Mesalamine Delayed-Release Tablets

Type of Posting	Revision Bulletin
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Expert Committee	Chemical Medicines Monographs 2
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Chemical Medicines Monographs 2 Expert Committee has revised the Mesalamine 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 Mesalamine 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 ($C_7H_7NO_3$).

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 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: 0.01 mg/mL each of 3-aminosalicylic acid and salicylic acid in water from the *System suitability stock solution*

Standard stock 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, mix, and pass through a filter of 0.5-µm or finer pore size.

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 × 3.0-cm; each containing 10-µm packing L1 and located between the pump and the injector

Analytical: 4.6-mm × 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 ($C_7H_7NO_3$) in the portion of Tablets taken:

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

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

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

C_S = 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▲ (RB 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 ($C_7H_7NO_3$)

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 ($C_7H_7NO_3$) 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 ($C_7H_7NO_3$)

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 ($C_7H_7NO_3$) dissolved by comparing the

UV maximum absorbance at about 330 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.

Table 1

Level	Number Tested	Acceptance Criteria
L_1	6	No individual value exceeds 1% dissolved.
L_2	6	Average of the 12 units ($L_1 + L_2$) is NMT 1% dissolved, and no individual unit is greater than 10% dissolved.
L_3	12	Average of the 24 units ($L_1 + L_2 + L_3$) is NMT 1% dissolved, and NMT one individual unit is greater than 10% dissolved.

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 ($C_7H_7NO_3$) 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 ($C_7H_7NO_3$) 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*
Calculate the percentage of the labeled amount of mesalamine ($C_7H_7NO_3$) dissolved:

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

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of USP Mesalamine RS in the *Standard solution* (mg/mL)
V = volume of *Medium*, 750 mL
L = label claim of mesalamine (mg/Tablet)

Tolerances: NMT 1% of the labeled amount of mesalamine ($C_7H_7NO_3$) is dissolved.
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, withdraw a 10-mL aliquot and proceed immediately as directed in *Buffer stage 2*.
Standard solution: 0.0125 mg/mL of USP Mesalamine RS in *Medium*. Sonicate to dissolve.
Sample solution: Pass a portion of the withdrawn 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: 330 nm
Blank: *Medium*
Analysis: Proceed as directed in the *Analysis* at *Acid stage*, using the *Medium* for *Buffer stage 1*.
Tolerances: NMT 1% of the labeled amount of mesalamine ($C_7H_7NO_3$) is dissolved.
Buffer stage 2
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: 332 nm
Blank: *Medium*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the concentration (C_i) of mesalamine ($C_7H_7NO_3$) in the sample withdrawn from the vessel at each time point (i):

$$\text{Result} = (A_U/A_S) \times C_S \times D$$

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of USP Mesalamine RS in the *Standard solution* (mg/mL)
D = dilution factor of the *Sample solution*, 40

Calculate the percentage of the labeled amount of mesalamine ($C_7H_7NO_3$) dissolved at each time point i:

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$
$$\text{Result}_2 = [(C_2 \times V) + (C_1 \times V_S)] \times (1/L) \times 100$$
$$\text{Result}_3 = \{(C_3 \times V) + [(C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

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*.

Table 2

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	1	NMT 35
2	2	35–60
3	6	NLT 80▲ (RB 1-May-2020)

• **Uniformity of Dosage Units** ⟨905⟩**,** *Weight Variation***:** Meet the requirements

IMPURITIES

• **Organic Impurities**

Mobile phase, System suitability stock solution, System suitability solution, Standard stock solution, Standard solution, Chromatographic system, and **System suitability:** Proceed as directed in the *Assay*.

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:

$$\text{Result} = (r_U/r_T) \times 100$$

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