Azithromycin Tablets

DEFINITION

Azithromycin Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of azithromycin \((C_{38}H_{72}N_{2}O_{12})\).

IDENTIFICATION

- 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

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

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

  Solution B: 1.7 mg/mL of monobasic ammonium phosphate. Adjust with ammonium hydroxide to a pH of 10.00 ± 0.05.

  Diluent A: Methanol, acetonitrile, and Solution B (7:6:7)

  Standard solution: Dissolve USP Azithromycin RS in Diluent A using about 75% of the final volume, sonicate to dissolve, dilute with Diluent A to volume, and mix to obtain a solution having a known concentration of 0.4 mg/mL of azithromycin.

  System suitability stock solution: 0.2 mg/mL of USP Azithromycin A RS in acetonitrile. [NOTE—Sonicate if necessary to dissolve.]

  System suitability solution: 0.02 mg/mL of azithromycin from the System suitability stock solution and 0.02 mg/mL of azithromycin from the Standard solution in Diluent A

  Sample stock solution: Weigh and finely powder NLT 20 Tablets. Transfer an equivalent to 667 mg of azithromycin to a 200-mL volumetric flask. Add 75 mL of Diluent A, and sonicate for NLT 15 min. Shake by mechanical means for NLT 15 min. Allow the solution to equilibrate to room temperature, dilute with Diluent A to volume, and mix.

  Sample solution: Prepare 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 A to obtain a

PERFORMANCE TESTS

- DISSOLUTION (711)
  - Medium: pH 6.0 phosphate buffer; 900 mL
  - Apparatus 2: 75 rpm
  - Time: 30 min
  - Solution A and Mobile phase: Proceed as directed in the Assay.
  - 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 having a known concentration of about \((L/1000)\) mg/mL, where L is the Tablet label claim, in mg.
  - Standard solution: Dilute the Standard stock solution with Diluent to obtain a solution having a known concentration of about \((L/2000)\) mg/mL, where L is the Tablet label claim, in mg.
  - 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 having a theoretical concentration of about (L/2000) mg/mL, where L is the Tablet label claim, in mg, 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 size:** 50 µL

**System suitability**

Sample: Standard solution

Suitability requirements:

- Column efficiency: NLT 1000 theoretical plates
- Tailing factor: NMT 2.0
- Relative standard deviation: NMT 2.0%

**Analysis**

Samples: Standard solution and Sample solution

Determine the amount of C38H72N2O12 dissolved:

\[ \text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{L} \right) \times V \times 100 \]

- \( r_U = \) peak response of azithromycin from the Sample solution
- \( r_S = \) peak response of azithromycin from the Standard solution
- \( C_S = \) concentration of the Standard solution (mg/mL)
- \( L = \) Tablet label claim (mg)
- \( V = \) volume of Medium, 900 mL

Tolerances: NLT 80% (Q) of the labeled amount of C38H72N2O12 is dissolved.

**Uniformity of Dosage Units (905):** Meet the requirements

**Impurities**

**Organic Impurities**

- **Procedure**
  
  [NOTE—Use low-actinic glassware. 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 C: 1.8 mg/mL of dibasic sodium phosphate in water

  Solution D: Acetonitrile and methanol (3:1)

  Mobile phase: See the gradient table below.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution C (%)</th>
<th>Solution D (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>25</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>30</td>
<td>45</td>
<td>55</td>
</tr>
<tr>
<td>40</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>55</td>
<td>35</td>
<td>65</td>
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<td>60</td>
<td>35</td>
<td>65</td>
</tr>
<tr>
<td>61</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>70</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

Diluent B: Methanol and Solution B (1:1)

Blank: Use Diluent A.

**Standard stock solution:** Use the Standard solution as directed in the Assay.

**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:** Weigh and finely powder NLT 20 Tablets. Transfer an equivalent to 1335 mg of azithromycin 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:** Centrifuge an aliquot of the Sample solution for 15 min. Transfer 3.0 mL of the supernatant to a 10-mL volumetric flask, dilute with Diluent B to volume, and mix to obtain a solution having a nominal concentration of about 4 mg/mL of azithromycin. Pass through a filter of 0.45-µm pore size.

**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:** 60°

**Flow rate:** 0.8 mL/min

**Autosampler temperature:** 4°

**Injection size:** 100 µL

**System suitability**

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

**Suitability requirements**

- Signal-to-noise ratio: NLT 10, Sensitivity solution
- Resolution: NLT 2.5 between azithromycin A and azithromycin, System suitability solution
- **Relative standard deviation:** NMT 10.0%, Standard solution

**Analysis**

Samples: Blank and Sample solution

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

\[ \text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times P \times F_1 \times \left( \frac{1}{F_2} \right) \times 100 \]

- \( r_U = \) 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)
- \( F_1 = \) unit conversion factor, 0.001 mg/µg
- \( F_2 = \) relative response factor (see Impurity Table 1)

**Acceptance criteria**

[NOTE—The reporting level for impurities is 0.1%. Disregard any peaks in the Sample solution that correspond to peaks in the Blank.]

**Individual impurities:** See Impurity Table 1.

**Total impurities:** See Impurity Table 1.

**Impurity Table 1**

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Relative Response Factor</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycin 3’-N-oxide</td>
<td>0.28</td>
<td>0.45</td>
<td>1.0</td>
</tr>
<tr>
<td>3’-(N,N’-Didemethyl)-3’-N-formylazithromycin</td>
<td>0.38</td>
<td>1.9</td>
<td>1.0</td>
</tr>
<tr>
<td>3’-(N,N’-Didemethyl) azithromycin (aminoazithromycin)</td>
<td>0.40</td>
<td>0.52</td>
<td>0.5</td>
</tr>
<tr>
<td>Desosaminylazithromycin</td>
<td>0.47</td>
<td>1.1</td>
<td>0.5</td>
</tr>
</tbody>
</table>

* 3’-(N-Demethyl)-3’-N-formylazithromycin.

* These compounds are synthetic process impurities of azithromycin.

They are controlled in the drug substance and are listed here for information only. The total impurities specification does not include these impurities.
Aztreonam, which may be anhydrous or hydrated, contains
INFRARED ABSORPTION
²-methyl-4-oxo-ZS.

2582 Azithromycin

Propanoic acid, 2-[(1-(2-amino-4-thiazolyl)-2-[(2-methyl-4-oxo-1-sulfo-3-azetidinyl)amino]-2-oxoethylidene]amino]oxy]-2-methylpropionic acid [78110-38-0].

DEFINITION
Aztreonam, which may be anhydrous or hydrated, contains
NLT 92.0% and NMT 105.0% of C₁₃H₁₇N₅O₈S₂, calculated on the anhydrous and solvent-free basis.

IDENTIFICATION
• INFRARED ABSORPTION (197K): If a difference appears in the IR spectra of the analyte and the standard, dissolve equal portions of the test specimen and the reference

standard in equal volumes of methanol. [NOTE—To achieve a complete dissolution, it is suggested to use about 25 mL of methanol for each 50 mg of material, and stir the mixture for 40 min at room temperature.] Evaporate the solutions to dryness under vacuum, and dry at 40° for 4 h under vacuum. Perform the test on the residues.

ASSAY
• PROCEDURE

[NOTE—Store the System suitability solution, Standard solution, and Sample solution at 5°, and protect from light to prevent isomerization of aztreonam Z-isomer to aztreonam E-isomer.]

Buffer: 6.8 mg/mL of monobasic potassium phosphate in water. Adjust with 1 M phosphoric acid to a pH of 3.0.

Mobile phase: Methanol and Buffer (1:4)

System suitability solution: 1 mg/mL of USP Aztreonam RS and 1 mg/mL of USP Aztreonam E-isomer RS in Mobile phase

Standard solution: 1 mg/mL of USP Aztreonam RS in Mobile phase

Sample solution: 1 mg/mL of Aztreonam in Mobile phase

Chromatographic system
(See Chromatography (621), System Suitability.)

Mode: LC
Detector: UV 254 nm
Column: 3.9-mm × 30-cm; 10-µm packing L1
Flow rate: 1.5 mL/min
Injection size: 10 µL

System suitability
Samples: System suitability solution and Standard solution

[NOTE—The relative retention times for aztreonam and aztreonam E-isomer are 1.0 and 1.8, respectively.]

Suitability requirements
Resolution: NLT 2.0 between aztreonam and aztreonam E-isomer, System suitability solution
Tailing factor: NMT 2 for aztreonam, System suitability solution

Relative standard deviation: NMT 2.0%, Standard solution

Analysis
Samples: Standard solution and Sample solution

Calculate the percentage of aztreonam (C₁₃H₁₇N₅O₈S₂) in the portion of Aztreonam taken:

\[
\text{Result} = \frac{r_U}{r_S} \times \frac{C_S}{C_U} \times P \times F \times 100
\]

\(r_U\) = peak response from the Sample solution
\(r_S\) = peak response from the Standard solution
\(C_S\) = concentration of USP Aztreonam RS in the Standard solution (mg/mL)
\(C_U\) = concentration of Aztreonam in the Sample solution (mg/mL)
\(P\) = potency of USP Aztreonam RS (µg/µg)
\(F\) = unit conversion factor, 0.001 mg/µg

Acceptance criteria: 92.0%–105.0% on the anhydrous and solvent-free basis

IMPURITIES
Inorganic Impurities
• RESIDUE ON IGNITION (281): NMT 0.1%, the charred residue being moistened with 2 mL of nitric acid and 5 drops of sulfuric acid

• HEAVY METALS, Method II (231): NMT 30 ppm

Organic Impurities
• PROCEDURE

[NOTE—Store the System suitability solution, Standard solution, and Sample solution at 5°, and protect from light to