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Oxaliplatin Injection

DEFINITION

Oxaliplatin Injection is a sterile solution of Oxaliplatin in Water for Injection. It contains NLT 90.0% and NMT 110.0% of the labeled amount of oxaliplatin ($C_8H_{14}N_2O_4Pt$).

IDENTIFICATION

Change to read:

• **A.** ▲**Spectroscopic Identification Tests ⟨197⟩, *Ultraviolet-Visible Spectroscopy*: 197U**▲ (Official 1-May-2020)

Sample solution: 100 µg/mL

Medium: Water

Acceptance criteria: Meets the requirements

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

ASSAY

• **Procedure**

[Note—All HPLC autosampler vials should be made of polypropylene.]

Acidified water: Adjust water with phosphoric acid to a pH of 3.0.

Mobile phase: Acetonitrile and *Acidified water* (1:99)

System suitability solution: 0.1 mg/mL of USP Oxaliplatin RS and 0.1 mg/mL of USP Oxaliplatin System Suitability RS in water. [Note—USP Oxaliplatin System Suitability RS is [*SP*-4-2-(1*R-trans*)]-(1,2-cyclohexanediamine-*N*,*N*′) dichloridoplatinum(II).]

Standard solution: 0.1 mg/mL of USP Oxaliplatin RS in water

Sample solution: Nominally 0.1 mg/mL of oxaliplatin in water from the combined contents of NLT 3 vials of Injection

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Column temperature: 40°

Flow rate: 1.2 mL/min

Injection volume: 20 µL

System suitability

Sample: *System suitability solution*

[Note—The relative retention times for [*SP*-4-2-(1*R-trans*)]-(1,2-cyclohexanediamine-*N*,*N*′) dichloridoplatinum(II) and oxaliplatin are 0.9 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 2.0 between [*SP*-4-2-(1*R-trans*)]-(1,2-cyclohexanediamine-*N*,*N*′) dichloridoplatinum(II) and oxaliplatin

Tailing factor: NMT 2.0 for the oxaliplatin peak

Relative standard deviation: NMT 1.0% for the oxaliplatin peak

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of oxaliplatin ($C_8H_{14}N_2O_4Pt$) in the portion of Injection taken:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

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

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

Acceptance criteria: 90.0%–110.0%

IMPURITIES

• **Limit of Oxalic Acid**

[Note—All HPLC autosampler vials should be made of polypropylene.]

Mobile phase: 0.43 g/L of sodium carbonate and 0.04 g/L of sodium bicarbonate in water

Standard stock solution: 0.32 mg/mL of USP Oxaliplatin Related Compound A RS in water. [Note—USP Oxaliplatin Related Compound A RS is available as dihydrate oxalic acid.]

Tartaric acid standard stock solution: 0.25 mg/mL of tartaric acid in water

System suitability solution: 23 µg/mL of USP Oxaliplatin Related Compound A RS and 12.5 µg/mL of tartaric acid in water from *Standard stock solution* and *Tartaric acid standard stock solution*.

Standard solution: 16.2 µg/mL of USP Oxaliplatin Related Compound A RS in water from *Standard stock solution*

Sensitivity solution: 1.94 µg/mL USP Oxaliplatin Related Compound A RS in water from *Standard solution*

Sample solution: Nominally equivalent to 2 mg/mL of oxaliplatin in water from Injection

Chromatographic system

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

Mode: LC

Detector: Conductivity with anion suppression. [Note—A recycle mode may be used.]

Column: 4.0-mm × 25-cm; packing L81

Autosampler temperature: 5°

Flow rate: 2.0 mL/min

Injection volume: 40 µL

System suitability

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

[Note—The relative retention times for tartaric acid and oxalic acid are 0.4 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 8 between tartaric acid and oxalic acid, *System suitability solution*

Tailing factor: 0.5–1.5 for the oxalic acid peak, *Standard solution*

Relative standard deviation: NMT 3.0%, *Standard solution*

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of oxalic acid in the portion of Injection taken:

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

r_U = peak response of oxalic acid from the *Sample solution*

r_S = peak response of oxalic acid from the *Standard solution*

C_S = concentration of USP Oxaliplatin Related Compound A RS in the *Standard solution* (mg/mL)

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

M_{r1} = molecular weight of anhydrous oxalic acid, 90.03

M_{r2} = molecular weight of oxaliplatin related compound A, 126.07

Acceptance criteria: NMT 0.6%

• **Limit of (*SP*-4-2)-Diaqua[(1*R*,2*R*)-cyclohexane-1,2-diamine-*N*,*N*']platinum and Unspecified Impurities**

[Note—All HPLC autosampler vials should be made of polypropylene.]

Solution A: Dissolve 1.36 g of monobasic potassium phosphate and 0.55 g of sodium heptanesulfonate in 1 L of water. Adjust with phosphoric acid to a pH of 3.0.

Solution B: Methanol and *Solution A* (19:81)

Solution C: Methanol and *Solution A* (50.5:49.5)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution B (%)	Solution C (%)
0	100	0
45.0	0	100
45.5	100	0
53.0	100	0

System suitability solution: 2 mg/mL of USP Oxaliplatin RS in 0.005 M sodium hydroxide. Allow this solution to stand at room temperature for at least 5 days. Transfer 5 mL of this solution into a 50-mL volumetric flask, and dilute with water to volume. [NOTE—The preparation of the *System suitability solution* forms (*SP*-4-2)-diaqua[(1*R*,2*R*)-cyclohexane-1,2-diamine-*N*,*N*']platinum and diaquodiaminocyclohexaneplatinum dimer.]

Standard stock solution: Transfer a weighed quantity of USP Oxaliplatin Related Compound B RS into a suitable volumetric flask, add a volume of methanol equivalent to about 25% of the final volume, and sonicate for approximately 2 min to disperse the solids. Add a volume of 0.01 M nitric acid equivalent to about 65% of the final volume, and sonicate for approximately 30 min to dissolve. Allow to cool, if necessary, and dilute with 0.01 M nitric acid to volume to obtain a solution with a concentration of 0.125 mg/mL.

Standard solution: 31.25 µg/mL of USP Oxaliplatin Related Compound B RS in 0.01 M nitric acid from the *Standard stock solution*. [NOTE—USP Oxaliplatin Related Compound B RS is converted to (*SP*-4-2)-diaqua[(1*R*,2*R*)-cyclohexane-1,2-diamine-*N*,*N*']platinum in the *Standard solution* preparation.]

Sample solution: Combined contents of NLT 3 vials of Injection

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 7.5-cm; 3-µm packing L1

Column temperature: 10°

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

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

Suitability requirements

Resolution: NLT 8.0 between the peaks of (*SP*-4-2)-diaqua[(1*R*,2*R*)-cyclohexane-1,2-diamine-*N*,*N*']platinum and diaquodiaminocyclohexaneplatinum dimer, *System suitability solution*

Tailing factor: NMT 2.0 for the (*SP*-4-2)-diaqua[(1*R*,2*R*)-cyclohexane-1,2-diamine-*N*,*N*']platinum peak, *System suitability solution*

Relative standard deviation: NMT 3.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Injection taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times (1/F) \times 100$$

r_U = peak response of each impurity from the *Sample solution*

r_S = peak response of (*SP*-4-2)-diaqua[(1*R*,2*R*)-cyclohexane-1,2-diamine-*N*,*N*']platinum from the *Standard solution*

C_S = concentration of USP Oxaliplatin Related Compound B RS in the *Standard solution* (mg/mL)

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

M_{r1} = molecular weight of (*SP*-4-2)-diaqua[(1*R*,2*R*)-cyclohexane-1,2-diamine-*N*,*N*']platinum, 345.30

M_{r2} = molecular weight of oxaliplatin related compound B, 433.28

F = relative response factor for each individual impurity (see *Table 2*)

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
(*SP*-4-2)-Diaqua[(1*R*,2*R*)-cyclohexane-1,2-diamine-*N*,*N*']platinum	1.0	1.0	0.65
Diaquodiaminocyclohexaneplatinum dimer[a]	1.4	2.5	0.50
Any individual unspecified impurity	—	4.0	0.2
Total impurities	—	—	2.45[b]

[a] (*SP*-4-2)-Di-μ-oxobis[(1*R*,2*R*)-cyclohexane-1,2-diamine-k*N*,k*N*']diplatinum.

[b] From the tests for *Limit of Oxalic Acid* and *Limit of (SP-4-2)-Diaqua[(1R,2R)-cyclohexane-1,2-diamine-N,N']platinum and Unspecified Impurities*.

SPECIFIC TESTS

- **Bacterial Endotoxins Test ⟨85⟩:** Meets the requirements
- **Sterility Tests ⟨71⟩, *Test for Sterility of the Product to Be Examined, Membrane Filtration*:** Meets the requirements
- **pH ⟨791⟩:** 4.0–7.0 using a polymer combination electrode
- **Particulate Matter in Injections ⟨788⟩:** It meets the requirements for small-volume injections.
- **Other Requirements:** It meets the requirements in *Injections and Implanted Drug Products ⟨1⟩*.

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in single-dose or multiple-dose containers, preferably of Type I glass, protected from light. Store at controlled room temperature. Do not freeze.
- **Labeling:** Label it to indicate that it is to be diluted with a 5% dextrose solution. Oxaliplatin Injection must not be diluted in sodium chloride solutions or in chloride-containing solutions.
- **USP Reference Standards ⟨11⟩**

USP Oxaliplatin RS

USP Oxaliplatin Related Compound A RS

Oxalic acid dihydrate.

$C_2H_2O_4 \cdot 2H_2O$ 126.07

USP Oxaliplatin Related Compound B RS

[*SP*-4-2-(1*R-trans*)]-(1,2-Cyclohexanediamine-*N*,*N*') dinitratoplatinum(II).

$C_6H_{14}N_4O_6Pt$ 433.28

USP Oxaliplatin System Suitability RS

[*SP*-4-2-(1*R-trans*)]-(1,2-Cyclohexanediamine-*N*,*N*') dichloridoplatinum(II).

$C_6H_{14}Cl_2N_2Pt$ 380.17

Topic/Question	Contact	Expert Committee
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM32020 Small Molecules 3

Chromatographic Database Information: Chromatographic Database

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