Metolazone Tablets

Type of Posting	Notice of Intent to Revise
Posting Date	18-Dec-2020
Targeted Official Date	To Be Determined, Revision Bulletin
Expert Committee	Small Molecules 2

In accordance with the Rules and Procedures of the Council of Experts and the Pending Monograph Guideline, this is to provide notice that the Small Molecules 2 Expert Committee intends to revise the Metolazone Tablets monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to add *Dissolution Test 3* to accommodate drug products with different dissolution conditions and tolerances than the existing dissolution tests.

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

The proposed revision is contingent on FDA approval of a product that meets the proposed monograph specifications. The proposed revision will be published as a Revision Bulletin and an official date will be assigned to coincide as closely as possible with the FDA approval of the associated product.

See below for additional information about the proposed text.[1]

Should you have any questions, please contact Donald Min, Senior Scientific Liaison to the Small Molecules 2 Expert Committee (301-230-7457 or ddm@usp.org).

[1] This text is not the official version of a *USP–NF* monograph and may not reflect the full and accurate contents of the currently official monograph. Please refer to the current edition of the *USP–NF* for official text.

USP provides this text to indicate changes that we anticipate will be made official once the product subject to this proposed revision under the Pending Monograph Program receives FDA approval. Once FDA approval is granted for the associated revision request, a Revision Bulletin will be posted that will include the changes indicated herein, as well as any changes indicated in the product's final approval, combined with the text of the monograph as effective on the date of approval. Any revisions made to a monograph under the Pending Monograph Program that are posted without prior publication for comment in the *Pharmacopeial Forum* must also meet the requirements outlined in the USP Guideline on Use of Accelerated Processes for Revisions to the *USP–NF*.

Metolazone Tablets

DEFINITION

Metolazone Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of metolazone ($C_{16}H_{16}ClN_3O_3S$).

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 ($C_{16}H_{16}ClN_3O_3S$) in the portion of Tablets taken:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Metolazone RS in the *Standard solution* (µg/mL)

C_U = 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 ($C_{16}H_{16}ClN_3O_3S$) dissolved:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of the *Standard solution* (mg/mL)

L = label claim (mg/Tablet)

V = volume of *Medium*, 900 mL

Tolerances: NLT 75% (*Q*) of the labeled amount of metolazone ($C_{16}H_{16}ClN_3O_3S$) 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 ($C_{16}H_{16}ClN_3O_3S$) dissolved:

$$\text{Result} = (A_U/A_S) \times (C_S/L) \times V \times 100$$

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

C_S = concentration of the *Standard solution* (mg/mL)

L = label claim (mg/Tablet)

V = volume of *Medium*, 900 mL

Tolerances: NLT 75% (Q) of the labeled amount of metolazone ($C_{16}H_{16}ClN_3O_3S$) 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 1

Time (min)	Solution A (%)	Solution B (%)
0.0	100	0
12.0	100	0
12.1	0	100

Time (min)	Solution A (%)	Solution B (%)
15.0	0	100
15.1	100	0
20.0	100	0

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):

$$\text{Result}_i = (r_U/r_S) \times C_S$$

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 2

Time Point (*i*)	Time (min)	Amount Dissolved (%)
1	30	NLT 50
2	90	NLT 80

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*. ▲ (TBD)

- **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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