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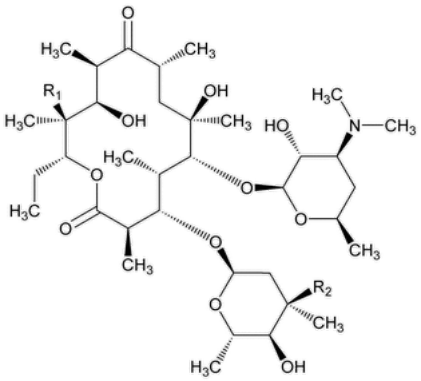
Erythromycin

Change to read:



Erythromycin	R_1	R_2
A	OH	OCH_3
B	H	OCH_3
C	OH	OH

$C_{37}H_{67}NO_{13}$ 733.94

▲Erythromycin A

(3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*R*,13*S*,14*R*)-4-[(2,6-Dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-14-ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexamethyl-6-[(3,4,6-trideoxy-3-dimethylamino-β-D-*xylo*-hexopyranosyl)oxy]oxacyclotetradecane-2,10-dione;

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

Erythromycin B

(3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*R*,13*S*,14*R*)-4-[(2,6-Dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-14-ethyl-7,12-dihydroxy-3,5,7,9,11,13-hexamethyl-6-[(3,4,6-trideoxy-3-dimethylamino-β-D-*xylo*-hexopyranosyl)oxy]oxacyclotetradecane-2,10-dione;

12-Deoxyerythromycin CAS RN®: 527-75-3.

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

Erythromycin C

(3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*R*,13*S*,14*R*)-4-[(2,6-Dideoxy-3-*C*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-14-ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexamethyl-6-[(3,4,6-trideoxy-3-dimethylamino-β-D-*xylo*-hexopyranosyl)oxy]oxacyclotetradecane-2,10-dione;

3″-*O*-Demethylerythromycin CAS RN®: 1675-02-1.▲ (USP 1-Dec-2024)

Erythromycin

▲▲ (USP 1-Dec-2024) CAS RN®: 114-07-8; UNII: 63937KV33D.

Change to read:

DEFINITION

Erythromycin consists primarily of erythromycin A ($C_{37}H_{67}NO_{13}$). The sum of the percentages of erythromycin A, erythromycin B, and erythromycin C is NLT ▲93.0%▲ (USP 1-Dec-2024) and NMT ▲102.0%,▲ (USP 1-Dec-2024) calculated on the anhydrous basis.

IDENTIFICATION

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

Standard solution: 50 mg/mL of USP Erythromycin RS, previously dried at a pressure not exceeding 5 mm of mercury at 60° for 3 h, in chloroform

Sample solution: 50 mg/mL of Erythromycin, previously dried at a pressure not exceeding 5 mm of mercury at 60° for 3 h, in chloroform

Spectral range: 4000–2050 cm^{-1} and 1980–400 cm^{-1}

Acceptance criteria: Meets the requirements

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

ASSAY

Change to read:

• **Procedure**

▲Prepare the erythromycin solutions immediately before use.

Diluted phosphoric acid: Dilute 7 mL of phosphoric acid with water to 100 mL.

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Phosphate buffer solution pH 8.0: Dissolve 11.5 g of dibasic potassium phosphate in 900 mL of water. Adjust to a pH of 8.0 with *Diluted phosphoric acid* and dilute with water to 1000 mL.

Diluent: *Phosphate buffer solution pH 8.0* and methanol (60:40)

Phosphate buffer solution pH 7.0: Dissolve 35 g of dibasic potassium phosphate in 900 mL of water. Adjust to a pH of 7.0 with *Diluted phosphoric acid* and dilute with water to 1000 mL.

Solution A: *Phosphate buffer solution pH 7.0*, water, and acetonitrile (5:60:35)

Solution B: *Phosphate buffer solution pH 7.0*, water, and acetonitrile (5:45:50)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
T_R [a]	100	0
$T_R + 2$	0	100
$T_R + 15$	0	100

[a] T_R = retention time of erythromycin B, determined by injecting 10 µL of *Standard solution 2* and eluting with *Solution A*.

Standard solution 1: 4 mg/mL of USP Erythromycin RS in *Diluent*

Standard solution 2: 0.2 mg/mL of USP Erythromycin B RS and USP Erythromycin C RS in *Diluent*

Sample solution: 4 mg/mL of Erythromycin in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 25-cm; 3.5-µm packing L1

Temperatures

Column: 65°, preheating the *Mobile phase* may be required, for instance by extending the inlet tubing in the oven to 30 cm

Sampler: 4°

Flow rate: 1.0 mL/min

Injection volume: 100 µL

System suitability

Sample: *Standard solution 1*

Suitability requirements

Tailing factor: NMT 2.0 for erythromycin A

Relative standard deviation: NMT 1.0% for erythromycin A, 6 replicate injections

Analysis

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

Calculate the percentage of erythromycin A in the portion of Erythromycin 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, calculated on the anhydrous basis, in the *Sample solution* (mg/mL)

P = percentage of erythromycin A in USP Erythromycin RS

Calculate the percentages of erythromycin B and erythromycin C in the portion of Erythromycin 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*

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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, calculated on the anhydrous basis, in the *Sample solution* (mg/mL)

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

Acceptance criteria

Sum of Erythromycin A, Erythromycin B, and **Erythromycin C:** 93.0%–102.0% on the anhydrous basis

Erythromycin B: NMT 5.0% on the anhydrous basis

Erythromycin C: NMT 5.0% on the anhydrous basis▲ (USP 1-Dec-2024)

IMPURITIES

• **Residue on Ignition ⟨281⟩:** NMT 0.2%

Change to read:

• **Limit of Thiocyanate**

Use the *Standard solutions*, *Sample solution*, and *Blank solution* within 30 min.

Standard stock solutions 1 and **2:** 0.2 mg/mL of potassium thiocyanate prepared in duplicate as follows. Transfer 100 mg of potassium thiocyanate, previously dried at 105° for 1 h and cooled, to a 50-mL volumetric flask. Add about 20 mL of methanol to each flask, swirl to dissolve, and dilute with methanol to volume. Transfer 5.0 mL of this solution to a 50-mL volumetric flask and dilute with methanol to volume.

Standard solutions 1 and **2:** 0.02 mg/mL of potassium thiocyanate prepared in duplicate as follows. Transfer 5.0 mL of each of the *Standard stock solutions* to separate 50-mL low-actinic volumetric flasks, add 1.0 mL of ferric chloride TS, dilute with methanol to volume.

Sample solution: 2 mg/mL of Erythromycin prepared as follows. Transfer 100 mg of Erythromycin to a 50-mL low-actinic volumetric flask, add 20 mL of methanol, and swirl to dissolve. Add 1.0 mL of ferric chloride TS and dilute with methanol to volume.

Blank solution: Add 1.0 mL of ferric chloride TS to a 50-mL low-actinic volumetric flask. Dilute with methanol to volume.

Instrumental conditions

(See *Ultraviolet-Visible Spectroscopy ⟨857⟩*.)

Mode: UV-Vis

Analytical wavelength: 492 nm

System suitability

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

Use the *Blank solution* to zero the instrument. Measure the absorbance of the two *Standard solutions*.

Suitability: 0.985–1.015

Calculate the suitability, *S*:

$$\text{Result} = (A_1/W_1) \times (W_2/A_2)$$

A_1 = absorbance of *Standard solution 1*

W_1 = weight of the potassium thiocyanate taken to prepare *Standard solution 1* (mg)

W_2 = weight of the potassium thiocyanate taken to prepare *Standard solution 2* (mg)

A_2 = absorbance of *Standard solution 2*

Analysis

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

Calculate the percentage of thiocyanate in the portion of Erythromycin taken:

$$\text{▲Result} = (M_{r1}/M_{r2}) \times (A_U/W_U) \times 0.5 \times [(W_1/A_1) + (W_2/A_2)]\text{▲ (USP 1-Dec-2024)}$$

M_{r1} = molecular weight of thiocyanate, 58.08

M_{r2} = molecular weight of potassium thiocyanate, 97.18

A_U = absorbance of the *Sample solution*

W_U = weight of Erythromycin taken to prepare the *Sample solution* (mg)

W_1 = weight of the potassium thiocyanate taken to prepare *Standard* ▲*stock*▲ *(USP 1-Dec-2024) solution 1* (mg)

A_1 = absorbance of *Standard solution 1*

W_2 = weight of the potassium thiocyanate taken to prepare *Standard* ▲*stock*▲ *(USP 1-Dec-2024) solution 2* (mg)

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A_2 = absorbance of *Standard solution 2*

Acceptance criteria: NMT 0.3%

Change to read:

• **Organic Impurities**

▲**Diluent, Solution A, Solution B, Mobile phase, Standard solution 1, Standard solution 2, Sample solution,** and **Chromatographic system:** Proceed as directed in the *Assay*. Prepare the erythromycin solutions immediately before use.

Diluted standard solution: 0.04 mg/mL of USP Erythromycin RS prepared as follows. Dilute 1.0 mL of *Standard solution 1* to a 100-mL volumetric flask and dilute with *Diluent* to volume.

System suitability solution: Dissolve 4 mg of USP Erythromycin System Suitability Mixture RS in 1 mL of *Diluent*.

System suitability

Sample: *System suitability solution*

[Note—See *Table 2* for the relative retention times. Use the reference chromatogram provided with USP Erythromycin System Suitability Mixture RS and the chromatogram obtained with *System suitability solution* to identify the specified impurity peaks. Use the chromatogram obtained with *Standard solution 2* to identify erythromycin B and erythromycin C.]

Suitability requirements

Peak-to-valley ratio: NLT 1.5 for the ratio of the height of the pseudoerythromycin A enol ether peak to the height of the valley between the pseudoerythromycin A enol ether peak and the erythromycin B peak; NLT 2.0 for the ratio of the height of the erythromycin E peak to the height of the valley between erythromycin E peak and erythromycin A peak

Resolution: NLT 1.2 between 3″-*N*-demethylerythromycin A and erythromycin C

Analysis

Samples: *Standard solution 2*, *Sample solution*, and *Diluted standard solution*

Calculate the percentage of any individual impurity in the portion of Erythromycin taken:

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

r_U = peak response of any individual impurity (the peak other than erythromycin A, erythromycin B, and erythromycin C) from the *Sample solution*

r_S = peak response of erythromycin A from the *Diluted standard solution*

C_S = concentration of USP Erythromycin RS in the *Diluted standard solution* (mg/mL)

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

P = percentage of erythromycin A in USP Erythromycin RS

F = relative response factor (see *Table 2*)

Acceptance criteria: See *Table 2*. The reporting threshold is 0.2%.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Erythromycin A *N*-oxide[a]	0.3	1	1.0
Erythromycin F[b]	0.4	1	2.0
3″-*N*-Demethylerythromycin A[c]	0.5	1	2.0
Erythromycin C	0.55	—	—
3″-*N*-Demethyl-3″-*N*-formyl erythromycin A[d]	0.63	9.1	0.4
Erythromycin E[e]	0.9	1	3.0
Erythromycin A	1.0	—	—
Anhydroerythromycin A[f]	1.61	0.5	1.0

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Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Erythromycin B	1.75	—	—
Pseudoerythromycin A enol ether[g]	1.81	12.5	1.0
Erythromycin A enol ether[h]	2.3	12.5	1.0
Any other individual impurity	—	—	0.4
Total impurities	—	—	7.0

[a] (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*R*,13*S*,14*R*)-4-[(2,6-Dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-14-ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexamethyl-6-[(3,4,6-trideoxy-3-dimethylamino-β-D-*xylo*-hexopyranosyl)oxy]oxacyclotetradecane-2,10-dione *N*-oxide.

[b] (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*R*,13*S*,14*R*)-4-[(2,6-Dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-14-ethyl-7,12,13-trihydroxy-3-hydroxymethyl-5,7,9,11,13-pentamethyl-6-[(3,4,6-trideoxy-3-dimethylamino-β-D-*xylo*-hexopyranosyl)oxy]oxacyclotetradecane-2,10-dione.

[c] (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*R*,13*S*,14*R*)-4-[(2,6-Dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-14-ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexamethyl-6-[(3,4,6-trideoxy-3-methylamino-β-D-*xylo*-hexopyranosyl)oxy]oxacyclotetradecane-2,10-dione.

[d] (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*R*,13*S*,14*R*)-4-[(2,6-Dideoxy-3-*C*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-14-ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexamethyl-6-[(3,4,6-trideoxy-3-formylmethylamino-β-D-*xylo*-hexopyranosyl)oxy]oxacyclotetradecane-2,10-dione.

[e] (2*S*,4a*R*,4′*R*,5′*S*,6′*S*,7*R*,8*S*,9*R*,10*R*,12*R*,14*R*,15*R*,16*S*,16a*S*)-7-Ethyl-5′,8,9,14-tetrahydroxy-4′-methoxy-4′,6′,8,10,12,14,16-heptamethyl-15-{[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy}hexadecahydrospiro[5*H*,11*H*-1,3-dioxino[5,4-c]oxacyclotetradecin-2,2′-pyrane]-5,11-dione.

[f] (1*S*,2*R*,3*R*,4*S*,5*R*,8*R*,9*S*,10*S*,11*R*,12*R*,14*R*)-9-[(2,6-Dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-5-ethyl-3-hydroxy-2,4,8,10,12,14-hexamethyl-11-{[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy}-6,15,16-trioxatricyclo[10.2.1.1^{1,4}]hexadecan-7-one.

[g] (2*R*,3*R*,6*R*,7*S*,8*S*,9*R*,10*R*)-7-[(2,6-Dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-3-[(1*R*,2*R*)-1,2-dihydroxy-1-methylbutyl]-2,6,8,10,12-pentamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-4,13-dioxabicyclo[8.2.1]tridec-1(12)-en-5-one.

[h] (2*R*,3*R*,4*S*,5*R*,8*R*,9*S*,10*S*,11*R*,12*R*)-9-[(2,6-Dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-{[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy}-6,15-dioxabicyclo[10.2.1]pentadec-1(14)-en-7-one.

▲ (USP 1-Dec-2024)

SPECIFIC TESTS

Delete the following:

▲• **Optical Rotation** ⟨781S⟩, *Procedures, Specific Rotation*▲ (USP 1-Dec-2024)

Change to read:

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

Sample solution: Use ▲▲ (USP 1-Dec-2024) methanol containing 10% of imidazole in place of methanol in the titration vessel.

Acceptance criteria: NMT ▲6.5%▲ (USP 1-Dec-2024)

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

ADDITIONAL REQUIREMENTS

Change to read:

• **Packaging and Storage:** ▲Preserve in hermetic containers, and protect from light.▲ (USP 1-Dec-2024)

Change to read:

• **USP Reference Standards** ⟨11⟩

USP Erythromycin RS

USP Erythromycin B RS ▲▲ (USP 1-Dec-2024)

USP Erythromycin C RS

▲ USP Erythromycin System Suitability Mixture RS▲ (USP 1-Dec-2024)

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

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

Chromatographic Database Information: Chromatographic Database

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