Metolazone Tablets

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Expert Committee        Small Molecules 2

In accordance with the Rules and Procedures of the Council of Experts, the Small Molecules 2 Expert Committee has revised the Metolazone Tablets monograph. The purpose of this revision is to add **Dissolution Test 3** to accommodate FDA-approved drug products with different dissolution conditions and/or tolerances than the existing dissolution test(s).

- **Dissolution Test 3** was validated using a Symmetry C8 brand of column with L7 packing. The typical retention time for metolazone is about 8.2 min.

The Metolazone Tablets Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Claire Chisolm, Senior Scientist II (301-230-3215 or cnc@usp.org).
Metolazone Tablets

DEFINITION
Metolazone Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of metolazone (C_{16}H_{16}ClN_{3}O_{3}S).

IDENTIFICATION
• A. SPECTROSCOPIC IDENTIFICATION TESTS (197), Ultraviolet-Visible Spectroscopy: 197U
  Sample solution: Dilute 3 mL of the Sample solution in the Assay with methanol to 25 mL.
  Acceptance criteria: Meet the requirements

ASSAY
• PROCEDURE
  [NOTE—Use low-actinic glassware throughout the Assay.]
  Buffer: 1.38 g of monobasic potassium phosphate monohydrate in 900 mL of water. Adjust with phosphoric acid to a pH of 3.0, and dilute with water to 1000 mL.
  Mobile phase: Methanol, acetonitrile, and Buffer (28:7:65)
  Standard stock solution: 0.25 mg/mL of USP Metolazone RS in methanol
  Standard solution: 5 µg/mL of USP Metolazone RS in Mobile phase from Standard stock solution
  Sample stock solution: Transfer 10 Tablets to a 200-mL volumetric flask. Add 3 mL of water and 100 mL of methanol, and sonicate for 30 min. If disintegration is not complete, sonicate for an additional 30 min. Shake by mechanical means for 30 min. Dilute with methanol to volume.
  Sample solution: Nominally equivalent to 5 µg/mL of metolazone in Mobile phase from the Sample stock solution
  Chromatographic system
  (See Chromatography (621), System Suitability.)
  Mode: LC
  Detector: UV 235 nm
  Column: 3.9-mm × 15-cm; packing L1
  Flow rate: 1.1 mL/min
  Injection volume: 100 µL
  System suitability
  Sample: Standard solution
  Suitability requirements
  Relative standard deviation: NMT 2.0%
  Analysis
  Samples: Standard solution and Sample solution
  Calculate the percentage of the labeled amount of metolazone (C_{16}H_{16}ClN_{3}O_{3}S) in the portion of Tablets taken:

\[
\text{Result} = \left( \frac{r_d}{r_S} \right) \times \left( \frac{C_d}{C_U} \right) \times 100
\]
\[ r_U = \text{peak response from the Sample solution} \]
\[ r_S = \text{peak response from the Standard solution} \]
\[ C_S = \text{concentration of USP Metolazone RS in the Standard solution (µg/mL)} \]
\[ C_U = \text{nominal concentration of the Sample solution (µg/mL)} \]

**Acceptance criteria:** 90.0%–110.0%

**PERFORMANCE TESTS**

**Change to read:**

- **Dissolution** (711)

[Note—Protect all solutions from light.]

Test 1

**Medium:** 2% w/v sodium lauryl sulfate in 0.05 M monobasic sodium phosphate. Heat the mixture to about 37° to dissolve the sodium lauryl sulfate, and adjust with 10 N sodium hydroxide to a pH of 7.5; 900 mL, deaerated

**Apparatus 2:** 75 rpm

**Time:** 120 min

**Buffer:** 0.05 M monobasic potassium phosphate. Adjust with phosphoric acid to a pH of 3.00.

**Mobile phase:** Acetonitrile, methanol, and Buffer (270:50:680)

**Standard stock solution:** 0.28 mg/mL of USP Metolazone RS. Initially add methanol to 2% of the volume of the flask. Sonicate to dissolve, and dilute with Medium to volume.

**Standard solution:** \((L/900)\) mg/mL in Medium from the Standard stock solution, 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.

**Chromatographic system**

(See Chromatography (621), System Suitability.)

**Mode:** LC

**Detector:** UV 254 nm

**Column:** 4.6-mm × 15-cm; 5-µm packing L7

**Column temperature:** 30°

**Flow rate:** 1.2 mL/min

**Injection volume:** 50 µL

**System suitability**

**Sample:** Standard solution

**Suitability requirements**

- **Tailing factor:** NMT 2.0
- **Column efficiency:** NLT 2000 theoretical plates
- **Relative standard deviation:** NMT 2.0%

**Analysis**

**Samples:** Standard solution and Sample solution

Calculate the percentage of the labeled amount of metolazone \((C_{16}H_{16}ClN_{3}O_{3}S)\) dissolved:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{L} \right) \times V \times 100
\]
\[ r_U = \text{peak response from the Sample solution} \]
\[ r_S = \text{peak response from the Standard solution} \]
\[ C_S = \text{concentration of the Standard solution (mg/mL)} \]
\[ L = \text{label claim (mg/Tablet)} \]
\[ V = \text{volume of Medium, 900 mL} \]

**Tolerances:** NLT 75% (Q) of the labeled amount of metolazone \((\text{C}_{16}\text{H}_{16}\text{ClN}_3\text{O}_3\text{S})\) is dissolved.

**Test 2:** If the product complies with this test, the labeling indicates that the product meets USP Dissolution Test 2.

**Medium:** Prepare a solution of 0.05 M dibasic sodium phosphate in a suitable flask, and adjust with phosphoric acid to a pH of 7.5. Dissolve a suitable amount of sodium lauryl sulfate to obtain a 20-g/L solution; 900 mL

**Apparatus 2:** 75 rpm

**Time:** 120 min

**Standard stock solution:** 0.275 mg/mL of USP Metolazone RS. Initially add methanol to 10% of the volume of the flask. Sonicate to dissolve, and dilute with Medium to volume.

**Standard solution:** \((L/900)\) mg/mL in Medium from the Standard stock solution, 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.

**Detector:** UV 238 nm

**Path length:** 1 cm

**Analysis**

**Samples:** Standard solution and Sample solution

Calculate the percentage of the labeled amount of metolazone \((\text{C}_{16}\text{H}_{16}\text{ClN}_3\text{O}_3\text{S})\) dissolved:

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

\[ A_U = \text{absorbance of the Sample solution} \]
\[ A_S = \text{absorbance of the Standard solution} \]
\[ C_S = \text{concentration of the Standard solution (mg/mL)} \]
\[ L = \text{label claim (mg/Tablet)} \]
\[ V = \text{volume of Medium, 900 mL} \]

**Tolerances:** NLT 75% (Q) of the labeled amount of metolazone \((\text{C}_{16}\text{H}_{16}\text{ClN}_3\text{O}_3\text{S})\) is dissolved.

**Test 3:** If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 3.

**Medium:** 0.05 M phosphate buffer pH 7.5 with 2% sodium lauryl sulfate. (Dissolve 6.9 g of monobasic sodium phosphate monohydrate in 1000 mL of water. Adjust with 10 N sodium hydroxide solution to a pH of 7.5. Dissolve 20 g of sodium lauryl sulfate in the solution. Sonicate for defoaming and deaeration.); 900 mL

**Apparatus 2:** 75 rpm

**Times:** 30 and 90 min

**Buffer:** Dissolve 6.8 g of monobasic potassium phosphate in 1000 mL of water. Adjust with diluted phosphoric acid to a pH of 3.0.

**Solution A:** Acetonitrile, methanol, and Buffer (27:5:68)
Solution B: Methanol and water (80:20)

Mobile phase: See Table 1.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>12.0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>12.1</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>15.0</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>15.1</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>20.0</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>

Standard stock solution: 0.28 mg/mL of USP Metolazone RS prepared as follows. Transfer a suitable amount of USP Metolazone RS into a suitable volumetric flask. Add methanol to 2% of the volume of the flask. Sonicate to dissolve, and dilute with Medium to volume.

Standard solution: \((L/900)\) mg/mL of USP Metolazone RS in Medium from the Standard stock solution, 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. Replace the portion withdrawn with an equal volume of Medium at the specified time point.

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

Mode: LC
Detector: UV 254 nm
Column: 4.6-mm × 15-cm; 5-μm packing L7
Column temperature: 30°
Flow rate: 1.2 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 concentration \((C_i)\) of metolazone \((C_{16}H_{16}ClN_3O_3S)\) in the sample withdrawn from the vessel at each time point \((i)\): 

\[
\text{Result}_i = \left(\frac{r_i}{r_S}\right) \times C_S
\]
$r_U$ = peak response of metolazone from the Sample solution

$r_S$ = peak response of metolazone from the Standard solution

$C_S$ = concentration of USP Metolazone RS in the Standard solution (mg/mL)

Calculate the percentage of the labeled amount of metolazone ($C_{16}H_{16}ClN_3O_3S$) dissolved at each time point ($i$):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$

$$\text{Result}_2 = [(C_2 \times V) + (C_1 \times V_S)] \times (1/L) \times 100$$

$C_i$ = concentration of metolazone in the portion of sample withdrawn at the specified time point (mg/mL)

$V$ = volume of Medium, 900 mL

$L$ = label claim (mg/Tablet)

$V_S$ = volume of the Sample solution withdrawn at each time point, 10 mL

**Tolerances:** See Table 2

<table>
<thead>
<tr>
<th>Time Point ($i$)</th>
<th>Time (min)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>NLT 50</td>
</tr>
<tr>
<td>2</td>
<td>90</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of metolazone ($C_{16}H_{16}ClN_3O_3S$) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2,▲ (RB 15-Apr-2022)

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

**ADDITIONAL REQUIREMENTS**

- **Packaging and Storage:** Preserve in tight, light-resistant containers, and store below 30°.

- **Labeling:** When more than one test for Dissolution is given, the Labeling section states the test for Dissolution used only if Test 1 is not used.

- **USP Reference Standards** (11).
  USP Metolazone RS

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**Page Information:**

Not Applicable

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