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Azithromycin Tablets

DEFINITION

Azithromycin Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of azithromycin ($C_{38}H_{72}N_2O_{12}$).

IDENTIFICATION

- **A.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.
- **B.** **Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*: 197A**

Standard solution: 25 mg/mL of USP Azithromycin RS in acetonitrile. Pass the solution through a suitable filter, and remove the solvent by natural evaporation.

Sample solution: Equivalent to 25 mg/mL of azithromycin from Tablets in acetonitrile. Pass the solution through a suitable filter, and remove the solvent by natural evaporation.

Acceptance criteria: Meet the requirements

ASSAY

- **Procedure**

Buffer: Dissolve 4.6 g of monobasic potassium phosphate anhydrous in 900 mL of water. Adjust with 1 N sodium hydroxide to a pH of 7.5, and dilute with water to 1 L.

Mobile phase: Acetonitrile and *Buffer* (65:35)

Standard solution: 1 mg/mL of USP Azithromycin RS in *Mobile phase*. Sonicate and shake as needed to dissolve.

Sample solution: Nominally 1 mg/mL of azithromycin in *Mobile phase* from NLT 20 Tablets, finely powdered. Sonicate and shake as needed to dissolve.

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

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

Column temperature: 50°

Flow rate: 2 mL/min

Injection volume: 100 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of azithromycin ($C_{38}H_{72}N_2O_{12}$) in the portion of Tablets taken:

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

r_U = peak response of azithromycin from the *Sample solution*

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

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

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

P = potency of USP Azithromycin RS (µg/mg)

F = conversion factor, 0.001 mg/µg

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

• **Dissolution ⟨711⟩**

Medium: pH 6.0 phosphate buffer; 900 mL

Apparatus 2: 75 rpm

Time: 30 min

Solution A: 4.4 mg/mL of dibasic potassium phosphate and 0.5 mg/mL of sodium 1-octanesulfonate; adjusted with phosphoric acid to a pH of 8.20 ± 0.05

Mobile phase: Acetonitrile, methanol, and *Solution A* (9:3:8)

Diluent: 17.5 mg/mL of dibasic potassium phosphate. Adjust with phosphoric acid to a pH of 8.00 ± 0.05. Prepare a mixture of this solution and acetonitrile (80:20).

Standard stock solution: Dissolve USP Azithromycin RS in *Medium* to obtain a solution with a known concentration of about (*L*/1000) mg/mL, where *L* is the label claim in mg/Tablet.

Standard solution: Dilute the *Standard stock solution* with *Diluent* to obtain a solution with a known concentration of about (*L*/2000) mg/mL, where *L* is the label claim in mg/Tablet.

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. Dilute a portion of the filtrate with *Diluent* to obtain a solution with a theoretical concentration of about (*L*/2000) mg/mL, where *L* is the label claim in mg/Tablet, assuming complete dissolution.

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1

Column temperature: 50°

Flow rate: 1.5 mL/min

Injection volume: 50 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of azithromycin ($C_{38}H_{72}N_2O_{12}$) dissolved:

$$\text{Result} = (r_U/r_S) \times (C_S/L) \times V \times D \times 100$$

r_U = peak response of azithromycin from the *Sample solution*

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

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

L = label claim (mg/Tablet)

V = volume of *Medium*, 900 mL

D = dilution factor for the *Sample solution*, if necessary

Tolerances: NLT 80% (*Q*) of the labeled amount of azithromycin ($C_{38}H_{72}N_2O_{12}$) is dissolved.

• **Uniformity of Dosage Units ⟨905⟩:** Meet the requirements

IMPURITIES

• **Organic Impurities**

Protect all solutions containing azithromycin from light. Refrigerate the *Standard solution* and the *Sample solution* after preparation and during analysis, using a refrigerated autosampler set at 4°. The solutions must be analyzed within 24 h of preparation.

Solution A: Water and ammonium hydroxide (2000:1.2). The pH of this solution is about 10.5.

Solution B: Acetonitrile, methanol, and ammonium hydroxide (1800:200:1.2)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	54	46
20	54	46
35	10	90
35.1	54	46
50.1	54	46

Buffer: 1.7 g/L of monobasic ammonium phosphate in water. Adjust with ammonium hydroxide to a pH of 10 ± 0.05.

Diluent A: Methanol, acetonitrile, and *Buffer* (350:300:350). [NOTE—*Diluent A* is stable for 24 h after mixing the organic and buffer phases.]

Diluent B: Methanol and *Buffer* (1:1)

System suitability stock solution: 0.1 mg/mL each of USP Desosaminylazithromycin RS, USP Azithromycin Related Compound F RS, and USP *N*-Demethylazithromycin RS in acetonitrile

System suitability solution: 0.028 mg/mL each of USP Desosaminylazithromycin RS, USP Azithromycin Related Compound F RS, and USP *N*-Demethylazithromycin RS from the *System suitability stock solution* in *Diluent A*

Peak identification solution: 0.004 mg/mL each of USP Desosaminylazithromycin RS, USP Azithromycin Related Compound F RS, and USP *N*-Demethylazithromycin RS from the *System suitability solution* in *Diluent A*

Standard stock solution: 0.4 mg/mL of USP Azithromycin RS in acetonitrile. Sonicate and shake as needed to dissolve.

Standard solution: 0.02 mg/mL of azithromycin from the *Standard stock solution* in *Diluent A*

Sensitivity solution: 0.004 mg/mL of azithromycin from the *Standard solution* in *Diluent A*

Sample stock solution: Nominally 14.3 mg/mL of azithromycin prepared as follows. Transfer nominally 1430 mg of azithromycin, from finely powdered Tablets (NLT 20), to a 100-mL volumetric flask. Add 75 mL of acetonitrile, and sonicate for NLT 15 min. Shake by mechanical means for NLT 15 min. Allow the solution to equilibrate to room temperature, dilute with acetonitrile to volume, and mix.

Sample solution: Nominally 4 mg/mL of azithromycin prepared as follows. Centrifuge an aliquot of the *Sample stock solution* for NLT 15 min. Transfer 7.0 mL of the supernatant to a 25-mL volumetric flask, and dilute with *Diluent B* to volume.

Blank: *Diluent A*

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 15-cm; 3.5-µm packing L1

Temperatures

Autosampler: 4°

Column: 50°

Flow rate: 1.2 mL/min

Injection volume: 100 µL

System suitability

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

Suitability requirements

Resolution: NLT 1.0 between desosaminylazithromycin and azithromycin related compound F, *System suitability solution*

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

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Analysis

Samples: *Standard solution*, *Sample solution*, and *Blank*

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

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times P \times F_1 \times (1/F_2) \times 100$$

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

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

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

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

P = potency of USP Azithromycin RS (µg/mg)

F_1 = conversion factor, 0.001 mg/µg

F_2 = relative response factor (see *Table 2*)

Acceptance criteria: See *Table 2*. The reporting threshold is 0.1%. Disregard any peaks in the *Sample solution* that correspond to peaks in the *Blank*.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Azithromycin *N*-oxide[a]	0.20	0.46	1.0
3'-(*N*,*N*-Didemethyl)-3'-*N*-formylazithromycin[b,c]	0.29 0.30	1.7	1.0
3'-(*N*,*N*-Didemethyl)azithromycin (aminoazithromycin)[d]	0.34	0.44	0.5
Azithromycin related compound F[c,e]	0.40 0.46	5.5	1.0
Desosaminylazithromycin[f]	0.47	1.1	0.5
N-Demethylazithromycin[g]	0.50	0.47	0.7
3'-De(dimethylamino)-3'-oxoazithromycin[h]	0.87	1.7	1.0
Azaerythromycin A[i,j]	0.94	—	—
Azithromycin	1.0	—	—
2-Desethyl-2-propylazithromycin[i,k]	1.10	—	—
3'-*N*-Demethyl-3'-*N*-[(4-methylphenyl)sulfonyl]azithromycin[i,l]	1.11	—	—
3-Deoxyazithromycin (azithromycin B)[i,m]	1.14	—	—
Any individual unspecified impurity[i]	—	1.0	0.2
Total impurities[i]	—	—	5.0

[a] (2*R*,3*S*,4*R*,5*R*,8*R*,10*R*,11*R*,12*S*,13*S*,14*R*)-13-[(2,6-Dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylazinoyl)-β-D-*xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one.

[b] (2*R*,3*S*,4*R*,5*R*,8*R*,10*R*,11*R*,12*S*,13*S*,14*R*)-13-[(2,6-Dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3-formamido-3,4,6-trideoxy-β-D-*xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one.

[c] The system may resolve two rotamers. The limit is for the sum of the two rotamers.

[d] (2*R*,3*S*,4*R*,5*R*,8*R*,10*R*,11*R*,12*S*,13*S*,14*R*)-13-[(2,6-Dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3-amino-3,4,6-trideoxy-β-D-*xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one.

[e] 3'-(*N*-Demethyl)-3'-*N*-formylazithromycin; (2*R*,3*S*,4*R*,5*R*,8*R*,10*R*,11*R*,12*S*,13*S*,14*R*)-13-[(2,6-Dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3-(*N*-methyl)formamido-3,4,6-trideoxy-β-D-*xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one.

[f] (2*R*,3*S*,4*R*,5*R*,8*R*,10*R*,11*R*,12*S*,13*S*,14*R*)-2-Ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-dimethylamino-β-D-*xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one.

[g] (2*R*,3*S*,4*R*,5*R*,8*R*,10*R*,11*R*,12*S*,13*S*,14*R*)-13-[(2,6-Dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-methylamino-β-D-*xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one.

[h] (2*R*,3*S*,4*R*,5*R*,8*R*,10*R*,11*R*,12*S*,13*S*,14*R*)-13-[(2,6-Dideoxy-3,3-dimethyl-α-L-*ribo*-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-oxo-β-D-*xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one.

[i] Process impurities that are controlled in the drug substance are not to be reported. They are listed here for information only. The unspecified impurities and total impurities limits do not include these impurities.

[j] 9-Deoxo-9a-aza-9a-homoerythromycin A.

[k] (2*R*,3*S*,4*R*,5*R*,8*R*,10*R*,11*R*,12*S*,13*S*,14*R*)-13-[(2,6-Dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-2-propyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one dihydrate.

[l] (2*R*,3*S*,4*R*,5*R*,8*R*,10*R*,11*R*,12*S*,13*S*,14*R*)-13-[(2,6-Dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3-[*N*-(4-methylphenylsulfonyl)-*N*-methylamino]-3,4,6-trideoxy-β-D-*xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one.

[m] (2*R*,3*R*,4*S*,5*R*,8*R*,10*R*,11*R*,12*S*,13*S*,14*R*)-13-[(2,6-Dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-2-ethyl-4,10-dihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one.

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight containers. Store at controlled room temperature.

Change to read:

• **USP Reference Standards** ⟨11⟩

USP Azithromycin RS

USP Azithromycin Related Compound F RS

3'-(*N*-Demethyl)-3'-*N*-formylazithromycin;
(2*R*,3*S*,4*R*,5*R*,8*R*,10*R*,11*R*,12*S*,13*S*,14*R*)-13-[(2,6-Dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3-(*N*-methyl)formamido-3,4,6-trideoxy-β-D-*xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one.

$C_{38}H_{70}N_2O_{13}$ ▲762.98▲ (CN 1-Aug-2024)

USP *N*-Demethylazithromycin RS

(2*R*,3*S*,4*R*,5*R*,8*R*,10*R*,11*R*,12*S*,13*S*,14*R*)-13-[(2,6-Dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-methylamino-β-D-*xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one.

$C_{37}H_{70}N_2O_{12}$ ▲734.97▲ (CN 1-Aug-2024)

USP Desosaminylazithromycin RS

(2*R*,3*S*,4*R*,5*R*,8*R*,10*R*,11*R*,12*S*,13*S*,14*R*)-2-Ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-dimethylamino-β-D-*xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one.

$C_{30}H_{58}N_2O_9$ ▲590.80▲ (CN 1-Aug-2024)

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

Topic/Question	Contact	Expert Committee
AZITHROMYCIN TABLETS	Documentary Standards Support Associate Scientific Liaison.	NBDS2020 Non-botanical Dietary Supplements

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