Mesalamine Delayed-Release Tablets

**Type of Posting**  Revision Bulletin

**Posting Date**  24–Apr–2020; updated 01–May–2020*

**Official Date**  01–Nov–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 Delayed-Release Tablets monograph. The purpose for the revision is to add *Dissolution Test 3* to accommodate FDA-approved drug products with different dissolution conditions and tolerances than the existing dissolution tests.

• *Dissolution Test 3* was validated using a Zorbax 300 SCX brand of L9 column. The typical retention time for mesalamine is about 3.1 min.

The Mesalamine Delayed-Release Tablets Revision Bulletin replaces the version which is scheduled to become official on Aug. 1, 2020. Please note that Section 3.10 of *USP-NF General Notices* discusses Early Adoption. For questions regarding compliance, please consult your relevant regulatory authority.

Should you have any questions, please contact Tsion Bililign, Scientific Liaison (301-816-8286 or tb@usp.org).

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*This Revision Bulletin was updated on May 1, 2020 to correct the official date based on this Notice.*
PRECAUTIONS

Test 1

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 500-mL volumetric flask, dissolve in water from the flask. Add 50 mL of 1 N hydrochloric acid, and sonicate to dissolve, dilute with water to volume, and mix. Adjust with 1 N sodium hydroxide or phosphoric acid to a pH of 6.0, and mix.

Buffer stages: 500 mL of 0.1 N hydrochloric acid

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 (C₇H₇NO₄). Solutions prepared in Medium.

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

Instrumental conditions

Mode: LC

Detector: UV 230 nm

Column: 4.6-mm × 3.3-cm; 3-µm base-deactivated packing L1

Revision Bulletin
Official November 1, 2020

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2 Mesalamine

**Analytical wavelength:** 302 nm (maximum absorbance)

**Analysis**

**Samples:** Standard solution and Sample solution
Calculate the percentage of the labeled amount of mesalamine (C₆H₇NO₃) dissolved:

\[
\text{Result} = \left( \frac{A_s}{A_l} \right) \times C_s \times V \times \left( \frac{1}{L} \right) \times 100
\]

- \( A_s \) = absorbance of the Sample solution
- \( A_l \) = absorbance of the Standard solution
- \( C_s \) = concentration of USP Mesalamine RS in the Standard solution (mg/mL)
- \( V \) = volume of Medium, 900 mL
- \( L \) = label claim of mesalamine (mg/Tablet)

**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°C.] 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 (C₆H₇NO₃).

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

**Instrumental conditions**

**Mode:** UV
**Analytical wavelength:** 332 nm (maximum absorbance)

**Analysis**

**Samples:** Standard solution and Sample solution
Calculate the percentage of the labeled amount of mesalamine (C₆H₇NO₃) dissolved:

\[
\text{Result} = \left( \frac{A_s}{A_l} \right) \times C_s \times V \times \left( \frac{1}{L} \right) \times 100
\]

- \( A_s \) = absorbance of the Sample solution
- \( A_l \) = absorbance of the Standard solution
- \( C_s \) = concentration of USP Mesalamine RS in the Standard solution (mg/mL)
- \( V \) = volume of Medium, 900 mL
- \( L \) = label claim of mesalamine (mg/Tablet)

**Tolerances:** NLT 80% (Q) of the labeled amount of mesalamine (C₆H₇NO₃) is dissolved. The requirements are met if the quantities dissolved from the product conform to Dissolution (711). 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 (C₆H₇NO₃) dissolved:

\[
\text{Result} = \left( \frac{A_s}{A_l} \right) \times C_s \times V \times \left( \frac{1}{L} \right) \times 100
\]

- \( A_s \) = absorbance of the Sample solution
- \( A_l \) = absorbance of the Standard solution

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**Table 1**

<table>
<thead>
<tr>
<th>Level</th>
<th>Number Tested</th>
<th>Acceptance Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>L₁</td>
<td>6</td>
<td>No individual value exceeds 1% dissolved.</td>
</tr>
<tr>
<td>L₂</td>
<td>6</td>
<td>Average of the 12 units (L₁ + L₂) is NMT 1% dissolved, and no individual unit is greater than 10% dissolved.</td>
</tr>
<tr>
<td>L₃</td>
<td>12</td>
<td>Average of the 24 units (L₁ + L₂ + L₃) is NMT 1% dissolved, and NMT 1 individual unit is greater than 10% dissolved.</td>
</tr>
</tbody>
</table>

**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.
C_i = 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_iH_2NO_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_iH_2NO_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_iH_2NO_3) in the sample withdrawn from the vessel at each time point (i):

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

Where:
\[
\begin{align*}
A_i & = \text{absorbance of the Sample solution} \\
A_s & = \text{absorbance of the Standard solution} \\
C_i & = \text{concentration of USP Mesalamine RS in the Standard solution (mg/mL)} \\
D & = \text{dilution factor of the Sample solution, 40}
\end{align*}
\]

Calculate the percentage of the labeled amount of mesalamine (C_iH_2NO_3) dissolved at each time point i:

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

\[
\text{Result}_1 = [C_i \times V + (C_i \times V)] \times \left( \frac{1}{L} \right) \times 100
\]

\[
\text{Result}_2 = (C_i \times V + [C_i + C_i] \times V) \times \left( \frac{1}{L} \right) \times 100
\]

\[
C_i = \text{concentration of mesalamine in the portion of sample withdrawn at time point i (mg/mL)}
\]

Tolerances: See Table 2.

<table>
<thead>
<tr>
<th>Time Point (h)</th>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>NMT 35</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>35-60</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

*Test 3: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 3.
Solution A: pH 6.4 phosphate buffer [6.8 g/L of potassium phosphate, monobasic and 0.53 g/L of sodium hydroxide in water, adjusted with 1 N (or 5 N) sodium hydroxide solution or phosphoric acid to a pH of 6.4]
Solution B: pH 7.2 phosphate buffer [6.8 g/L of potassium phosphate, monobasic and 1.4 g/L of sodium hydroxide in water, adjusted with 1 N (or 5 N) sodium hydroxide solution or phosphoric acid to a pH of 7.2]

Medium
Acid stage: 0.1 N hydrochloric acid, 750 mL
Buffer stage 1: Solution A, 950 mL
Buffer stage 2: Solution B, 960 mL

Apparatus 2
Acid stage: 100 rpm
Buffer stage 1: 100 rpm
Buffer stage 2: 100 rpm

Times
Acid stage: 2 h
Buffer stage 1: 1 h
Buffer stage 2: 1 h and 2 h
Buffer: 5 g/L of potassium phosphate, monobasic in water, adjusted with phosphoric acid to a pH of 2.0 ± 0.05

Mobile phase: Acetonitrile and Buffer (20:80)

Standard solution: 1.25 mg/mL of USP Mesalamine RS in Solution B. Sonicate to dissolve.

Sample solutions
Acid stage: Place 1 Tablet in each vessel containing Medium, Acid stage. At the specified Times, withdraw a portion of the solution under test using a suitable filter of 10-μm pore size. Centrifuge if necessary. Remove the Tablets from solution, dry the Tablets with a paper towel, and retain in the proper order. Proceed as directed in Buffer stage 1.

Buffer stage 1: Transfer each Tablet from Acid stage into the respective vessel containing Medium, Buffer stage 1. At the specified Times, withdraw a portion of the solution under test using a suitable filter of 10-μm pore size. Centrifuge if necessary. Remove the Tablets from solution, dry the Tablets with a paper towel, and retain in the proper order. Proceed as directed in Buffer stage 2.

Buffer stage 2: Transfer each Tablet from Buffer stage 1 into the respective vessel containing Medium, Buffer stage 2. At the specified Times, withdraw a portion of the solution under test using a suitable filter of 10-μm pore size. Centrifuge if necessary.

Chromatographic system
(See Chromatography (621), System Suitability.)
Mode: LC
Detector: UV 330 nm
Column: 4.6-mm x 15-cm; 5-μm packing L9
Column temperature: 30°C

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4 Mesalamine

**Flow rate:** 1.2 mL/min  
**Injection volume:** 5 µL  
**Run time:** NLT 2.5 times the retention time of mesalamine

**System suitability**  
**Sample:** Standard solution  
**Suitability requirements**  
**Tailing factor:** NMT 2.0, Standard solution  
**Relative standard deviation:** NMT 2.0%, Standard solution

**Analysis**  
**Acid stage**  
**Samples:** Standard solution and Sample solution  
Calculate the percentage of the labeled amount of mesalamine (C₇H₆NO₃) dissolved:

\[
\text{Result} = \frac{(r_o/r_s) \times C_s \times V \times (1/L) \times 100}{V}
\]

- \(r_o\) = 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)  
- \(V\) = volume of Medium, 750 mL  
- \(L\) = label claim (mg/Tablet)

**Buffer stage 1:** Proceed as directed for the Acid stage except the volume of Medium is 950 mL.  
**Buffer stage 2**  
**Samples:** Standard solution and Sample solution  
Calculate the concentration (C) of mesalamine (C₇H₆NO₃) in the sample withdrawn from the vessel at each time point (i) as shown in Table 3:

\[
\text{Result}_i = \frac{(r_o/r_s) \times C_s \times V \times (1/L) \times 100}{V}
\]

- \(C_i\) = concentration of USP Mesalamine RS in the Standard solution (mg/mL)  
- \(V\) = volume of Medium, 960 mL  
- \(L\) = label claim (mg/Tablet)  
- \(V_s\) = volume of the Sample solution withdrawn at each time point (mL)

**Tolerances**  
**Acid stage:** See Table 3.  
**Buffer stage 1:** See Table 3.

**Buffer stage 2:** See Table 4.

**Table 3**

<table>
<thead>
<tr>
<th>Level</th>
<th>Number Tested</th>
<th>Acceptance Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>L₁</td>
<td>6</td>
<td>No individual value exceeds 1% dissolved.</td>
</tr>
</tbody>
</table>

**Table 4**

<table>
<thead>
<tr>
<th>Level</th>
<th>Number Tested</th>
<th>Acceptance Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>L₁</td>
<td>6</td>
<td>Average of the 12 units (L₁ + L₂) is NMT 1% dissolved, and no individual unit is &gt;10% dissolved.</td>
</tr>
<tr>
<td>L₁</td>
<td>12</td>
<td>Average of the 24 units (L₁ + L₂ + L₃) is NMT 1% dissolved, and NMT 1 individual unit is &gt;10% dissolved.</td>
</tr>
</tbody>
</table>

**Buffer stage 2:** See Table 4.

**IMPURITIES**

**Change to read:**

**ORGANIC IMPURITIES**  
**Sample solution:** *Prepare as directed for Sample stock solution in the Assay.* [USP 1-Aug-2020]  
**Analysis**  
**Sample:** Sample solution  
Calculate the percentage of each individual impurity in the portion of Tablets taken:

\[
\text{Result} = \frac{(r_o/r_f) \times 100}{V}
\]

- \(r_o\) = peak response of each individual impurity  
- \(r_f\) = 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**

**Change to read:**

**PACKAGING AND STORAGE:** Preserve in tight containers.  
*Store at controlled room temperature.* [USP 1-Aug-2020]  
**LABELING:** When more than one Dissolution test is given, the labeling states the Dissolution test used only if Test 1 is not used.
• **USP Reference Standards** (11)
  - USP Mesalamine RS
  - USP Salicylic Acid RS