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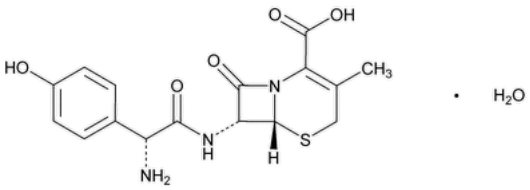
Cefadroxil



$C_{16}H_{17}N_3O_5S \cdot H_2O$ 381.40

5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7- [[amino(4-hydroxyphenyl)acetyl]amino]-3-methyl-8-oxo-, monohydrate, [6*R*-[6α,7β (*R**)]]-; (6*R*,7*R*)-7-[(*R*)-2-Amino-2-(*p*-hydroxyphenyl)acetamido]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid monohydrate CAS RN®: 66592-87-8; UNII: 280111G160.

Hemihydrate 372.40 CAS RN®: 119922-85-9; UNII: J9CMF6461M.

Anhydrous 363.39 CAS RN®: 50370-12-2; UNII: Q525PA8JJB.

DEFINITION

Cefadroxil has a potency equivalent to NLT 950 µg/mg and NMT 1050 µg/mg of cefadroxil ($C_{16}H_{17}N_3O_5S$), calculated on the anhydrous basis.

IDENTIFICATION

Change to read:

• **A.** ▲**Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*: 197K**▲ (CN 1-May-2020)

• **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

• **Procedure**

Buffer: 2.7 g/L of monobasic potassium phosphate

Mobile phase: Acetonitrile and *Buffer* (4:96)

Standard solution: 50 µg/mL of USP Cefadroxil RS in *Mobile phase* prepared as follows. Transfer a suitable quantity of USP Cefadroxil RS to a suitable volumetric flask, dissolve in *Mobile phase* using 50% of the final volume, sonicate to dissolve, and dilute with *Mobile phase* to volume.

Sample solution: 50 µg/mL of Cefadroxil in *Mobile phase* prepared as follows. Transfer a suitable quantity of Cefadroxil to a suitable volumetric flask, dissolve in *Mobile phase* using 50% of the final volume, sonicate to dissolve, and dilute with *Mobile phase* to volume.

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

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

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5

Relative standard deviation: NMT 0.73%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the quantity, in µg/mg, of cefadroxil ($C_{16}H_{17}N_3O_5S$) in the portion of Cefadroxil 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 Cefadroxil RS in the *Standard solution* (µg/mL)

C_U = concentration of Cefadroxil in the *Sample solution* (µg/mL)

P = potency of cefadroxil in USP Cefadroxil RS (µg/mg)

Acceptance criteria: 950–1050 µg/mg on the anhydrous basis

IMPURITIES

• **Organic Impurities**

Solution A: 50 mg/mL of sodium hydroxide

Solution B: 4 g/L of monobasic sodium phosphate dihydrate adjusted with *Solution A* to a pH of 5.0

Solution C: Acetonitrile and *Solution B* (1:1)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution B (%)	Solution C (%)
0	100	0
35	85	15
50	40	60
60	0	100
61	100	0
70	100	0

Diluent: 3.5 g/L of monobasic potassium phosphate and 4.6 g/L of dibasic sodium phosphate anhydrous

System suitability stock solution 1: 0.5 mg/mL of USP Cefadroxil Related Compound D RS in *Diluent*. Sonicate as needed to dissolve.

System suitability stock solution 2: 0.5 mg/mL of USP Cefadroxil Related Compound I RS in *Diluent*. Sonicate as needed to dissolve.

System suitability solution: 10 µg/mL of cefadroxil related compound D from *System suitability stock solution 1*, 10 µg/mL of cefadroxil related compound I from *System suitability stock solution 2*, and 1 mg/mL of USP Cefadroxil System Suitability Mixture RS in *Solution B*. Store the sample in the refrigerator, and discard after 14 h.

Standard solution: 10 µg/mL of USP Cefadroxil RS in *Solution B*. Store the sample in the refrigerator, and discard after 14 h.

Sample solution: 1 mg/mL of Cefadroxil in *Solution B*. Store the sample in the refrigerator, and discard after 14 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

Autosampler temperature: 6°

Injection volume: 20 µL

System suitability

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

Suitability requirements

Resolution: NLT 1.5 between cefadroxil related compound D and cefadroxil related compound I, *System suitability solution*

Relative standard deviation: NMT 5.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Cefadroxil taken:

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

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

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

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

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

P = potency of cefadroxil in USP Cefadroxil RS (µg/mg)

F = conversion factor, 0.001 mg/µg

Acceptance criteria: See *Table 2*. The reporting threshold is 0.03%.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Amoxicillin related compound I[a]	0.16	0.5
Cefadroxil *R*-sulfoxide[b]	0.22	0.15
Cefadroxil *S*-sulfoxide[c]	0.41	0.15
Cefadroxil related compound B[d]	0.49	0.5
Dimethylformamide[e]	0.55	—
Cefadroxil related compound D[f]	0.71	0.5
Cefadroxil related compound I[g]	0.80	0.15
Diketopiperazine derivative[h]	0.87	0.5
Cefadroxil	1.0	—
N-Phenylglycyl delta-3 cefadroxil[i]	1.4	0.15
Cefadroxil ethyl homolog[j]	1.5	0.15
N-Phenylglycyl cefadroxil[k]	1.8	0.5
3-Hydroxy-4-methylthiophenone[l]	2.0	0.5
N-Ethoxycarbonyl 7-aminodesacetoxycephalosporanic acid[m]	2.1	0.15
O-Ethoxycarbonyl cefadroxil[n]	2.3	0.3
Cefadroxil dimer[o]	2.4	0.15
Any individual unspecified impurity	—	0.10
Total impurities	—	2.0

[a] D-Hydroxyphenylglycine; (*R*)-2-Amino-2-(4-hydroxyphenyl)acetic acid.

[b] (6*R*,7*R*)-7-[(*R*)-2-Amino-2-(4-hydroxyphenyl)acetamido]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid 5*R*-oxide.

[c] (6*R*,7*R*)-7-[(*R*)-2-Amino-2-(4-hydroxyphenyl)acetamido]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid 5*S*-oxide.

[d] 7-Aminodesacetoxycephalosporanic acid; (6*R*,7*R*)-7-Amino-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

[e] This impurity is listed here for information only. It is not to be reported as an impurity in this test.

[f] L-Cefadroxil; (6*R*,7*R*)-7-[(*S*)-2-Amino-2-(4-hydroxyphenyl)acetamido]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

[g] Delta-3 cefadroxil; (6*R*,7*R*)-7-[(*R*)-2-Amino-2-(4-hydroxyphenyl)acetamido]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-3-ene-2-carboxylic acid.

[h] 3-(Aminomethylene)-6-(4-hydroxyphenyl)piperazine-2,5-dione.

[i] (6*R*,7*R*)-7-{(2*R*)-2-[2-Amino-2-(4-hydroxyphenyl)acetamido]-2-(4-hydroxyphenyl)acetamido}-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-3-ene-2-carboxylic acid.

[j] (6*R*,7*R*)-7-[(*R*)-2-Amino-2-(4-hydroxyphenyl)acetamido]-3-ethyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

[k] (6*R*,7*R*)-7-{(2*R*)-2-[2-Amino-2-(4-hydroxyphenyl)acetamido]-2-(4-hydroxyphenyl)acetamido}-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

[l] 3-Hydroxy-4-methylthiophen-2(5*H*)-one.

[m] (6*R*,7*R*)-7-(Ethoxycarbonylamino)-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

[n] (6*R*,7*R*)-7-((*R*)-2-Amino-2-{4-[(ethoxycarbonyl)oxy]phenyl}acetamido)-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

[o] (6*R*,7*R*)-7-[(*R*)-2-{(6*R*,7*R*)-7-[(*R*)-2-Amino-2-(4-hydroxyphenyl)acetamido]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxamido}-2-(4-hydroxyphenyl)acetamido]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

• **Dimethylaniline ⟨223⟩:** Meets the requirements

SPECIFIC TESTS

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

Sample solution: 10 mg/mL in water

Acceptance criteria: +165.0° to +178.0°

• **Crystallinity ⟨695⟩:** Meets the requirements

• **pH ⟨791⟩**

Sample solution: 50 mg/mL suspension in water

Acceptance criteria: 4.0–6.0

• **Water Determination,** *Method I* ⟨921⟩**:** 4.2%–6.0%, except where it is labeled as being in the hemihydrate form it is between 2.4% and 4.5%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight containers.

• **Labeling:** The hemihydrate form is so labeled.

• **USP Reference Standards ⟨11⟩**

USP Cefadroxil RS

USP Cefadroxil Related Compound D RS

(6*R*,7*R*)-7-[(*S*)-2-Amino-2-(4-hydroxyphenyl)acetamido]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

$C_{16}H_{17}N_3O_5S$ 363.39

USP Cefadroxil Related Compound I RS

(6*R*,7*R*)-7-[(*R*)-2-Amino-2-(4-hydroxyphenyl)acetamido]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-3-ene-2-carboxylic acid.

$C_{16}H_{17}N_3O_5S$ 363.39

USP Cefadroxil System Suitability Mixture RS

This is a mixture of cefadroxil and *O*-ethoxycarbonyl cefadroxil [(6*R*,7*R*)-7-((*R*)-2-Amino-2-{4-[(ethoxycarbonyl)oxy]phenyl}acetamido)-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid].

$C_{19}H_{21}N_3O_7S$ 435.45

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

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

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