Oxacillin Sodium for Oral Solution

Oxacillin Sodium for Oral Solution contains the equivalent of not less than 90.0 percent and not more than 120.0 percent of the labeled amount of oxacillin (C₁₉H₁₉N₃O₅S). It contains one or more suitable buffers, colors, flavors, preservatives, and stabilizers.

Packaging and storage—Preserve in tight containers at controlled room temperature.

USP Reference standards (11)—
USP Oxacillin Sodium RS

Identification—The chromatogram of the Assay preparation obtained as directed in the Assay exhibits a major peak for oxacillin, the retention time of which corresponds to that exhibited in the chromatogram of the Standard preparation obtained as directed in the Assay.

Uniformity of dosage units (905)—

For solid packaged in single-unit containers: meets the requirements.

Deliverable volume (698): meets the requirements.

pH (791): between 5.0 and 7.5, in the solution constituted as directed in the labeling.

Water, Method I (921): not more than 1.0%.

Assay—

Mobile phase and Chromatographic system—Proceed as directed in the Assay under Oxacillin Sodium.

Diluent—Prepare a mixture of water and acetonitrile (700:300).

Standard preparation—Prepare a solution of USP Oxacillin Sodium RS in Diluent having a known concentration of about 0.11 mg per mL. [NOTE—Use this solution on the day prepared.]

Assay preparation—Transfer an accurately measured volume of Oxacillin Sodium for Oral Solution, constituted as directed in the labeling, equivalent to about 250 mg of oxacillin (C₁₉H₁₉N₃O₅S), to a 250-mL volumetric flask, dilute with water to volume, and mix. Transfer 5.0 mL of this solution to a 30-mL volumetric flask, dilute with Diluent to volume, and mix. Filter about 5 mL of this solution through a 0.5-μm or finer porosity filter, discarding the first 2 mL of the filtrate. Use the clear filtrate as the Assay preparation. [NOTE—Use this Assay preparation on the day prepared.]

Procedure—Proceed as directed for Procedure in the Assay under Oxacillin Sodium. Calculate the quantity, in mg, of oxacillin (C₁₉H₁₉N₃O₅S) in each mL of the constituted Oxacillin Sodium for Oral Solution taken by the formula:

\[
2.5(CE / V(r₀ / r))
\]

in which \(V\) is the volume, in mL, of the constituted Oxacillin Sodium for Oral Solution taken, and the other terms are as defined therein.

Oxaliplatin

C₈H₁₄N₂O₄Pt 397.29

Oxaliplatin contains NLT 98.0% and NMT 102.0% of C₈H₁₄N₂O₄Pt, calculated on the dried basis. Oxaliplatin RS in water, from Oxaliplatin RS in water under System suitability solution, is the volume, in mL, of the constituted Oxaliplatin in water, from Oxaliplatin standard stock solution.

Sample solution: 0.1 mg/mL of Oxaliplatin in water

Chromatographic system

(See Chromatography (621), System Suitability.)
LIMIT OF SILVER

• Inorganic Impurities
  chromium, copper, iron, nickel, lead, and yttrium (commercially available).

Acceptance criteria: NMT 5 ppm

HEAVY METALS

Standard stock solution: Transfer 1 mL each of 1000-ppm standard solutions of cadmium, chromium, copper, iron, nickel, and lead (commercially available) to a 100-mL volumetric flask. Add 5 mL of nitric acid, and dilute with water to volume.

Internal standard solution: Transfer 1 mL of a 10,000-ppm standard solution of yttrium (commercially available) to a 100-mL volumetric flask, and dilute with 5% nitric acid to volume.

Sample solution: Weigh 1 g of Oxaliplatin into a 100-mL volumetric flask, and add 80 mL of water. Stir vigorously for several min with a magnetic stirrer until no more sample seems to be dissolving. Add 5 mL of nitric acid, and mix again until the sample is completely dissolved. Remove the stirrer bar from the flask, rinsing it before removal. Add 1.0 mL of the Internal standard solution, and dilute with water to volume.

Spectrometric conditions

(See Plasma Spectrochemistry (730).)

Measure the responses of the elements cadmium, chromium, copper, iron, nickel, lead, and yttrium (internal standard), using an inductively coupled plasma–atomic emission spectrometer (ICP–AES), by measuring the emissions at 226.502, 283.563, 327.395, 259.940, and 220.353 nm, respectively. Optimize the instrument settings as directed by the manufacturer.

System suitability

Before samples are analyzed, the instrument must pass a suitable performance check. Generate the calibration curve, using the Blank solution and the Standard solutions, and run these solutions in the following order: the Blank solution, then the 0.02-, 0.20-, and 2.00-ppm solutions. The linear regression coefficient is NLT 0.99; the response of the Blank solution is between −5.0 and 5.0 ppb for each element; and the responses of yttrium obtained from the Standard solutions are drifted by NMT 5.0% of the response obtained from the Blank solution. Run the Standard solution of 0.20 ppm, and record the responses of each element: the relative standard deviations for replicate runs are NMT 5.0%; and the recovery against the calibration curve is between 95% and 105%. After samples are analyzed, the instrument must pass the same suitable performance check to ensure that the calibration is still valid.

Analysis

Sample: Sample solution

Record the responses of each element, and determine the concentration of each element, using the calibration graph. Calculate the content of total elements, in ppm, in the portion of Oxaliplatin taken:

Result = [(ΣC)/W] × 100

Acceptance criteria: NMT 20 ppm

CONTENT OF PLATINUM

Sample: Ignite an empty porcelain crucible fitted with a lid in a furnace at 800° for 30 min. Cool in a desiccator, and...
weight. Add 200 mg of the Oxaliplatin, weighed, to the crucible, and ignite in a furnace by stepwise increments as follows: introduce into the furnace; and increase the temperature to 200° within 15 min, then to 400° within 15 min, then to 600° within 15 min, then finally to 800° within 15 min. Allow to remain in the furnace at 800° for 30 min. Remove, cool in a desiccator, and reweigh.

Calculate the percentage of platinum in the portion of Oxaliplatin taken:

\[
\text{Result} = \left( \frac{W_2}{W_1} \right) \times 100
\]

\(W_2\) = weight of residue after ignition (mg)
\(W_1\) = weight of oxaliplatin before ignition (mg)

Acceptance criteria: 48.1%–50.1% of the oxaliplatin taken, on the dried basis

**Organic Impurities**

**Procedure 1: 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. Polypropylene HPLC autosampler vials should be used.] Buffer: Add 1.36 g of potassium dihydrogen phosphate to 10 mL of 10% tetrahydroammonium 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

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

**System suitability solution:** 0.05 mg/mL of sodium nitrate oxaliplatin related compound C peaks, 15 µg/mL of USP Oxaliplatin Related Compound A RS, 0.01 mg/mL of oxaliplatin, 0.01 mg/mL of oxaliplatin related compound B, and 0.004 mg/mL of oxaliplatin related compound C in water, from Oxaliplatin standard stock solution, Oxaliplatin related compound B standard stock solution, Oxaliplatin related compound C standard stock solution, respectively

**Sample solution:** 2 mg/mL of Oxaliplatin in water

**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 size:** 20 µL

**System suitability**

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

[NOTE—The elution order is sodium nitrate, followed by oxalic acid.]

**Suitability requirements**

**Resolution:** NLT 2.0 between oxalic acid and sodium nitrate, 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 taken:

\[
\text{Result} = \left( \frac{r_u}{r_s} \right) \times \left( \frac{C_u}{C_s} \right) \times \left( \frac{M_1/M_2}{} \right) \times 100
\]

\(r_u\) = peak response of oxalic acid from the Sample solution

\(r_s\) = peak response of oxalic acid from the Standard solution

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

\(C_s\) = concentration of Oxaliplatin in the Sample solution (mg/mL)

\(M_1\) = molecular weight of anhydrous oxalic acid, 90.03

\(M_2\) = molecular weight of USP Oxaliplatin Related Compound A RS, 126.07

Acceptance criteria: NMT 0.1%

**Procedure 2: Limit of (SP-4-2)-DIAQUA[[1R,2R]-CYCLOHEXANE-1,2-DIAMINE-N,N′]PLATINUM, OXALIPLATIN 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. Polypropylene HPLC autosampler vials should be used.]

**Mobile phase:** Oxaliplatin standard stock solution, Oxaliplatin related compound B standard stock solution, Oxaliplatin related compound C standard stock solution, System suitability solution, and Chromatographic system: Proceed as directed in the Assay.

**Standard solution:** 0.01 mg/mL of oxaliplatin, 0.01 mg/mL of oxaliplatin related compound B, and 0.004 mg/mL of oxaliplatin related compound C in water, from Oxaliplatin standard stock solution, Oxaliplatin related compound B standard stock solution, Oxaliplatin related compound C standard stock solution, respectively

**Sample solution:** 2 mg/mL of Oxaliplatin in water

**System suitability**

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

**Suitability requirements**

**Resolution:** NLT 2.0 between oxaliplatin and oxaliplatin related compound C, System suitability solution

**Tailing factor:** Between 0.8 and 2.0 for the oxaliplatin peak, System suitability solution

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

**Analysis**

**Samples:** Standard solution and Sample solution

Calculate the percentage of (SP-4-2)-DIAQUA[[1R,2R]-CYCLOHEXANE-1,2-DIAMINE-N,N′]PLATINUM in the portion of Oxaliplatin taken:

\[
\text{Result} = \left( \frac{r_u}{r_s} \right) \times \left( \frac{C_u}{C_s} \right) \times \left( \frac{M_1/M_2}{} \right) \times 100
\]

\(r_u\) = peak response of (SP-4-2)-DIAQUA[[1R,2R]-CYCLOHEXANE-1,2-DIAMINE-N,N′]PLATINUM from the Sample solution

\(r_s\) = peak response of (SP-4-2)-DIAQUA[[1R,2R]-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)

\(C_u\) = concentration of Oxaliplatin in the Sample solution (mg/mL)

\(M_1\) = molecular weight of (SP-4-2)-DIAQUA[[1R,2R]-CYCLOHEXANE-1,2-DIAMINE-N,N′]PLATINUM, 345.30

\(M_2\) = molecular weight of USP Oxaliplatin Related Compound B RS, 433.28

[NOTE—USP Oxaliplatin Related Compound B RS is converted to (SP-4-2)-DIAQUA[[1R,2R]-CYCLOHEXANE-1,2-DIAMINE-N,N′]PLATINUM in solution preparation.]

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

\[
\text{Result} = \left( \frac{r_u}{r_s} \right) \times \left( \frac{C_u}{C_s} \right) \times 100
\]

\(r_u\) = 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)

\(C_u\) = concentration of Oxaliplatin in the Sample solution (mg/mL)
Calculate the percentage of diaquodiaminocyclohexaneplatinum dimer in the portion of Oxaliplatin taken:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times \left( \frac{M_1}{M_2} \right) \times \left( 1/F \right) \times 100
\]

- \( r_U \) = peak response of diaquodiaminocyclohexaneplatinum dimer from the Sample solution
- \( r_S \) = peak response of oxaliplatin from the Standard solution
- \( C_S \) = concentration of oxaliplatin in the Standard solution (mg/mL)
- \( C_U \) = concentration of Oxaliplatin in the Sample solution (mg/mL)
- \( M_1 \) = molecular weight of (SP-4-2)-diaqua[(1R,2R)-cyclohexane-1,2-diamine-N,N']platinum, 345.30
- \( M_2 \) = molecular weight of USP Oxaliplatin Related Compound B RS in the Standard solution (mg/mL)
- \( F \) = relative response factor for diaquodiaminocyclohexaneplatinum dimer, measured with respect to USP Oxaliplatin Related Compound B RS, 2.5

Calculate the percentage of any other unspecified impurity in the portion of Oxaliplatin taken:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times 100
\]

- \( r_U \) = peak response of any other unspecified impurity from the Sample solution
- \( r_S \) = peak response of oxaliplatin from the Standard solution
- \( C_S \) = concentration of oxaliplatin in the Standard solution (mg/mL)
- \( C_U \) = concentration of Oxaliplatin in the Sample solution (mg/mL)

**Acceptance criteria**

**Individual impurities:** See *Impurity Table 1.**

**Total impurities:** NMT 0.30%. [NOTE—Total impurities include oxalic acid (from Procedure 1) and all impurities from Procedure 2 listed in Impurity Table 1.]

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Relative Response Factor</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxaliplatin related compound C</td>
<td>0.8</td>
<td>—</td>
<td>0.1</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>1.0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>(SP-4-2)-diaqua [(1R,2R)-cyclohexane-1,2-diamine-N,N’]platinum</td>
<td>2.7</td>
<td>—</td>
<td>0.1</td>
</tr>
<tr>
<td>Diaquodiaminocyclohexaneplatinum dimer</td>
<td>6</td>
<td>2.5</td>
<td>0.1</td>
</tr>
<tr>
<td>Any unspecified impurity</td>
<td>—</td>
<td>—</td>
<td>0.10</td>
</tr>
</tbody>
</table>

**PROCEDURE 3: LIMIT OF OXALIPLATIN RELATED COMPOUND D**

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

**Mobile phase:** Methanol and ethanol (7:3)

**Oxaliplatin related compound D standard stock solution:** 0.05 mg/mL of USP Oxaliplatin Related Compound D RS in methanol

**Oxaliplatin related compound D standard solution:** 15 µg/mL of USP Oxaliplatin Related Compound D RS in methanol, from Oxaliplatin related compound D standard stock solution

**Oxaliplatin standard stock solution:** 0.75 mg/mL of USP Oxaliplatin RS in methanol

**Oxaliplatin standard solution:** 37.5 µg/mL of USP Oxaliplatin RS in methanol, from the Oxaliplatin standard stock solution

**Standard solutions:** Transfer 40 mL of Oxaliplatin standard solution to separate 50-mL volumetric flasks. Add 1.0, 3.0, and 5.0 mL of Oxaliplatin related compound D standard solution to each flask, and dilute with methanol to volume. The concentration of oxaliplatin related compound D in these solutions is 0.6 mg/mL. The concentrations of oxaliplatin related compound D in these solutions are 0.3, 0.9, and 1.5 µg/mL, respectively.

**System suitability solution:** Transfer 5.0 mL of Oxaliplatin related compound D standard solution and 4.0 mL of Oxaliplatin related compound D standard stock solution to a 50-mL volumetric flask, and dilute with methanol to volume.

**Sample solution:** Transfer 30 mg of Oxaliplatin into a 50-mL volumetric flask, and dilute with methanol to volume.

**Chromatographic system**

(See Chromatography (621), System Suitability.)

**Mode:** LC

**Detector:** UV 254 nm

**Column:** 4.6-mm × 25-cm; 5-µm packing L70

**Column temperature:** 40°

**Flow rate:** 0.3 mL/min

**Injection size:** 20 µL

**Run time:** 30 min

**System suitability**

**Samples:** 0.9-µg/mL Standard solution and System suitability solution

**Suitability requirements**

**Resolution:** NLT 1.5 between oxaliplatin and oxaliplatin related compound C. System suitability solution

**Relative standard deviation:** NMT 3.0% for the peak height ratio of oxaliplatin related compound D to the sum of oxaliplatin and oxaliplatin related compound D; 0.9-µg/mL Standard solution

**Analysis**

**Samples:** Standard solutions and Sample solution

Plot a calibration curve for the Standard solutions with the peak response ratios of oxaliplatin related compound D to the sum of oxaliplatin and oxaliplatin related compound D on the y-axis and the concentrations of oxaliplatin related compound D, in µg/mL, on the x-axis. Read the concentration of oxaliplatin related compound D, in µg/mL, in the Sample solution from the calibration curve obtained.

Calculate the percentage of oxaliplatin related compound D in the portion of Oxaliplatin taken:

\[
\text{Result} = \left( \frac{C/W} {5} \right)
\]

- \( C \) = concentration of oxaliplatin related compound D in the Sample solution (µg/mL)
- \( W \) = weight of Oxaliplatin taken to prepare the Sample solution (mg)

**Acceptance criteria:** NMT 0.1%

**SPECIFIC TESTS**

**Acidity**

**Sample solution:** Dissolve 100 mg in 50 mL of carbon dioxide-free water, and add 0.5 mL of phenolphthalein TS.

**Acceptance criteria:** The solution is colorless, and NMT 0.6 mL of 0.01 M sodium hydroxide is required to change the color to pink.

**Bacterial Endotoxins Test (85):** NMT 1.0 USP Endotoxin Unit/mg of oxaliplatin

**Loss On Drying (731):** Dry 1 g at 100° to 105° for 2 h; it loses NMT 0.5% of its weight.

**Microbial Enumeration Tests (61) and Tests for Specified Microorganisms (62):** The total aerobic microbial count
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 (C₂H₁₄N₂O₄Pt).

IDENTIFICATION
A. ULTRAVIOLET ABSORPTION (197U)
Sample solution: 100 µg/mL
Medium: Water
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
[NOTE—All HPLC autosampler vials should be made of polypropylene.]

PROCEDURE
Acidified water: Adjust 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-(1R-trans)-[1,2-Cyclohexanediamine-N,N']dinitratoplatinum(II)].] Standard solution: 0.1 mg/mL of USP Oxaliplatin RS in water
Sample solution: 0.1 mg/mL of oxaliplatin in water, from the combined contents of NLT three 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 size: 20 µL
System suitability
Sample: System suitability solution
[NOTE—The relative retention times for USP Oxaliplatin System Suitability RS and oxaliplatin are 0.9 and 1.0, respectively.]

Suitability requirements
Resolution: NLT 2.0 between USP Oxaliplatin System Suitability RS and oxaliplatin
Tailing factor: NMT 2.0, oxaliplatin peak
Relative standard deviation: NMT 1.0%, oxaliplatin peak

Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of C₂H₁₄N₂O₄Pt in the portion of Injection taken:
\[ \text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times 100 \]

rₚ = peak response from the Sample solution
rₛ = peak response from the Standard solution
Cₛ = concentration of USP Oxaliplatin RS in the Standard solution (mg/mL)
Cₛ = nominal concentration of oxaliplatin in the Sample solution (mg/mL)
Acceptance criteria: 90.0%–110.0%

IMPURITIES
Organic Impurities

PROCEDURE 1: LIMIT OF OXALIC ACID
[NOTE—All HPLC autosampler vials should be made of polypropylene.]
Solution A: Dissolve 1.36 g of monobasic potassium phosphate in 10 mL of 10% tetrabutylammonium hydroxide, dilute with water to 1 L, and adjust with phosphoric acid to a pH of 6.0.
Mobile phase: Acetonitrile and Solution A (1:4)
Standard solution: 35 µg/mL of USP Oxaliplatin Related Compound A RS in water. [NOTE—USP Oxaliplatin Related Compound A RS is available as dihydrate oxalic acid.]
System suitability solution: 0.1 mg/mL of succinic acid in Standard solution
Sensitivity solution: 3.5 µg/mL of USP Oxaliplatin Related Compound A RS in water, from the Standard solution
Sample solution: Combined contents of NLT three 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: 2 mL/min
Injection size: 10 µL
System suitability
Samples: Standard solution, System suitability solution, and Sensitivity solution
[NOTE—The relative retention times for succinic acid and oxalic acid are 0.8 and 1.0, respectively.]

Suitability requirements
Resolution: NLT 2.0 between succinic acid and oxalic acid, System suitability solution
Tailing factor: Between 0.5 and 2.0, oxalic acid peak, System suitability solution
Signal-to-noise ratio: NLT 10, Sensitivity solution
Relative standard deviation: NMT 3.0%, Standard solution

Analysis
Sample: Standard solution and Sample solution
Calculate the percentage of each impurity in the portion of Injection taken:
\[ \text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times 100 \]

rₚ = peak response of oxalic acid from the Sample solution
rₛ = peak response of oxalic acid from the Standard solution
Cₛ = concentration of USP Oxaliplatin Related Compound A RS in the Standard solution (mg/mL)