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Oxaliplatin for Injection

DEFINITION

Oxaliplatin for Injection is a sterile, lyophilized mixture of Oxaliplatin and Lactose Monohydrate. It contains NLT 90.0% and NMT 110.0% of the labeled amount of oxaliplatin ($C_8H_{14}N_2O_4Pt$).

IDENTIFICATION

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

Add the following:

▲• **B.** The UV spectrum of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.▲2S *(USP41)*

ASSAY

Change to read:

• **Procedure**

[Note—Use vigorous shaking and very brief sonication to dissolve the substance to be examined. Inject the *Sample solution* within 20 min of preparation. Use polypropylene HPLC autosampler vials.]

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 each of USP Oxaliplatin RS and 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 equivalent to 0.1 mg/mL of oxaliplatin obtained by constituting a suitable number of vials of Oxaliplatin for Injection with the appropriate amount of water

Chromatographic system

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

Mode: LC

Detector: UV 210 nm. ▲For *Identification B*, use a diode array detector in the range of 200–400 nm.▲2S *(USP41)*

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

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

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

Suitability requirements

Resolution: NLT 2.0 between the peaks of [*SP*-4-2-(1*R-trans*)]-(1,2-cyclohexanediamine-*N,N'*) dichloridoplatinum(II) and oxaliplatin, *System suitability solution*

Tailing factor: NMT 2.0 for the oxaliplatin peak, *System suitability solution*

Relative standard deviation: NMT 1.0%, *Standard solution*

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 Oxaliplatin for Injection taken:

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

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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%

PERFORMANCE TESTS

• **Uniformity of Dosage Units ⟨905⟩:** Meets the requirements

IMPURITIES

Change to read:

• **Limit of Oxalic Acid**

[Note—Use vigorous shaking and very brief sonication to dissolve the substance to be examined. Inject the *Sample solution* within 20 min of preparation. Use polypropylene HPLC autosampler vials.]

Buffer: Add 1.36 g of ▲monobasic potassium phosphate▲2S *(USP41)* to 10 mL of 10% tetrabutylammonium hydroxide in water, and dilute with water to 1000 mL. Adjust with phosphoric acid to a pH of 6.0.

Mobile phase: Acetonitrile and *Buffer* (1:4)

Standard stock solution: 0.06 mg/mL of USP Oxaliplatin Related Compound A RS in water. [Note—USP Oxaliplatin Related Compound A RS is available as oxalic acid dihydrate.]

Standard solution: 15 µg/mL of USP Oxaliplatin Related Compound A RS in water, from the *Standard stock solution*

System suitability stock solution: 0.05 mg/mL of sodium nitrate in water

System suitability solution: 1.0 µg/mL of sodium nitrate and 15 µg/mL of oxaliplatin related compound A in water, from the *System suitability stock solution* and *Standard stock solution*, respectively

Sensitivity solution: ▲1.5 µg/mL of USP Oxaliplatin Related Compound A RS in water, from the *Standard solution*▲2S *(USP41)*

Sample solution: Nominally equivalent to 2.0 mg/mL of oxaliplatin in water from Oxaliplatin for Injection

Chromatographic system

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

Mode: LC

Detector: UV 205 nm

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

Column temperature: 40°

Flow rate: 2 mL/min

Injection volume: 20 µL

System suitability

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

[Note—The relative retention times for the sodium nitrate and oxalic acid peaks are about 0.6 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 2.0 between the oxalic acid and sodium nitrate peaks, *System suitability solution*

Relative standard deviation: NMT 3.0% for the oxalic acid peak, *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 Oxaliplatin for 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)

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

M_{r2} = molecular weight of USP Oxaliplatin Related Compound A RS, 126.07

Acceptance criteria: NMT 0.5%

Change to read:

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

[Note—Use vigorous shaking and very brief sonication to dissolve the substance to be examined. Inject the *Sample solution* within 20 min of preparation. Use polypropylene HPLC autosampler vials.]

Buffer: Dissolve 1.36 g of ▲monobasic potassium phosphate▲2S *(USP41)* and 1 g of sodium 1-heptanesufonate in 1 L of water. Adjust with phosphoric acid to a pH of 3.0.

Mobile phase: Acetonitrile and *Buffer* (1:4)

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. [Note—Sonicate if necessary.] 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 diaquodiaminocyclohexaneplatinum dimer and (*SP*-4-2)-diaqua[(1*R*,2*R*)-cyclohexane-1,2-diamine-*N*,*N*′]platinum.]

Standard solution: 0.0125 mg/mL of USP Oxaliplatin Related Compound B RS prepared as follows. Transfer USP Oxaliplatin Related Compound B RS to a suitable volumetric flask, add 25% of the final volume of methanol, and sonicate for approximately 30 min to dissolve. Allow to cool, if necessary, and dilute with water to volume. [Note—When preparing the solution, USP Oxaliplatin Related Compound B RS is converted to (*SP*-4-2)-diaqua[(1*R*,2*R*)-cyclohexane-1,2-diamine-*N*,*N*′] platinum.]

Sample solution: Use the *Sample solution* from the test for *Limit of Oxalic Acid*.

Chromatographic system

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

Mode: LC

Detector: UV 215 nm

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

Column temperature: 40°

Flow rate: 2 mL/min

Injection volume: 20 µL

System suitability

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

[Note—The relative retention times for (*SP*-4-2)-diaqua[(1*R*,2*R*)-cyclohexane-1,2-diamine-*N*,*N*′]platinum and diaquodiaminocyclohexaneplatinum dimer are about 1.0 and 1.5, respectively.]

Suitability requirements

Resolution: NLT 2.0 between (*SP*-4-2)-diaqua[(1*R*,2*R*)-cyclohexane-1,2-diamine-*N*,*N*′]platinum and diaquodiaminocyclohexaneplatinum dimer, *System suitability solution*

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of (*SP*-4-2)-diaqua[(1*R*,2*R*)-cyclohexane-1,2-diamine-*N*,*N*′]platinum in the portion of Oxaliplatin for 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 (*SP*-4-2)-diaqua[(1*R*,2*R*)-cyclohexane-1,2-diamine-*N*,*N*′]platinum 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 USP Oxaliplatin Related Compound B RS, 433.28

Acceptance criteria: NMT 0.5%

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• **Limit of Related Compound C and Unspecified Impurities**

[Note—Use vigorous shaking and very brief sonication to dissolve the substance to be examined. Inject the *Sample solution* within 20 min of preparation. Use polypropylene HPLC autosampler vials.]

Mobile phase: Prepare as directed in the *Assay*.

Standard stock solution: 0.1 mg/mL each of USP Oxaliplatin RS and USP Oxaliplatin Related Compound C RS in water

Standard solution: 0.01 mg/mL each of USP Oxaliplatin RS and USP Oxaliplatin Related Compound C RS in water, from the *Standard stock solution*

System suitability stock solution: 0.1 mg/mL of USP Oxaliplatin System Suitability RS in methanol. Sonicate for approximately 10 min to aid the dissolution.

System suitability solution: Transfer 10 mL each of the *Standard stock solution* and the *System suitability stock solution* into a 100-mL volumetric flask, and dilute with water to volume.

Sample solution: Use the *Sample solution* from the test for *Limit of Oxalic Acid*.

Chromatographic system: Proceed as directed in the *Assay*, except for the *Injection volume*.

Injection volume: 10 µL

System suitability

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

Suitability requirements

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

Tailing factor: NMT 2.0 for the oxaliplatin peak, *System suitability solution*

Relative standard deviation: NMT 3.0% each for the oxaliplatin and oxaliplatin related compound C peaks, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of oxaliplatin related compound C in the portion of Oxaliplatin for Injection taken:

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

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

r_S = peak response of oxaliplatin related compound C from the *Standard solution*

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

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

Calculate the percentage of each unspecified impurity in the portion of Oxaliplatin for Injection taken:

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

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

r_S = peak response of oxaliplatin 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: See *Table 1*.

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Oxaliplatin related compound C▲▲2S *(USP41)*	0.6	0.3

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Name	Relative Retention Time	Acceptance Criteria, NMT (%)
[*SP*-4-2-(1*R*-*trans*)]-(1,2-Cyclohexanediamine-*N*,*N*′) dichloridoplatinum(II)[a]	0.8	—
Oxaliplatin	1.0	—
Any individual unspecified impurity	—	0.2
Total impurities[b]	—	1.5

▲ ▲2S *(USP41)*

[a] The relative retention time is included for system suitability purposes only.

[b] Includes oxalic acid, (*SP*-4-2)-diaqua[(1*R*,2*R*)-cyclohexane-1,2-diamine-*N*,*N*′]platinum, oxaliplatin related compound C, and the total of the individual unspecified impurities.

SPECIFIC TESTS

- **pH ⟨791⟩:** 4.0–7.0 using a polymer combination electrode, determined in a solution constituted as directed in the labeling
- **Particulate Matter in Injections ⟨788⟩:** It meets the requirements for small-volume injections.
- **Constituted Solution:** At the time of use, it meets the requirements in *Injections and Implanted Drug Products ⟨1⟩, Product Quality Tests Common to Parenteral Dosage Forms, Specific Tests, Completeness and Clarity of Solutions*.
- **Bacterial Endotoxins Test ⟨85⟩:** NMT 1.0 USP Endotoxin Unit/mg of oxaliplatin
- **Sterility Tests ⟨71⟩:** Meets the requirements
- **Water Determination ⟨921⟩, *Method I*:** NMT 4.0%
- **Other Requirements:** It meets the requirements in *Injections and Implanted Drug Products ⟨1⟩*.

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve as described in *Packaging and Storage Requirements ⟨659⟩, Injection Packaging, Packaging for Constitution*. Store at controlled room temperature.
- **Labeling:** Label it to indicate that it is to be diluted with a suitable parenteral vehicle before intravenous infusion.

Change to read:

- **USP Reference Standards ⟨11⟩**

▲ ▲ (CN 1-May-2018)

USP Oxaliplatin RS ▲▲2S *(USP41)*

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 Related Compound C RS
[1*R*-*trans*-(1,2-Cyclohexanediamine-*N*,*N*′)]-*trans*-dihydroxido-[oxalato(2-)-*O*,*O*′]platinum(IV).
$C_8H_{16}N_2O_6Pt$ 431.30

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

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

Topic/Question	Contact	Expert Committee
OXALIPLATIN FOR INJECTION	Documentary Standards Support	SM32020 Small Molecules 3
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM32020 Small Molecules 3

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Chromatographic Database Information: Chromatographic Database

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