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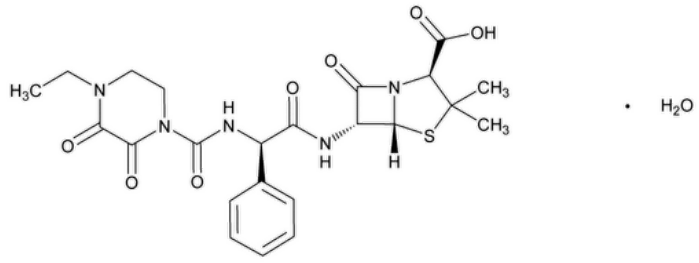
Piperacillin



$C_{23}H_{27}N_5O_7S \cdot H_2O$ 535.57
$C_{23}H_{27}N_5O_7S$ 517.56

4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[[[[(4-ethyl-2,3-dioxo-1-piperazinyl)carbonyl] amino]phenylacetyl]amino]-3,3-dimethyl-7-oxo-, monohydrate, [2*S*-2α,5α,6β(*S**)]]; (2*S*,5*R*,6*R*)-6-[(*R*)-2-(4-Ethyl-2,3-dioxo-1-piperazinecarboxamido)-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid monohydrate CAS RN®: 66258-76-2; UNII: X00B0D5O0E.

Anhydrous CAS RN®: 61477-96-1; UNII: 9I628532GX.

DEFINITION

Piperacillin contains NLT 960 µg/mg and NMT 1030 µg/mg of piperacillin ($C_{23}H_{27}N_5O_7S$), calculated on the anhydrous basis.

IDENTIFICATION

• **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*: 197K**

ASSAY

• **Procedure**

Mobile phase: Methanol, water, 0.2 M monobasic sodium phosphate, and 0.4 M tetrabutylammonium hydroxide (450:447:100:3). Adjust with phosphoric acid to a pH of 5.50.

System suitability solution: 0.1 mg/mL of USP Ampicillin RS and 0.2 mg/mL of USP Piperacillin RS in *Mobile phase*

Standard solution: 0.4 mg/mL of USP Piperacillin RS in *Mobile phase*. Dissolve in a few drops of methanol, and dilute with *Mobile phase* to volume. Use this solution within 1 h.

Sample solution: 0.4 mg/mL of Piperacillin in *Mobile phase*. Dissolve in a few drops of methanol, and dilute with *Mobile phase* to volume. Use this solution within 1 h.

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

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

Flow rate: 1 mL/min

Injection volume: 10 µL

System suitability

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

[Note—See *Table 1* for the relative retention times.]

Suitability requirements

Resolution: NLT 16 between ampicillin and piperacillin, *System suitability solution*

Tailing factor: NMT 1.2 for the piperacillin peak, *System suitability solution*

Relative standard deviation: NMT 2%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the potency of piperacillin ($C_{23}H_{27}N_5O_7S$) in the portion of Piperacillin taken:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

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

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

P = potency of piperacillin in USP Piperacillin RS (µg/mg)

Acceptance criteria: 960–1030 µg/mg on the anhydrous basis

IMPURITIES

• **Ampicillin, Piperacillin Penicilloic Acid, Piperacillin Related Compound E, and Acetylated Penicilloic Acid of Piperacillin**

Mobile phase, Sample solution, Chromatographic system, and **System suitability:** Proceed as directed in the *Assay*.

Standard solution 1: 0.08 mg/mL of USP Ampicillin RS in *Mobile phase*

Standard solution 2: 0.04 mg/mL of USP Piperacillin RS in *Mobile phase*. Dissolve in a few drops of methanol, and dilute with *Mobile phase* to volume. Use this solution within 1 h.

Analysis

Samples: *Standard solution 1*, *Standard solution 2*, and *Sample solution*

Calculate the percentage of ampicillin in the portion of Piperacillin taken:

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

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

r_S = peak response of ampicillin from *Standard solution 1*

C_S = concentration of USP Ampicillin RS in *Standard solution 1* (mg/mL)

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

P = potency of ampicillin in USP Ampicillin RS (µg/mg)

F = conversion factor, 0.001 mg/µg

Calculate the percentages of specified impurities other than ampicillin in the portion of Piperacillin taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times P \times (1/F_1) \times F_2 \times 100$$

r_U = peak response of each specified impurity other than ampicillin from the *Sample solution*

r_S = peak response of piperacillin from *Standard solution 2*

C_S = concentration of USP Piperacillin RS in *Standard solution 2* (mg/mL)

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

P = potency of piperacillin in USP Piperacillin RS (µg/mg)

F_1 = relative response factor (see *Table 1*)

F_2 = conversion factor, 0.001 mg/µg

Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Piperacillin related compound E[a]	0.24	2.4	0.2
Ampicillin	0.31	1.0	0.2
Acetylated penicilloic acid of piperacillin[b]	0.37	1.1	0.4
Piperacillin penicilloic acid[c]	0.62	0.7	1.0
Piperacillin	1.0	—	—

[a] 1-Ethyl-2,3-piperazinedione.

[b] (2*R*,4*S*)-3-Acetyl-2-{(1*R*)-carboxy[2-(4-ethyl-2,3-dioxopiperazine-1-carboxamido)-2-phenylacetamido]methyl}-5,5-dimethylthiazolidine-4-carboxylic acid.

[c] (2*R*,4*S*)-2-{(1*R*)-Carboxy[2-(4-ethyl-2,3-dioxopiperazine-1-carboxamido)-2-phenylacetamido]methyl}-5,5-dimethylthiazolidine-4-carboxylic acid.

- **Piperacillinylampicillin**

Mobile phase: Methanol, water, 0.2 M monobasic sodium phosphate, and 0.4 M tetrabutylammonium hydroxide (615:282:100:3). Adjust with phosphoric acid to a pH of 5.50.

Standard solution: 0.04 mg/mL of USP Piperacillin RS in *Mobile phase*. Dissolve in a few drops of methanol, and dilute with *Mobile phase* to volume. Use this solution within 1 h.

Sample solution: 0.4 mg/mL of Piperacillin in *Mobile phase*. Dissolve in a few drops of methanol, and dilute with *Mobile phase* to volume. Use this solution within 1 h.

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

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

Flow rate: 1 mL/min

Injection volume: 10 µL

System suitability

Sample: *Standard solution*

[Note—See *Table 2* for the relative retention times.]

Suitability requirements

Relative standard deviation: NMT 2%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of piperacillinylampicillin in the portion of Piperacillin taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times P \times (1/F_1) \times F_2 \times 100$$

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

r_S = peak response of piperacillin from the *Standard solution*

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

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

P = potency of piperacillin in USP Piperacillin RS (µg/mg)

F_1 = relative response factor (see *Table 2*)

F_2 = conversion factor, 0.001 mg/µg

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Piperacillin	1.0	—	—
Piperacillinylampicillin[a]	2.55	0.7	2.0
Total impurities[b]	—	—	3.8

[a] (2*S*,5*R*,6*R*)-6-((*R*)-2-{(2*S*,5*R*,6*R*)-6-[(*R*)-2-(4-Ethyl-2,3-dioxopiperazine-1-carboxamido)-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxamido}-2-phenylacetamido)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.

[b] Total impurities is the sum of all impurities reported in the tests for *Ampicillin*, *Piperacillin Penicilloic Acid*, *Piperacillin Related Compound E*, *and Acetylated Penicilloic Acid of Piperacillin*, and *Piperacillinylampicillin*.

SPECIFIC TESTS

• **Water Determination,** *Method I* ⟨921⟩**:** 2.0%–4.0%

• **Optical Rotation,** *Specific Rotation* ⟨781S⟩

Sample solution: 40 mg/mL in methanol

Acceptance criteria: +155° to +175°

• **Bacterial Endotoxins Test** ⟨85⟩**:** Where the label states that Piperacillin is sterile or that it must be subjected to further processing during the preparation of injectable dosage forms, it contains NMT 0.07 USP Endotoxin Unit/mg of piperacillin.

Change to read:

• **Sterility Tests** ⟨71⟩**:** ▲Where the label states that Piperacillin is sterile, it meets the requirements when tested as directed in *Test for Sterility of the Product to Be Examined, Membrane Filtration*.▲ (ERR 1-Aug-2023)

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in well-closed containers.

• **Labeling:** Where it is intended for use in preparing injectable dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms.

• **USP Reference Standards** ⟨11⟩

USP Ampicillin RS

USP Piperacillin RS

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

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

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
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