and NLT 90.0% and NMT 110.0% of the labeled amount of dexamethasone ($C_{22}H_{29}FO_5$).

IDENTIFICATION

• **A.** The *Sample solution*, obtained as directed in the *Assay* for *Ciprofloxacin*, exhibits a major peak for ciprofloxacin, the retention time of which corresponds to that of the *Standard solution*, obtained as directed in the *Assay* for *Ciprofloxacin*.

• **B.** The *Sample solution*, obtained as directed in the *Assay* for *Dexamethasone*, exhibits a major peak for dexamethasone, the retention time of which corresponds to that of the *Standard solution*, obtained as directed in the *Assay* for *Dexamethasone*.

ASSAY

• **Ciprofloxacin**

Buffer: Add 6.0 mL of phosphoric acid and 8 g of diethylamine phosphate to 2.0 L of water. Adjust with 50% sodium hydroxide to a pH of 3.0.

Mobile phase: Acetonitrile and *Buffer* (11:89)

System suitability solution: 1.6 µg/mL each of USP Ciprofloxacin Hydrochloride RS and USP Ciprofloxacin Ethylenediamine Analog RS in *Mobile phase*

Standard solution A: 1.48 mg/mL of USP Ciprofloxacin Hydrochloride RS in 0.1 N hydrochloric acid. Dilute with *Mobile phase* to 0.13 mg/mL of ciprofloxacin.

Standard solution B: 0.0025 mg/mL of ciprofloxacin from *Standard solution A* in *Mobile phase*

Sample solution: Nominally 0.12 mg/mL in *Mobile phase* prepared as follows. Transfer the equivalent to 3 mg of ciprofloxacin from freshly mixed Otic Suspension to a 25-mL volumetric flask, and dilute with *Mobile phase* to volume.

Chromatographic system

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

Mode: LC

Detector: UV 280 nm

Column: 3.9-mm × 15-cm; packing L1

Flow rate: 1.5 mL/min

Injection volume: 20 µL

System suitability

Samples: *System suitability solution, Standard solution A,* and *Standard solution B*

Suitability requirements

Resolution: NLT 3.0 between ciprofloxacin and the ciprofloxacin ethylenediamine analog, *System suitability solution*

Column efficiency: NLT 2500 theoretical plates for ciprofloxacin, *System suitability solution*

Tailing factor: NMT 2.0 for ciprofloxacin, *System suitability solution*

Relative standard deviation: NMT 2.0%, *Standard solution A* and *Standard solution B*

Analysis

Samples: *Standard solution A* and *Sample solution*

Calculate the percentage of the labeled amount of ciprofloxacin ($C_{17}H_{18}FN_3O_3$) in the portion of Otic Suspension taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response of ciprofloxacin from the *Sample solution*

r_S = peak response of ciprofloxacin from *Standard solution A*

C_S = concentration of USP Ciprofloxacin Hydrochloride RS in *Standard solution A* (mg/mL)

C_U = nominal concentration of ciprofloxacin in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of ciprofloxacin, 331.34

M_{r2} = molecular weight of anhydrous ciprofloxacin hydrochloride, 367.81

Acceptance criteria: 90.0%–110.0% of the labeled amount of ciprofloxacin ($C_{17}H_{18}FN_3O_3$)

• **Dexamethasone**

Buffer and **Mobile phase:** Prepare as directed in the test for *Limit of Ciprofloxacin Formamide*.

Standard stock solution: 2 mg/mL of USP Dexamethasone RS in acetonitrile

System suitability solution: 0.2 mg/mL of USP Dexamethasone RS and 0.2 mg/mL of USP Dexamethasone Acetate RS in *Mobile phase*

Standard solution A: 0.2 mg/mL of USP Dexamethasone RS from *Standard stock solution* in *Mobile phase*

Standard solution B: 0.004 mg/mL of USP Dexamethasone RS from *Standard solution A* in *Mobile phase*

Sample solution: Nominally 0.2 mg/mL in *Mobile phase* prepared as follows. Transfer freshly mixed Otic Suspension equivalent to 2 mg of dexamethasone to a 10-mL volumetric flask, and dilute with *Mobile phase* to volume.

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 3.9-mm × 15-cm; packing L1

Flow rate: 1.5 mL/min

Injection volume: 50 µL

System suitability

Samples: *System suitability solution, Standard solution A,* and *Standard solution B*

Suitability requirements

Resolution: NLT 12 between dexamethasone and dexamethasone acetate, *System suitability solution*

Column efficiency: NLT 2000 theoretical plates for dexamethasone, *System suitability solution*

Tailing factor: NMT 2.0 for dexamethasone, *System suitability solution*

Relative standard deviation: NMT 2.0%, *Standard solution A* and *Standard solution B*

Analysis

Samples: *Standard solution A* and *Sample solution*

Calculate the percentage of the labeled amount of dexamethasone ($C_{22}H_{29}FO_5$) in the portion of Otic Suspension taken:

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

r_U = peak response of dexamethasone from the *Sample solution*

r_S = peak response of dexamethasone from *Standard solution A*

C_S = concentration of USP Dexamethasone RS in *Standard solution A* (mg/mL)

C_U = nominal concentration of dexamethasone in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0% of the labeled amount of dexamethasone ($C_{22}H_{29}FO_5$)

IMPURITIES

• **Limit of Ciprofloxacin Formamide**

Buffer: Phosphoric acid and water (3:997). Adjust with 50% sodium hydroxide to a pH of 3.0.

Mobile phase: Acetonitrile and *Buffer* (27:73)

Standard stock solution: 0.25 mg/mL of USP Ciprofloxacin Formamide RS in methanol

System suitability solution: 0.025 mg/mL of USP Dexamethasone RS and 0.025 mg/mL of USP Ciprofloxacin Formamide RS prepared as follows. Transfer 2.5 mg of USP Dexamethasone RS and 2.5 mg of USP Ciprofloxacin Formamide RS in a 100-mL volumetric flask, and dissolve in 15 mL of methanol before diluting with *Mobile phase* to volume.

Standard solution: 0.015 mg/mL from *Standard stock solution* in *Mobile phase*

Sample solution: Nominally 0.6 mg/mL in *Mobile phase* prepared as follows. Transfer an amount of freshly mixed Otic Suspension, equivalent to 6 mg, to a 10-mL volumetric flask, and dilute with *Mobile phase* to volume.

Chromatographic system

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

Mode: LC

Detector: UV 280 nm

Column: 3.9-mm × 15-cm; packing L1

Flow rate: 1.5 mL/min

Injection volume: 50 µL

System suitability

Samples: *System suitability solution* and *Standard solution*

Suitability requirements

Resolution: NLT 8 between ciprofloxacin formamide and dexamethasone, *System suitability solution*

Column efficiency: NLT 2000 theoretical plates for ciprofloxacin formamide, *Standard solution*

Tailing factor: NMT 2.0 for ciprofloxacin formamide, *Standard solution*

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each related compound in the portion of Otic Suspension taken:

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

r_U = peak response of ciprofloxacin formamide from the *Sample solution*

r_S = peak response of ciprofloxacin formamide from the *Standard solution*

C_S = concentration of USP Ciprofloxacin Formamide RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of ciprofloxacin in the *Sample solution* (mg/mL)

Acceptance criteria: NMT 0.5% of the labeled amount of ciprofloxacin

- **Ciprofloxacin Related Compounds**

Analysis: From the chromatogram of the *Sample solution*, obtained as directed in the *Assay* for *Ciprofloxacin*, measure the responses for the ciprofloxacin ethylenediamine analog and the other minor peaks. Calculate the percentage of each related compound in the portion of Otic Suspension taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times (100/F)$$

r_U = peak response of each related compound from the *Sample solution*

r_S = peak response of ciprofloxacin from *Standard solution B*

C_S = concentration of USP Ciprofloxacin Hydrochloride RS in *Standard solution B*, calculated on the anhydrous basis (mg/mL)

C_U = nominal concentration of ciprofloxacin in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of ciprofloxacin, 331.34

M_{r2} = molecular weight of anhydrous ciprofloxacin hydrochloride, 367.81

F = relative response factor (1.3 for ciprofloxacin ethylenediamine analog and 1.0 assumed for all other degradation products)

Acceptance criteria

Ciprofloxacin ethylenediamine analog: NMT 0.4% of the labeled amount of ciprofloxacin

Other single related compound: NMT 0.2%

Sum of all related compounds: NMT 0.8%

- **Dexamethasone Related Compounds**

Analysis: From the chromatogram of the *Sample solution*, obtained as directed in the *Assay* for *Dexamethasone*, measure the responses for the dexamethasone glyoxal analog, the 17-carboxy-17-deoxy analog, and other minor peaks. Calculate the percentage of each related compound in the portion of Otic Suspension taken:

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

r_U = peak response of each related compound from the *Sample solution*

r_S = peak response of dexamethasone from *Standard solution B*

C_S = concentration of USP Dexamethasone RS in *Standard solution B* (mg/mL)

C_U = nominal concentration of dexamethasone in the *Sample solution* (mg/mL)

Acceptance criteria

Dexamethasone glyoxal analog: NMT 1.0%

17-Carboxy-17-deoxy analog: NMT 2.6%

Other single related compound: NMT 0.3%

Sum of all related compounds: NMT 3.5%

[Note—The relative retention times for the dexamethasone glyoxal analog (9-Fluoro-11β-hydroxy-16α-methylandrosta-1,4-diene-3-one-17-ylglyoxal) and the 17-carboxy-17-deoxy analog (9-fluoro-11β-hydroxy-16α-methylandrosta-1,4-diene-3-one-17β-carboxylic acid) are about 1.4–1.6 and about 2.8–3.2, respectively.]

SPECIFIC TESTS

• **pH ⟨791⟩:** 3.8–4.8

• **Sterility Tests ⟨71⟩:** It meets the requirements when tested as directed under *Test for Sterility of the Product to Be Examined, Membrane Filtration*.

• **Particle Size**

Carrier fluid: Heat Purified Water to a temperature of 40°–50°, add 100 mg/L of dexamethasone while stirring, cool to room temperature while stirring, pass through a 0.2-µm filter, and store in a clean, covered container.

Sample solution: Dilute a volume of 10 µL of Otic Suspension with *Carrier fluid* to 25 mL.

Analysis

(See *Particulate Matter in Injections ⟨788⟩, Light Obscuration Particle Count Test*.)

Analyze the *Sample solution* using an electronic, liquid-borne particle counting system that employs a light obscuration sensor with a suitable sample feeding device.

Acceptance criteria: NLT 99.5% of the particles are ≤25 µm, NLT 99.95% are ≤50 µm, and NLT 99.995% are ≤100 µm.

Change to read:

• ▲**Osmolality and Osmolarity ⟨785⟩**

Osmolality: ▲ (Official 1-Aug-2022) 270–330 mOsmol/kg

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight containers, protected from light. Avoid freezing.

• **USP Reference Standards ⟨11⟩**

USP Ciprofloxacin Ethylenediamine Analog RS

1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-[(2-aminoethyl)amino]-3-quinolinecarboxylic acid hydrochloride.

$C_{15}H_{16}FN_3O_3 \cdot HCl$ 341.77

USP Ciprofloxacin Formamide RS

1-Cyclopropyl-6-fluoro-7-(4-formyl-1-piperazinyl)-1,4-dihydro-4-oxo-3-quinolone-carboxylic acid.

$C_{18}H_{18}FN_3O_4$ 359.35

USP Ciprofloxacin Hydrochloride RS

USP Dexamethasone RS

USP Dexamethasone Acetate RS

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
CIPROFLOXACIN AND DEXAMETHASONE OTIC SUSPENSION	Documentary Standards Support	SM12020 Small Molecules 1
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM12020 Small Molecules 1

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