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Erythromycin Stearate

$C_{37}H_{67}NO_{13} \cdot C_{18}H_{36}O_2$ 1018.40
Erythromycin octadecanoate (salt);
Erythromycin stearate (salt) CAS RN®: 643-22-1; UNII: LXW024X05M.

DEFINITION

Erythromycin Stearate is the stearic acid salt of Erythromycin, with an excess of Stearic Acid. The sum of the percentages of erythromycin A, erythromycin B, and erythromycin C is NLT 55.0%, calculated on the anhydrous basis.

IDENTIFICATION

Change to read:

• ▲**A.**▲ (USP 1-Dec-2019) ▲**Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*: 197M**▲ (CN 1-May-2020)

Add the following:

▲• **B.** The retention times of the erythromycin A, erythromycin B, and erythromycin C peaks in the *Sample solution* correspond to those of *Standard solution 2*, as obtained in the *Assay*.▲ (USP 1-Dec-2019)

ASSAY

Change to read:

• **Procedure**

▲Use solutions containing erythromycin promptly, or within 1 day if stored in a refrigerator.▲ (USP 1-Dec-2019)

Diluted phosphoric acid: Dilute 10 mL of phosphoric acid with water to 100 mL.

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 potassium hydroxide TS or *Diluted phosphoric acid*, as appropriate, to a pH of 9.0.

Solution C: 20 mL of *Solution A*. Adjust 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: 40 mg of USP Erythromycin RS in a conical flask. Add 5.0 mL of methanol, and swirl to dissolve. Add 5.0 mL of *Solution A*.

Standard solution 2: 6 mg each of USP Erythromycin RS, USP Erythromycin B RS, USP Erythromycin C RS, and USP Erythromycin Related Compound N RS in a 50-mL conical flask. Add 15.0 mL of methanol and swirl to dissolve. Add 15.0 mL of *Solution A*.

▲▲ (USP 1-Dec-2019)

Sample solution: 165 mg of Erythromycin Stearate in a 100-mL conical flask. Add 15.0 mL of methanol and swirl to dissolve. Add 15.0 mL of *Solution A* and mix. Allow the resulting suspension to settle, and pass a portion of the supernatant through a filter of 0.2-µm or finer pore size. Use the clear filtrate.

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: 100 µL

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

System suitability

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

The elution order 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, *Standard solution 2*

Relative standard deviation: NMT 2.0%, *Standard solution 1*

Analysis

Samples: *Standard solution 1*, *Standard solution 2*, ▲▲ (USP 1-Dec-2019) and *Sample solution* ▲▲ (USP 1-Dec-2019)

Calculate the percentage of erythromycin A in the portion of Erythromycin Stearate 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 Stearate 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 Stearate 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 Stearate in the *Sample solution* (mg/mL)

P = ▲potency of erythromycin B or erythromycin C in the corresponding Reference Standard (mg/mg)▲ (USP 1-Dec-2019)

Acceptance criteria: The sum of the percentages of erythromycin A, erythromycin B, and erythromycin C is NLT 55.0% 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: The charred residue is moistened with 2 mL of nitric acid and 5 drops of sulfuric acid.

Acceptance criteria: NMT 1.0%

Change to read:

• **Organic Impurities**

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

▲**Peak identification solution:** 5 mg of USP Erythromycin RS in 1 mL of methanol. Add 5 mL of *Solution C*, mix, and allow to stand for about 30 min.▲ (USP 1-Dec-2019)

Analysis

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

Identify the erythromycin A enol ether peak using the *Peak identification solution*.▲ (USP 1-Dec-2019)

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

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

r_U = peak response of pseudoerythromycin 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 Stearate 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 (%)
Pseudoerythromycin A enol ether▲[a]▲ (USP 1-Dec-2019)	1.5	6.6	3.0
Erythromycin A enol ether▲[b]▲ (USP 1-Dec-2019)	4.3–4.7	11	3.0
Erythromycin A	1.0	—	—
Largest single impurity[c]	—	—	3.0

▲[a] (2*R*,3*S*,6*R*,7*S*,8*S*,9*R*,10*R*)-3-[(2*R*,3*R*)-2,3-Dihydroxypentan-2-yl]-9-{[(2*S*,3*R*,4*S*,6*R*)-4-(dimethylamino)-3-hydroxy-6-methyltetrahydro-2*H*-pyran-2-yl]oxy}-7-{[(2*R*,4*R*,5*S*,6*S*)-5-hydroxy-4-methoxy-4,6-dimethyltetrahydro-2*H*-pyran-2-yl]oxy}-2,6,8,10,12-pentamethyl-4,13-dioxabicyclo[8.2.1]tridec-1(12)-en-5-one.

[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.▲ (USP 1-Dec-2019)

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

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 4.0%

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

ADDITIONAL REQUIREMENTS

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

Change to read:

• **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 1-Dec-2019)

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 1-Dec-2019)

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.▲ (USP 1-Dec-2019)

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

USP Erythromycin Stearate RS

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

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

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