Methazolamide Tablets

Type of Posting	Notice of Intent to Revise
Posting Date	28-Oct-2022
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 Methazolamide Tablets monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to add *Dissolution Test 2* to the monograph to accommodate FDA-approved drug products with different tolerances than the existing dissolution test(s). Labeling information also has been incorporated to support the inclusion of *Dissolution Test 2*.

Additional editorial changes were made to update the monograph to current *USP* style.

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 Yanyin Yang, Senior Scientist III (301-692-3623 or yanyin.yang@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*.

Notice of Intent to Revise
Official: To Be Determined

Methazolamide Tablets

DEFINITION

Methazolamide Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of methazolamide ($C_5H_8N_4O_3S_2$).

IDENTIFICATION

- **A.**

  Sample: Transfer an amount of 250 mg of methazolamide, from finely powdered Tablets, to a suitable container. Extract with 50 mL of acetone. Filter and add solvent hexane until a heavy white precipitate is formed. Collect the solid on a filter and dry.

  Acceptance criteria: The IR absorption spectrum of a potassium bromide dispersion of the methazolamide so obtained exhibits maxima only at the same wavelengths as that of a similar preparation of USP Methazolamide RS.

- **B.**

  Sample solution: Dissolve 100 mg of the dried *Sample* obtained in *Identification A* in 5 mL of 1 N sodium hydroxide.

  Analysis: To the *Sample solution* add 5 mL of a mixture of 1 g of hydroxylamine hydrochloride and 500 mg of cupric sulfate in 100 mL of water. Heat the solution on a steam bath for 15 min.

  Acceptance criteria: The solution turns dark amber, then a black precipitate is formed.

- **C.** 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: Transfer 16.8 mL of dibutylamine to a beaker containing 70 mL of water. Adjust with phosphoric acid to a pH of 2.5, and dilute with water to 100 mL.

  Mobile phase: Methanol, *Solution A*, and water (15:6:375).

  Diluent: Dissolve 2.99 g of sodium acetate and 1.66 mL of glacial acetic acid in water. Dilute with water to 1000 mL. Adjust, if necessary, with glacial acetic acid or sodium hydroxide to a pH of 4.5.

  Standard stock solution: 0.5 mg/mL of USP Methazolamide RS in methanol

  Standard solution: 50 µg/mL of USP Methazolamide RS from the *Standard stock solution* in *Diluent*.

  Sample stock solution: Nominally 200 µg/mL of methazolamide from Tablets, prepared as follows. Finely powder NLT 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to 50 mg of methazolamide, to a 250-mL volumetric flask. Add 65 mL of *Diluent*, and sonicate to dissolve. Add 65 mL of methanol, and sonicate again until dissolved. Dilute with *Diluent* to volume, and filter.

  Sample solution: Nominally 50 µg/mL of methazolamide from the *Sample stock solution* in *Diluent*.

  Chromatographic system

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

  Mode: LC

  Detector: UV 252 nm

Column: 8-mm × 10-cm; packing L10

Flow rate: 2 mL/min

Injection volume: 25 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5

Relative standard deviation: NMT 3.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of methazolamide ($C_5H_8N_4O_3S_2$) in the portion of Tablets taken:

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

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

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

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

C_U = nominal concentration of methazolamide in the *Sample solution* (µg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- **Dissolution** ⟨711⟩

▲**Test 1**▲ (TBD)

Medium: pH 4.5 acetate buffer (2.99 g/L of sodium acetate and 1.66 mL/L of glacial acetic acid in water), 900 mL

Apparatus 2: 75 rpm

Time: 45 min

Standard solution: A known concentration of USP Methazolamide RS in *Medium*

Sample solution: Pass a portion of the solution under test through a suitable filter. Suitably dilute with *Medium* to obtain a concentration similar to that of the *Standard solution*.

Instrumental conditions

Mode: UV

Analytical wavelength: 252 nm

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of methazolamide ($C_5H_8N_4O_3S_2$) dissolved.

Tolerances: NLT 75% (*Q*) of the labeled amount of methazolamide ($C_5H_8N_4O_3S_2$) is dissolved.

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

Medium: pH 4.5 acetate buffer (13.61 g/L of sodium acetate and 8 mL/L of glacial acetic acid in water), 900 mL, deaerated

Apparatus 2: 100 rpm, with sinkers (See *Dissolution* ⟨711⟩, *Figure 2a*)

Time: 45 min

Standard stock solution: 0.28 mg/mL of USP Methazolamide RS prepared as follows. Weigh and transfer suitable amount of USP Methazolamide RS into a suitable volumetric flask. Add methanol to 10% of the flask volume and sonicate with intermittent shaking, in a water bath maintained at 20°–25°. Cool to room temperature and dilute with *Medium* to volume.

Standard solution: 0.028 mg/mL of USP Methazolamide RS from the *Standard stock solution* in *Medium*

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size, discarding the first 3 mL of the filtrate. Suitably dilute with *Medium* to obtain a concentration similar to that of the *Standard solution*.

Instrumental conditions

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

Mode: UV

Analytical wavelength: 252 nm

Blank: *Medium*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of methazolamide ($C_5H_8N_4O_3S_2$) dissolved.

$$\text{Result} = (A_U/A_S) \times C_S \times V \times D \times (1/L) \times 100$$

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

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

V = volume of *Medium*, 900 mL

D = dilution factor of the *Sample solution*, as needed

L = label claim (mg/Tablet)

Tolerances: NLT 75% (Q) of the labeled amount of methazolamide ($C_5H_8N_4O_3S_2$) is dissolved. ▲ (TBD)

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

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in well-closed containers.

Add the following:

▲● **Labeling:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used. ▲ (TBD)

- **USP Reference Standards** ⟨11⟩

  USP Methazolamide RS

Page Information:

Not Applicable

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