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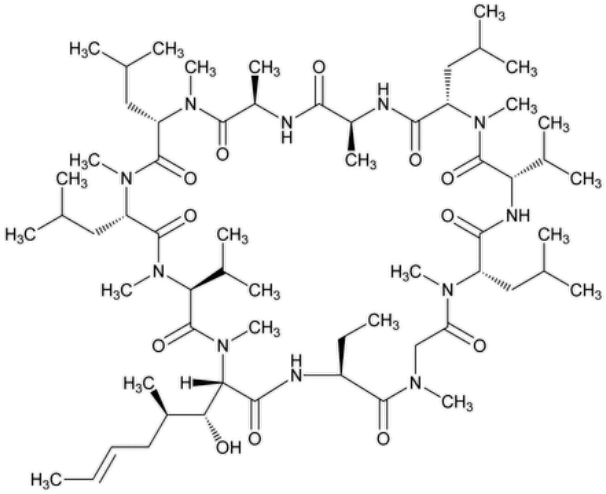
Cyclosporine



$C_{62}H_{111}N_{11}O_{12}$ 1202.61

Cyclo[[(*E*)-(2*S*,3*R*,4*R*)-3-hydroxy-4-methyl-2-(methylamino)oct-6-enoyl]-L-2-aminobutyryl-*N*-methylglycyl-*N*-methyl-L-leucyl-L-valyl-*N*-methyl-L-leucyl-L-alanyl-D-alanyl-*N*-methyl-L-leucyl-*N*-methyl-L-leucyl-*N*-methyl-L-valyl];
[*R*-[*R**,*R**-(*E*)]]-Cyclic(L-alanyl-D-alanyl-*N*-methyl-L-leucyl-*N*-methyl-L-leucyl-*N*-methyl-L-valyl-3-hydroxy-*N*,4-dimethyl-L-2-amino-6-octenoyl-L-α-aminobutyryl-*N*-methylglycyl-*N*-methyl-L-leucyl-L-valyl-*N*-methyl-L-leucyl) CAS RN®: 59865-13-3; UNII: 83HN0GTJ6D.

DEFINITION

Cyclosporine contains NLT 97.0% and NMT 101.5% of cyclosporine A ($C_{62}H_{111}N_{11}O_{12}$), calculated on the dried basis.

IDENTIFICATION

Add the following:

▲• **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197A or 197K▲ (USP 1-Dec-2021)

Change to read:

• ▲**B.**▲ (USP 1-Dec-2021) The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

Change to read:

• **Procedure**

Mobile phase: Acetonitrile, *tert*-butyl methyl ether, water, and phosphoric acid (430:50:520:1)

Diluent: Acetonitrile and water (1:1)

System suitability solution: 1.25 mg/mL of USP Cyclosporine Resolution Mixture RS in *Diluent*

Standard solution: 1.25 mg/mL of USP Cyclosporine RS in *Diluent*

Sample solution: 1.25 mg/mL of Cyclosporine in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 4-mm × 25-cm; 3- to 5-µm packing L1. ▲If needed, tubing may be▲ (USP 1-Dec-2021) connected to the column inlet ▲to support the *Column temperature*.▲ (USP 1-Dec-2021)

Column temperature: 80°. ▲If used,▲ (USP 1-Dec-2021) the tubing ▲may be▲ (USP 1-Dec-2021) maintained at 80°, to ensure that the *Mobile phase* entering the column is heated to 80°.

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 cyclosporine U and cyclosporine are 0.95 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 1.0 between cyclosporine U and cyclosporine, *System suitability solution*

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of cyclosporine ($C_{62}H_{111}N_{11}O_{12}$) in the portion of Cyclosporine taken:

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

r_U = peak area of cyclosporine from the *Sample solution*

r_S = peak area of cyclosporine from the *Standard solution*

C_S = concentration of ▲USP Cyclosporine RS in▲ (USP 1-Dec-2021) the *Standard solution* (mg/mL)

C_U = concentration of ▲Cyclosporine in▲ (USP 1-Dec-2021) the *Sample solution* (mg/mL)

P = potency of cyclosporine in USP Cyclosporine RS (mg/mg)

Acceptance criteria: 97.0%–101.5% on the dried basis

IMPURITIES

Change to read:

• **ORGANIC IMPURITIES**

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

Standard solution: 0.01 mg/mL of USP Cyclosporine RS in *Diluent*

System suitability

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

[NOTE—The relative retention times for cyclosporine U and cyclosporine are 0.95 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 1.0 between cyclosporine U and cyclosporine, *System suitability solution*

Relative standard deviation: NMT 10.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of ▲any individual▲ (USP 1-Dec-2021) impurity in the portion of Cyclosporine taken:

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

r_U = peak area of ▲each▲ (USP 1-Dec-2021) individual impurity from the *Sample solution*

r_S = peak area of cyclosporine from the *Standard solution*

C_S = concentration of ▲USP Cyclosporine RS in▲ (USP 1-Dec-2021) the *Standard solution* (mg/mL)

C_U = concentration of ▲Cyclosporine in▲ (USP 1-Dec-2021) the *Sample solution* (mg/mL)

P = potency of cyclosporine in USP Cyclosporine RS (mg/mg)

Acceptance criteria: The reporting threshold is 0.05%.

Any individual impurity: NMT 0.7%

Total impurities: NMT 1.5%

SPECIFIC TESTS

Change to read:

• **Loss on Drying** ⟨731⟩

▲▲ (USP 1-Dec-2021)

Analysis: Dry in a capillary-stoppered bottle under vacuum at a pressure not exceeding 5 mm of mercury at 60° for 3 h.

Acceptance criteria: NMT 2.0%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight, light-resistant containers.

Change to read:

• **USP Reference Standards** ⟨11⟩

USP Cyclosporine RS

USP Cyclosporine Resolution Mixture RS

Contains a mixture of the following two compounds [in a 100:1 (w/w) mixture of cyclosporine and cyclosporine U]:

Cyclosporine.

Cyclosporine U: ▲Cyclo[[(*E*)-(2*S*,3*R*,4*R*)-3-hydroxy-4-methyl-2-(methylamino)oct-6-enoyl]-L-2-aminobutyryl-*N*-methylglycyl-*N*-methyl-L-leucyl-L-valyl-L-leucyl-L-alanyl-D-alanyl-*N*-methyl-L-leucyl-*N*-methyl-L-leucyl-*N*-methyl-L-valyl].▲ (USP 1-Dec-2021)

$C_{61}H_{109}N_{11}O_{12}$ ▲1188.61▲ (USP 1-Dec-2021)

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

Topic/Question	Contact	Expert Committee
CYCLOSPORINE	Documentary Standards Support	SM12020 Small Molecules 1

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
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