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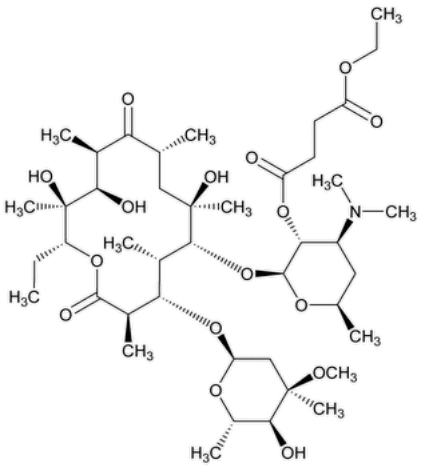
Erythromycin Ethylsuccinate



$C_{43}H_{75}NO_{16}$ 862.06

Erythromycin 2'-(ethyl butanedioate);

Erythromycin 2'-(ethyl succinate) CAS RN®: 1264-62-6; UNII: 1014KSJ86F.

DEFINITION

Erythromycin Ethylsuccinate consists primarily of the 2'-ethylsuccinate ester of erythromycin A. The sum of the percentages of erythromycin A, erythromycin B, and erythromycin C is NLT 76.5%, calculated on the anhydrous basis.

IDENTIFICATION

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

Sample solution: 10 mg/mL in chloroform

Cell: 1.0 mm

Acceptance criteria: Meets the requirements

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

ASSAY

• **Procedure**

Use solutions containing erythromycin promptly, or within 1 day if stored in a refrigerator.

Solution A: 20 mg/mL of dibasic potassium phosphate in water. Adjust with phosphoric acid to a pH of 8.0.

Solution B: 35 mg/mL of dibasic potassium phosphate in water. Adjust with phosphoric acid to a pH of 8.0.

Solution C: Adjust 20 mL of *Solution A* with phosphoric acid to a pH of 3.5.

Mobile phase: Acetonitrile, tertiary butyl alcohol, *Solution B*, and water (6:35:10:149)

Standard solution 1: 50 mg of USP Erythromycin RS in a 25-mL volumetric flask. Add 12.5 mL of methanol, and swirl to dissolve. Dilute with *Solution A* to volume.

Standard solution 2: 5 mg each of USP Erythromycin B RS and USP Erythromycin C RS, in a 50-mL volumetric flask. Add 25.0 mL of methanol, and swirl to dissolve. Add 2.5 mL of *Standard solution 1*, and dilute with *Solution A* to volume.

System suitability solution: 0.1 mg/mL of USP Erythromycin Related Compound N RS in *Standard solution 2*

Sample solution: 115 mg of Erythromycin Ethylsuccinate in a 50-mL volumetric flask. Add 25.0 mL of methanol, and swirl to dissolve. Add about 20 mL of *Solution A* and allow to stand at room temperature for about 12 h to effect hydrolysis. Dilute with *Solution A* to volume.

Chromatographic system

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

Mode: LC

Detector: UV 215 nm

Column: 4.6-mm × 25-cm; packing L21 (1000Å)

Column temperature: 70°

Flow rate: 2 mL/min

Injection volume: 200 µL

Run time: NLT 5 times the retention time of erythromycin A

System suitability

Samples: *Standard solution 1* and *System suitability solution*

The order of elution of the components is erythromycin related compound N, erythromycin C, erythromycin A, and erythromycin B.

Suitability requirements

Resolution: NLT 0.8 between erythromycin related compound N and erythromycin C; NLT 5.5 between erythromycin related compound N and erythromycin A, *System suitability solution*

Relative standard deviation: NMT 1.0%, *Standard solution 1*

Analysis

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

Calculate the percentage of erythromycin A in the portion of Erythromycin Ethylsuccinate taken:

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

r_U = peak response of erythromycin A from the *Sample solution*

r_S = peak response of erythromycin A from *Standard solution 1*

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

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

P = percentage of erythromycin A in USP Erythromycin RS

Calculate the percentage of erythromycin B and erythromycin C in the portion of Erythromycin Ethylsuccinate taken:

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

r_U = peak response of the relevant analyte from the *Sample solution*

r_S = peak response of the relevant analyte from *Standard solution 2*

C_S = concentration of the corresponding Reference Standard in *Standard solution 2* (mg/mL)

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

P = potency of erythromycin B or erythromycin C in the corresponding Reference Standard (mg/mg)

Acceptance criteria: NLT 76.5% for the sum of the percentages of erythromycin A, erythromycin B, and erythromycin C, on the anhydrous basis. The percentage of erythromycin B is NMT 12.0%, and the percentage of erythromycin C is NMT 5.0%.

IMPURITIES

• **Residue on Ignition ⟨281⟩**

Sample: After ignition at 550 ± 50°, the charred residue is moistened with 2 mL of nitric acid and 5 drops of sulfuric acid.

Acceptance criteria: NMT 1.0%

• **Organic Impurities**

Solution B, Solution C, Mobile phase, Standard solution 1, Standard solution 2, Sample solution, Chromatographic system, and **System suitability:** Proceed as directed in the *Assay*.

Peak identification solution: 10 mg of USP Erythromycin RS in 2 mL of methanol. Add 10 mL of *Solution C*, and allow to stand for about 30 min. Refrigerate this solution until used, and discard 8 h after preparation.

Analysis

Samples: *Standard solution 2*, *Sample solution*, and *Peak identification solution*

Identify the erythromycin A enol ether peak using the *Peak identification solution*. Begin peak integration of the *Sample solution* after the two peaks for succinates that elute just after the solvent front.

Calculate the percentage of the largest single impurity (the largest peak other than erythromycin A, erythromycin B, erythromycin C, erythromycin A enol ether, and erythromycin *N*-ethylsuccinate) in the portion of Erythromycin Ethylsuccinate taken:

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

r_U = peak response of the largest single impurity (the largest peak other than erythromycin A, erythromycin B, erythromycin C, erythromycin A enol ether, and erythromycin *N*-ethylsuccinate) from the *Sample solution*

r_S = peak response of erythromycin A from *Standard solution 2*

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

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

P = percentage of erythromycin A in USP Erythromycin RS

Calculate the percentage of erythromycin A enol ether in the portion of Erythromycin Ethylsuccinate taken:

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

r_U = peak response of erythromycin A enol ether from the *Sample solution*

r_S = peak response of erythromycin A from *Standard solution 2*

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

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

P = percentage of erythromycin A in USP Erythromycin RS

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

Calculate the percentage of erythromycin *N*-ethylsuccinate in the portion of Erythromycin Ethylsuccinate taken:

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

r_U = peak response of erythromycin *N*-ethylsuccinate from the *Sample solution*

r_S = peak response of erythromycin A from *Standard solution 2*

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

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

P = percentage of erythromycin A in USP Erythromycin RS

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

Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Erythromycin *N*-ethylsuccinate[a]	1.3	7.4	3.0
Erythromycin A enol ether[b]	4.3–4.7	11	3.0
Erythromycin A	1.0	—	—
Largest single impurity[c]	—	—	3.0

[a] Ethyl 4-{[(2*S*,3*R*,4*S*,6*R*)-2-{[(3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*R*,13*S*,14*R*)-14-ethyl-7,12,13-trihydroxy-4-{[(2*R*,4*R*,5*S*,6*S*)-5-hydroxy-4-methoxy-4,6-dimethyltetrahydro-2*H*-pyran-2-yl]oxy}-3,5,7,9,11,13-hexamethyl-2,10-dioxooxacyclotetradecan-6-yl]oxy}-3-hydroxy-6-methyltetrahydro-2*H*-pyran-4-yl](methyl)amino}-4-oxobutanoate.

[b] (2*R*,3*R*,4*S*,5*R*,8*R*,9*S*,10*S*,11*R*)-11-{[(2*S*,3*R*,4*S*,6*R*)-4-(Dimethylamino)-3-hydroxy-6-methyltetrahydro-2*H*-pyran-2-yl]oxy}-5-ethyl-3,4-dihydroxy-9-{[(2*R*,4*R*,5*S*,6*S*)-5-hydroxy-4-methoxy-4,6-dimethyltetrahydro-2*H*-pyran-2-yl]oxy}-2,4,8,10,12,14-hexamethyl-6,15-dioxabicyclo[10.2.1]pentadec-1(14)-en-7-one.

[c] The largest peak other than erythromycin A, erythromycin B, erythromycin C, erythromycin A enol ether, and erythromycin *N*-ethylsuccinate.

SPECIFIC TESTS

• **Water Determination ⟨921⟩, *Method I***

Sample solution: Use 20 mL of methanol containing 10% of imidazole in place of methanol in the titration vessel.

Acceptance criteria: NMT 3.0%

• **Crystallinity ⟨695⟩:** Meets the requirements except, where it is labeled as amorphous, most of the particles do not exhibit birefringence and extinction positions.

Change to read:

• **▲X-Ray Powder Diffraction ⟨941⟩▲ (CN 1-May-2022):** Where labeled as being amorphous, its X-ray diffraction pattern performed at high sensitivity

for angles of diffraction between 2° and 20° exhibits no reflection, and between 7° and 10° exhibits a more intense hachured baseline, creating a halo.

ADDITIONAL REQUIREMENTS

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

• **Labeling:** Erythromycin Ethylsuccinate that is noncrystalline is labeled to indicate that it is amorphous. Any preparation containing the amorphous form of Erythromycin Ethylsuccinate is so labeled.

• **USP Reference Standards** ⟨11⟩

USP Erythromycin RS

USP Erythromycin B RS

12-Deoxyerythromycin;
(3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*S*,13*R*,14*R*)-6-{[(2*S*,3*R*,4*S*,6*R*)-4-(Dimethylamino)-3-hydroxy-6-methyltetrahydro-2*H*-pyran-2-yl]oxy}-14-ethyl-7,12-dihydroxy-4-{[(2*R*,4*R*,5*S*,6*S*)-5-hydroxy-4-methoxy-4,6-dimethyltetrahydro-2*H*-pyran-2-yl]oxy}-3,5,7,9,11,13-hexamethyloxacyclotetradecane-2,10-dione.

$C_{37}H_{67}NO_{12}$ 717.94

USP Erythromycin C RS

3"-*O*-Demethylerythromycin;
(3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*R*,13*S*,14*R*)-4-{[(2*R*,4*R*,5*S*,6*S*)-4,5-Dihydroxy-4,6-dimethyltetrahydro-2*H*-pyran-2-yl]oxy}-6-{[(2*S*,3*R*,4*S*,6*R*)-4-(dimethylamino)-3-hydroxy-6-methyltetrahydro-2*H*-pyran-2-yl]oxy}-14-ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexamethyloxacyclotetradecane-2,10-dione.

$C_{36}H_{65}NO_{13}$ 719.91

USP Erythromycin Related Compound N RS

N-Demethylerythromycin A;
(3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*R*,13*S*,14*R*)-14-Ethyl-7,12,13-trihydroxy-4-{[(2*R*,4*R*,5*S*,6*S*)-5-hydroxy-4-methoxy-4,6-dimethyltetrahydro-2*H*-pyran-2-yl]oxy}-6-{[(2*S*,3*R*,4*S*,6*R*)-3-hydroxy-6-methyl-4-(methylamino)tetrahydro-2*H*-pyran-2-yl]oxy}-3,5,7,9,11,13-hexamethyloxacyclotetradecane-2,10-dione.

$C_{36}H_{65}NO_{13}$ 719.91

USP Erythromycin Ethylsuccinate RS

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

Topic/Question	Contact	Expert Committee
ERYTHROMYCIN ETHYLSUCCINATE	Julie Zhang Associate Science & Standards Liaison	BIO42020 Biologics Monographs 4 - Antibiotics

Chromatographic Database Information: Chromatographic Database

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