Mesalamine Extended-Release Capsules

Type of Posting	Revision Bulletin
Posting Date	29–May–2020
Official Date	01–Jun–2020
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 Extended-Release Capsules monograph. The purpose for the revision is to add *Dissolution Test 2* to accommodate FDA-approved drug products with different dissolution conditions and/or tolerances than the existing dissolution test. A *Labeling* section has also been added.

- *Dissolution Test 2* in *Buffer stage* was validated using a Hypersil ODS brand of column with L1 packing. The typical retention time for mesalamine is about 3 min.

The Mesalamine Extended-Release Capsules Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Hui-Zhi (Hillary) Cai, Senior Scientific Liaison (301-230-3379 or hzc@usp.org).

Revision Bulletin
Official: June 1, 2020

Mesalamine Extended-Release Capsules

DEFINITION

Mesalamine Extended-Release Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of mesalamine ($C_7H_7NO_3$).

IDENTIFICATION

- **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197K

Sample: Use the powdered, undried Capsule contents.

Analysis: Record the spectra in the range between 2000 cm^{-1} and 1240 cm^{-1}.

Acceptance criteria: Meet the requirements

ASSAY

- **Procedure**

Buffer: Dissolve 6.8 g of monobasic potassium phosphate and 1.65 g of sodium hydroxide in 800 mL of water. Adjust with 1 N sodium hydroxide to a pH of 7.5, dilute with water to 1000 mL, and mix.

Solution A: Dissolve 3.4 g of tetrabutylammonium hydrogen sulfate and 1.4 g of sodium acetate trihydrate in 1000 mL of water. Adjust with 1 N sodium hydroxide to a pH of 6.6. Add 200 mL of acetonitrile, mix, and pass through a filter of 0.5-µm or finer pore size. [Note—Increasing the proportion of acetonitrile decreases the retention times. Prepare fresh daily.]

Solution B: Dissolve 4.6 g of tetrabutylammonium hydrogen sulfate and 1.9 g of sodium acetate trihydrate in 1000 mL of water, and adjust with 1 N sodium hydroxide to a pH of 6.6. Add 650 mL of acetonitrile, mix, and pass through a filter of 0.5-µm or finer pore size. [Note—Prepare fresh daily.]

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
5	100	0
7	0	100
15	0	100
17	100	0
20	100	0

Internal standard solution: 35 mg/mL of sodium benzoate in *Buffer*

Standard solution: Transfer about 50 mg of USP Mesalamine RS to a 100-mL volumetric flask. Add 4.0 mL of the *Internal standard solution*, dilute with *Buffer* to volume, and mix. Dilute 5.0 mL of this solution with *Buffer* to 25 mL.

Sample solution: Transfer, as completely as possible, the contents of NLT 20 Capsules to a suitable tared container, and determine the average weight of the contents of a Capsule. Finely powder the Capsule contents so that the powder thus obtained passes through a No. 40 sieve (see *Powder Fineness ⟨811⟩*). Transfer a portion of the powder, nominally equivalent to about 250 mg of mesalamine, to a 500-mL

volumetric flask. Add 20.0 mL of the *Internal standard solution* and about 300 mL of *Buffer*, and shake by mechanical means for 1 h. Dilute with *Buffer* to volume, and mix. Transfer 5.0 mL of this solution to a 25-mL volumetric flask. Dilute with *Buffer* to volume, mix, and pass about 10 mL of this solution through a filter of 0.5-µm or finer pore size. Use the filtrate as the *Sample solution*.

Chromatographic system

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

Mode: LC

Detector: UV 240 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Flow rate: 1.5 mL/min

Injection volume: 10 µL

System suitability

Sample: *Standard solution*

[NOTE—The relative retention times for mesalamine and sodium benzoate are about 0.6 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 2.5 between mesalamine and sodium benzoate

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 Capsule contents taken:

$$\text{Result} = (R_U/R_S) \times (C_S/C_U) \times 100$$

R_U = peak response ratio of mesalamine to sodium benzoate from the *Sample solution*

R_S = peak response ratio of mesalamine to sodium benzoate 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-Jun-2020)

Buffer: 0.05 M pH 7.5 phosphate buffer prepared as follows. Dissolve 6.8 g of monobasic potassium phosphate and 1 g of sodium hydroxide in water to make 1000 mL of solution, and adjust with 10 N sodium hydroxide to a pH of 7.50 ± 0.05.

Medium: *Buffer*; 900 mL

Apparatus 2: 100 rpm

Times: 1, 2, 4, and 8 h

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

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

Analysis: Calculate the percentages of the labeled amount of mesalamine ($C_7H_7NO_3$) dissolved at the wavelength of maximum absorbance at about 330 nm by comparing the UV absorbances of the *Sample solution* with that of the *Standard solution*.

Tolerances: See *Table 2*.

Table 2

Time (h)	Amount Dissolved
1	5%–25%
2	30%–50%
4	60%–90%
8	NLT 85%

The percentages of the labeled amount of mesalamine ($C_7H_7NO_3$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

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

Acid stage

Medium: 0.1 N hydrochloric acid; 750 mL, deaerated. [Note—After *Acid stage*, do not discard the solution, and retain the Capsules in proper order and proceed immediately as directed for *Buffer stage*.]

Apparatus 1: 100 rpm

Time: 2 h

Standard solution: 0.06 mg/mL of USP Mesalamine RS in *Medium*

Sample solution: Withdraw a portion of the solution under test and pass through a suitable filter of 0.45-µm pore size and discard the first few milliliters. Add the same volume of *Medium* to the dissolution vessel.

Instrumental conditions

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

Mode: UV

Analytical wavelength: 302 nm

Cell: 0.5 cm

Blank: *Medium*

Analysis

Samples: *Standard solution* and *Sample solution*

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

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

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 (mg/Capsule)

Tolerances: NMT 10%. The percentage of the labeled amount of mesalamine ($C_7H_7NO_3$) dissolved at the time specified conforms to *Dissolution* ⟨711⟩, *Acceptance Table 3*.

Buffer stage

Medium: After the *Acid stage*, immediately add 250 mL of 0.20 M sodium phosphate buffer solution [dissolve about 76 g of sodium phosphate, tribasic (dodecahydrate), in 1000 mL of water; adjust, if

necessary, with 10% (v/v) phosphoric acid or 2 N sodium hydroxide to a pH of 12.2] to the dissolution vessels containing the *Acid stage medium* (750 mL of 0.1 N hydrochloric acid). Adjust, if necessary, with 2 N sodium hydroxide or 2 N hydrochloric acid to a pH of 6.8; deaerated.

Apparatus 1: 100 rpm

Times: 0.5, 1, and 7 h

Solution A: Dissolve 3.4 g of tetrabutylammonium hydrogen sulfate and 1.4 g of sodium acetate (trihydrate) in 1000 mL of water. Adjust with 1 N sodium hydroxide to a pH of 6.6. Add 200 mL of acetonitrile.

Solution B: Dissolve 4.6 g of tetrabutylammonium hydrogen sulfate and 1.9 g of sodium acetate (trihydrate) in 1000 mL of water. Adjust with 1 N sodium hydroxide to a pH of 6.6. Add 650 mL of acetonitrile.

Mobile phase: *Solution A* and *Solution B* (90:10)

Standard solution: 0.06 mg/mL of USP Mesalamine RS in *Medium*

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. Add the same volume of *Medium* to the dissolution vessel. Dilute with *Medium*, if necessary, to obtain a solution with a similar concentration as the *Standard solution*.

Chromatographic system

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

Mode: LC

Detector: UV 240 nm

Column: 4.6-mm × 10-cm; 3-µm packing L1

Temperatures

Autosampler: 5°

Column: 25°

Flow rate: 1.0 mL/min

Injection volume: 10 µL

Run time: NLT 1.7 times the retention time of mesalamine

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 mesalamine ($C_7H_7NO_3$) in the sample withdrawn from the vessel at each time point (i):

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

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)

D = dilution factor of the *Sample solution*

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 *Medium*, 1000 mL

L = label claim (mg/Capsule)

V_S = volume of the *Sample solution* withdrawn at each time point from the *Medium* (mL)

Tolerances: See *Table 3*.

Table 3

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	0.5	18–43
2	1	35–55
3	7	NLT 80

The percentages of the labeled amount of mesalamine ($C_7H_7NO_3$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*. ▲ (RB 1-Jun-2020)

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

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight, light-resistant 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-Jun-2020)

- **USP Reference Standards** ⟨11⟩

USP Mesalamine RS

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