Mesalazine Delayed-Release Tablets

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In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Chemical Medicines Monographs 2 Expert Committee has revised the Mesalazine Delayed-Release Tablets monograph. The purpose for the revision is to add Dissolution Test 2 to accommodate FDA-approved drug products with different dissolution conditions and tolerances than the existing dissolution test. Labeling information has been incorporated to support the inclusion of Dissolution Test 2.

The Mesalazine Delayed-Release Tablets Revision Bulletin supersedes the currently official monograph. Should you have any questions, please contact Yanyin Yang, Associate Scientific Liaison (301-692-3623 or yanyin.yang@usp.org).
Mesalamine Delayed-Release Tablets

**DEFINITION**
Mesalamine Delayed-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of mesalamine (C₇H₈NO₃).

**IDENTIFICATION**

Change to read:

- **A. SPECTROSCOPIC IDENTIFICATION TESTS** (197), Infrared Spectroscopy: 197K (CN 1-May-2020)

**Sample solution:** To about 50 mL of water add a quantity of finely powdered Tablets, nominally equivalent to about 800 mg of mesalamine. Boil the mixture for about 5 min, with constant stirring. Filter the hot solution, and allow the filtrate to cool. Collect the precipitated crystals, and dry at about 110°.

**Acceptance criteria:** Meet the requirements

**ASSAY**

- **PROCEDURE**

**Mobile phase:** Dissolve 4.3 g of sodium 1-octanesulfonate in 1 L of water. Adjust with phosphoric acid to a pH of 2.15, pass through a filter of a 0.45-µm or finer pore size, and degas.

**System suitability stock solution:** Transfer about 20 mg each of 3-aminosalicylic acid and USP Salicylic Acid RS to a 200-mL volumetric flask. Dissolve in 50 mL of 1 N hydrochloric acid, sonicate to dissolve, dilute with water to volume, and mix.

**System suitability solution:** Transfer about 25 mg of USP Mesalamine RS to a 25-mL volumetric flask. Dissolve in 5 mL of 0.25 N hydrochloric acid, sonicate to dissolve, dilute with water to volume, and mix.

**Standard solution:** Transfer 10.0 mL of the Standard stock solution and 5.0 mL of the System suitability solution to a 50-mL volumetric flask. Dilute with water to volume, and mix.

**Sample solution:** Pipet a 25.0-mL aliquot of the Sample solution, obtained as directed in Organic Impurities, into a 100-mL volumetric flask. Dilute with water to volume, and pass through a filter of 0.5-µm or finer pore size.

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

**Mode:** LC

**Detector:** UV 230 nm

**Columns**

- **Precolumns:** Two 4.6-mm x 3.0-cm; each containing 10-µm packing L1 and located between the pump and the injector
- **Analytical:** 4.6-mm x 3.3-cm; 3-µm base-deactivated packing L1

**Flow rate:** 2 mL/min

**Injection volume:** 20 µL

**System suitability**

- **Sample:** Standard solution

**Suitability requirements**

- **Resolution:** NLT 2 between mesalamine and salicylic acid or 3-aminosalicylic acid
- **Tailing factor:** NMT 2
- **Relative standard deviation:** NMT 2.0%

**Analysis**

- **Samples:** Standard solution and Sample solution

Calculate the percentage of the labeled amount of mesalamine (C₇H₈NO₃) in the portion of Tablets taken:

\[
\text{Result} = \left( \frac{r_s}{r_0} \right) \times \left( \frac{C_s}{C_u} \right) \times 100
\]

- **r₀** = peak response of mesalamine from the Sample solution
- **rₕ** = peak response of mesalamine from the Standard solution
- **Cₙ** = concentration of USP Mesalamine RS in the Standard solution (mg/mL)
- **C_u** = nominal concentration of mesalamine in the Sample solution (mg/mL)

**Acceptance criteria:** 90.0%–110.0%

**PERFORMANCE TESTS**

Change to read:

- **Dissolution** (711)

**Test 1** (88-1-May-2020)

**Solution A:** Transfer about 43.35 g of monobasic potassium phosphate and 1.65 g of sodium hydroxide to a 2-L volumetric flask. Dissolve in and dilute with water to volume, and mix. Adjust with 1 N sodium hydroxide or phosphoric acid to a pH of 6.0, and mix.

**Solution B:** Transfer 133.6 g of sodium hydroxide to a 2-L volumetric flask, dissolve in and dilute with water to volume, and mix.

**Medium**

- **Acid stage:** 500 mL of 0.1 N hydrochloric acid
- **Buffer stages:** 900 mL of Solution A

**Apparatus 2**

- **Acid stage:** 100 rpm
- **Buffer stage 1:** 100 rpm
- **Buffer stage 2:** 50 rpm

**Times**

- **Acid stage:** 2 h
- **Buffer stage 1:** 1 h
- **Buffer stage 2:** 90 min

**Acid stage**

After 2 h of operation, withdraw an aliquot of the fluid, discard the remaining solution, and retain the Tablets in proper order so that each will be returned later to its respective vessel. Blot the Tablets with a paper towel to dry, and proceed immediately as directed in Buffer stage 1.

**Standard solution:** A known concentration of USP Mesalamine RS in Medium, equivalent to about 1% of the labeled amount of mesalamine (C₇H₈NO₃)

**Sample solution:** Filter portions of the solution under test, and suitably dilute with Medium, if necessary.

**Analysis**

Calculate the percentage of the labeled amount of mesalamine (C₇H₈NO₃) dissolved by comparing the UV maximum absorbance at about 302 nm of the Sample solution with that of the Standard solution.

**Tolerances:** See Table 1. Continue testing through all levels unless the results conform at an earlier level.

**Buffer stage 1**

- **NOTE—Use Solution A that has been equilibrated to a temperature of 37 ± 0.5°.**

Transfer Solution A to each of the dissolution vessels, and place each Tablet from the Acid stage into its respective vessel. After 1 h, remove a 50-mL aliquot, and proceed immediately as directed in Buffer stage 2.

**Standard solution:** A known concentration of USP Mesalamine RS in Medium, equivalent to about 1% of the labeled amount of mesalamine (C₇H₈NO₃)

**Sample solution:** Filter portions of the solution under test, and suitably dilute with Medium, if necessary.

**Analysis**

Calculate the percentage of the labeled amount of mesalamine (C₇H₈NO₃) dissolved by comparing the
Buffer stage 2
Add 50 mL of Solution B to each dissolution vessel to adjust to a pH of 7.2, and continue the run.

Standard solution: A known concentration of USP Mesalamine RS in Medium
Sample solution: Filter portions of the solution under test, and suitably dilute with Medium, if necessary.
Analysis: Calculate the percentage of the labeled amount of mesalamine (C₇H₇NO₃) dissolved by comparing the UV maximum absorbance at about 332 nm of the Sample solution with that of the Standard solution.
Tolerances: NLT 80% (Q) of the labeled amount of mesalamine (C₇H₇NO₃) is dissolved. The requirements are met if the quantities dissolved from the product conform to Dissolution (711), Acceptance Table 4. Continue testing through all levels unless the results conform at an earlier level.

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

Solution A: pH 6.4 phosphate buffer (21.7 g/L of monobasic potassium phosphate and 0.8 g/L of sodium hydroxide in water, adjusted with 5 N sodium hydroxide or phosphoric acid to a pH of 6.4)
Solution B: 3.3 N sodium hydroxide (136 g/L of sodium hydroxide in water)
Medium
Acid stage: 750 mL of 0.1 N hydrochloric acid
Buffer stage 1: 950 mL of Solution A
Buffer stage 2: 960 mL of pH 7.2 phosphate buffer
Apparatus 2: 100 rpm
Times
Acid stage: 2 h
Buffer stage 1: 1 h
Buffer stage 2: 1, 2, and 6 h

Acid stage
After 2 h of operation, withdraw a portion of the solution under test, discard the remaining solution, and retain the Tablets in proper order so that each will be returned later to its respective vessel. Blot the Tablets with a paper towel to dry and proceed immediately as directed in Buffer stage 1.

Standard solution: 0.016 mg/mL of USP Mesalamine RS in Medium. Sonicate to dissolve.
Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-μm pore size and discard the first few milliliters.

Instrumental conditions (See Ultraviolet-Visible Spectroscopy (857).)
Mode: UV
Analytical wavelength: 302 nm
Blank: Medium
Analysis
Samples: Standard solution and Sample solution

Calculates the percentage of the labeled amount of mesalamine (C₇H₇NO₃) dissolved at each time point i:

\[
\text{Result} = \left( \frac{A_i}{A_0} \right) \times C_i \times V \times (1/L) \times 100
\]

\[
A_i = \text{absorbance of the Sample solution}
A_0 = \text{absorbance of the Standard solution}
C_i = \text{concentration of USP Mesalamine RS in the Standard solution (mg/mL)}
V = \text{volume of Medium, 750 mL}
L = \text{label claim of mesalamine (mg/Tablet)}
\]

Tolerances: NMT 1% of the labeled amount of mesalamine (C₇H₇NO₃) is dissolved.

Buffer stage 1
To adjust the pH of 940 mL of Solution A to pH 7.2, transfer 20 mL of Solution B into each dissolution vessel from Buffer stage 1 and start the dissolution immediately.
At the end of the specified time point, withdraw 10 mL of the solution under test from each dissolution vessel and replace with 10 mL of Medium for Buffer stage 2.

Standard solution: 0.0315 mg/mL of USP Mesalamine RS in Medium. Sonicate to dissolve.
Sample solution: Dilute 2.5 mL of the withdrawn solution under test with Medium to 100 mL. Pass through a suitable filter of 0.45-μm pore size and discard the first few milliliters.

Instrumental conditions (See Ultraviolet-Visible Spectroscopy (857).)
Mode: UV
Analytical wavelength: 330 nm
Blank: Medium
Analysis
Calculate the concentration (C) of mesalamine (C₇H₇NO₃) in the sample withdrawn from the vessel at each time point (i):

\[
\text{Result} = \left( \frac{A_i}{A_0} \right) \times C_i \times D
\]

\[
A_i = \text{absorbance of the Sample solution}
A_0 = \text{absorbance of the Standard solution}
C_i = \text{concentration of USP Mesalamine RS in the Standard solution (mg/mL)}
D = \text{dilution factor of the Sample solution, 40}
\]
Result 1 = $C_i \times V \times (1/L) \times 100$

Result 2 = $[(C_i \times V) + (C_i \times V_s)] \times (1/L) \times 100$

Result 3 = $[(C_i \times V) + (C_i + C_i) \times V_s] \times (1/L) \times 100$

$C_i$ = concentration of mesalamine in the portion of sample withdrawn at time point $i$ (mg/mL)
$V$ = volume of the Medium, 960 mL
$L$ = label claim (mg/Tablet)
$V_s$ = volume of the solution under test withdrawn at each time point (i) during Buffer stage 2, 10 mL

Tolerances: See Table 2.

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<td>Time Point (i)</td>
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• Uniformity of Dosage Units (905), Weight Variation: Meet the requirements

Impurities

• Organic Impurities
  Sample solution: Transfer a portion nominally equivalent to about 400 mg of mesalamine, from NLT 20 finely powdered Tablets, to a 500-mL volumetric flask. Add 50 mL of 1 N hydrochloric acid, and sonicate to dissolve. Shake by mechanical means for 10 min, dilute with water to volume, mix, and pass through a filter of 0.5-µm or finer pore size. [Note—Use an aliquot of this solution for the preparation of the Sample solution in the Assay.]

Analysis

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

Result = $\left(\frac{r_U}{r_T}\right) \times 100$

$r_U$ = peak response for each impurity
$r_T$ = sum of all the peak responses

Acceptance criteria

Individual impurity: The largest secondary peak is NMT 1.0% of the total area.
Any other individual impurity: NMT 0.5%
Total impurities: NMT 2.0%

Additional Requirements

• Packaging and Storage: Preserve in tight 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. (RB 1-May-2020)

• USP Reference Standards (11)
  USP Mesalamine RS
  USP Salicylic Acid RS