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Imipenem and Cilastatin for Injectable Suspension

DEFINITION

Imipenem and Cilastatin for Injectable Suspension is a sterile mixture of Imipenem and Cilastatin Sodium. It contains NLT 90.0% and NMT 115.0% of the labeled amounts of imipenem ($C_{12}H_{17}N_3O_4S$) and cilastatin ($C_{16}H_{26}N_2O_5S$).

IDENTIFICATION

• **A.** The retention times of the peaks for imipenem and cilastatin of the *Sample solution* correspond to those of *Standard solution 1* and *Standard solution 2*, as obtained in the *Assay*.

ASSAY

• **Procedure**

Buffer: Dissolve 0.54 g of monobasic potassium phosphate in 3600 mL of water, adjust with 0.5 N sodium hydroxide or 0.5 M phosphoric acid to a pH of 6.8 ± 0.1, dilute with water to make 4000 mL of solution, and mix. Pass this solution through a filter of 0.5-µm or finer pore size.

Solution A: 0.1% solution of sodium bicarbonate in water

Mobile phase: Dissolve 2.0 g of sodium 1-hexanesulfonate in 800 mL of *Buffer*, adjust with 0.5 N sodium hydroxide or 0.5 M phosphoric acid to a pH of 6.8 ± 0.1, and dilute with *Buffer* to make 1000 mL of solution. Pass this solution through a filter of 0.5-µm or finer pore size, and degas.

Standard solution 1: 0.5 mg/mL of imipenem from USP Imipenem Monohydrate RS prepared as follows. Transfer a suitable amount of USP Imipenem Monohydrate RS to a volumetric flask. Add saline TS, *Solution A*, and *Buffer*, using 20%, 2%, and 60% of the final volume, respectively. Dissolve by shaking and sonicating. The duration of sonication should not exceed 1 min. Dilute with *Buffer* to volume. Use this solution immediately.

Standard solution 2: 0.5 mg/mL of cilastatin from USP Cilastatin Ammonium Salt RS prepared as follows. Transfer a suitable amount of USP Cilastatin Ammonium Salt RS to a volumetric flask. Add saline TS, *Solution A*, and *Buffer*, using 20%, 2%, and 60% of the final volume, respectively. Dissolve by shaking and sonicating. The duration of sonication should not exceed 1 min. Dilute with *Buffer* to volume. Use this solution immediately.

Sample stock solution: Nominally 2.5 mg/mL of imipenem prepared as follows. Constitute Imipenem and Cilastatin for Injectable Suspension in a volume of saline TS corresponding to the volume of solvent specified in the labeling. Withdraw all of the withdrawable contents, using a suitable hypodermic needle and syringe, and dilute with saline TS to final volume.

Sample solution: Nominally 0.5 mg/mL each of imipenem and cilastatin from *Sample stock solution* in *Buffer*

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 30-cm; packing L1

Column temperature: 50 ± 1.0°

Flow rate: 2 mL/min

Injection volume: 10 µL

System suitability

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

Suitability requirements

Column efficiency: NLT 600 theoretical plates for the imipenem peak, *Standard solution 1*; NLT 600 theoretical plates for the cilastatin peak, *Standard solution 2*.

Calculate as follows:

$$\text{Result} = 5.545 \times (t_R/W_{h/2})^2$$

t_R = retention time of the peak in *Standard solution 1* or *Standard solution 2*

$W_{h/2}$ = width of the peak at half-height in *Standard solution 1* or *Standard solution 2*

Tailing factor: NMT 1.5 for the imipenem peak, *Standard solution 1*; NMT 1.5 for the cilastatin peak, *Standard solution 2*.

Calculate as follows:

$$\text{Result} = W_{0.1}/2f$$

$W_{0.1}$ = width of the peak at 10% height in *Standard solution 1* or *Standard solution 2*

f = distance from the peak maximum to the leading edge of the peak at 5% of the peak height in *Standard solution 1* or *Standard solution 2*

Relative standard deviation: NMT 2.0% for the imipenem peak, *Standard solution 1*; NMT 2.0% for the cilastatin peak, *Standard solution 2*

Analysis

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

Calculate the percentage of the labeled amount of anhydrous imipenem ($C_{12}H_{17}N_3O_4S$) in the portion of Imipenem and Cilastatin for Injectable Suspension taken:

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

r_U = peak response from the *Sample solution*

r_S = peak response from *Standard solution 1*

C_S = concentration of imipenem in *Standard solution 1* (mg/mL)

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

P = potency of imipenem in USP Imipenem Monohydrate RS (mg/mg)

Calculate the percentage of the labeled amount of cilastatin ($C_{16}H_{26}N_2O_5S$) in the portion of Imipenem and Cilastatin for Injectable Suspension taken:

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

r_U = peak response from the *Sample solution*

r_S = peak response from *Standard solution 2*

C_S = concentration of cilastatin in *Standard solution 2* (mg/mL)

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

P = potency of cilastatin in USP Cilastatin Ammonium Salt RS (µg/mg)

F = conversion factor, 0.001 mg/µg

Acceptance criteria: 90.0%–115.0% for each analyte

PERFORMANCE TESTS

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

SPECIFIC TESTS

• **Bacterial Endotoxins Test ⟨85⟩:** NMT 0.23 USP Endotoxin Unit/mg of imipenem and NMT 0.23 USP Endotoxin Unit/mg of cilastatin

• **pH ⟨791⟩**

Sample solution: Constitute as directed in the labeling.

Acceptance criteria: 6.0–7.5

• **Sterility Tests ⟨71⟩**

Sample solution: Dissolve the sample in *Fluid A*.

Acceptance criteria: Meets the requirements when tested as directed for *Test for Sterility of the Product to Be Examined, Membrane Filtration*

• **Loss on Drying** ⟨731⟩

Sample: 100 mg

Analysis: Dry the *Sample* under vacuum at a pressure not exceeding 5 mm of mercury at 60° for 3 h.

Acceptance criteria: NMT 3.5%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve as described in *Packaging and Storage Requirements* ⟨659⟩*, Injection Packaging, Packaging for constitution*, and store at controlled room temperature.

• **Labeling:** Label it to indicate that the suspension obtained when constituted as directed in the labeling is for intramuscular injection only.

• **USP Reference Standards** ⟨11⟩

USP Cilastatin Ammonium Salt RS

USP Imipenem Monohydrate RS

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

Topic/Question	Contact	Expert Committee
IMIPENEM AND CILASTATIN FOR INJECTABLE SUSPENSION	Documentary Standards Support	SM12020 Small Molecules 1

Chromatographic Database Information: Chromatographic Database

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