Diclofenac Sodium and Misoprostol Delayed-Release Tablets

**DEFINITION**

Diclofenac Sodium and Misoprostol Delayed-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of diclofenac sodium (C₁₄H₁₈Cl₂O₄) and NLT 90.0% and NMT 110.0% of the labeled amount of misoprostol (C₂₂H₃₈O₅).

**IDENTIFICATION**

- **A. ULTRAVIOLET ABSORPTION (197U)**
  - Misoprostol
    - Diluent: Methanol and water (4:1)
    - **Standard solution:** 16 µg/mL of USP Misoprostol RS in Diluent. [Note—If outer misoprostol layers of the Tablets contain hypromellose, the Standard solution should also contain hypromellose at the same concentration as in the Sample solution.]
    - **Sample solution:** Gently break up one by one a quantity of Tablets equivalent to 0.4 mg of misoprostol, and remove the inner diclofenac layers. [Note—Keep the diclofenac layers for Identification A, Diclofenac sodium.] Transfer the outer misoprostol layers to a 25-mL volumetric flask. Add about 15 mL of D iluent, shake for 30 min, dilute with D iluent to volume, and mix well. Transfer a portion of the solution into a glass centrifuge tube, and centrifuge for 10 min under refrigerated conditions (10°C). Use the supernatant.
    - **Blank:** D iluent
    - **Cell:** 1 cm
    - **Acceptance criteria:** Meet the requirements

- **DICLOFENAC SODIUM**
  - **Standard solution:** 0.1 mg/mL of USP Diclofenac Sodium RS in methanol
  - **Sample solution:** Transfer the diclofenac inner layers reserved from Identification A, Misoprostol, to a 100-mL volumetric flask. Add about 60 mL of methanol, shake for 10 min, dilute with methanol to volume, and mix well. Further dilute a suitable volume of the solution to obtain a solution containing about 0.1 mg/mL of diclofenac sodium, based on the label claim. Pass a portion of the solution through a polytetrafluoroethylene (PTFE) with glass microfiber (GMF) filter of 0.45-µm pore size.1 Discard the first few milliliters of the filtrate, and use the filtrate.
    - **Blank:** Methanol
    - **Cell:** 0.05 cm
    - **Acceptance criteria:** Meet the requirements

**ASSAY**

- **MISOPROSTOL**
  - **Buffer:** Prepare 0.025 M monobasic potassium phosphate, pH 6.5, as follows. Adjust a solution containing 3.4 g/L of monobasic potassium phosphate in water with 1 N sodium hydroxide to a pH of 6.5.
  - **Mobile phase:** Acetonitrile and Buffer (45:55)
  - **Standard solution:** 0.01 mg/mL of USP Misoprostol RS in Mobile phase, using sonication as needed
  - **Sample solution:** Nominally 0.01 mg/mL of misoprostol prepared as follows. Using a quantity of Tablets equivalent to 5 mg of misoprostol, place 1 Tablet at a time on its edge inside a well-folded piece of weighing paper. Tap very carefully the edge of the Tablet with a pestle to separate the Tablet into the outer and inner layers. Remove the inner core containing diclofenac sodium. [RA:1-Mar-2018] Transfer the outer portions of the Tablets, containing misoprostol, into a 500-mL volumetric flask containing a magnetic stir bar, and add 250 mL of acetonitrile. Stir the flask for 1 h. Add 150 mL of water, and stir for an additional 30 min or until the Tablets are completely disintegrated. Remove the stir bar, rinse it inside the flask with water, dilute with water to volume, and mix well. Transfer a portion of the solution into a glass centrifuge tube, and centrifuge for 10 min under refrigerated conditions (10°C). Use the supernatant.
  - **Chromatographic system**
    - **(See Chromatography (621), System Suitability.)**
    - **Mode:** LC
    - **Detector:** UV 200 nm
    - **Column:** 4.6-mm × 25-cm; 5-µm packing L10
    - **Temperatures**
      - **Autosampler:** 10°C
      - **Column:** 35°C
    - **Flow rate:** 1.0 mL/min
    - **Injection volume:** 80 µL
  - **System suitability**
    - **Sample:** Standard solution
    - **Suitability requirements**
    - **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 misoprostol (C₂₂H₃₈O₅) in the portion of Tablets taken:
      \[
      \text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_U}{C_S} \right) \times 100
      \]
      \( r_U \) = peak response from the Sample solution
      \( r_S \) = peak response from the Standard solution
      \( C_U \) = concentration of USP Misoprostol RS in the Standard solution (mg/mL)
      \( C_S \) = nominal concentration of misoprostol in the Sample solution (mg/mL)
    - **Acceptance criteria:** 90.0%–110.0%

- **DICLOFENAC SODIUM**
  - **Buffer:** Mix equal volumes of 0.01 M phosphoric acid and 0.01 M monobasic sodium phosphate. If necessary, adjust with additional portions of the appropriate component to a pH of 2.5.
  - **Mobile phase:** Methanol and Buffer (70:30)
  - **Diluent:** Methanol and water (70:30)
  - **System suitability solution:** 20 µg/mL of diethyl phthalate, 8 µg/mL of USP Diclofenac Related Compound A RS, and 0.75 mg/mL of USP Diclofenac Sodium RS in Diluent
  - **Standard solution:** 0.75 mg/mL of USP Diclofenac Sodium RS in Diluent, using sonication as needed
  - **Sample stock solution:** Transfer a quantity of Tablets, equivalent to 1500 mg of diclofenac sodium, into a 1000-mL volumetric flask containing a magnetic stir bar. Add 700 mL of Diluent, and stir for 60 min or until the Tablets are completely disintegrated. Remove the stir bar, rinse it with Diluent, and sonicate the sample
for 15 min. Allow the sample to cool to room temperature, dilute with Diluent to volume, and mix well.

Sample solution: Nominally 0.75 mg/mL of diclofenac sodium prepared as follows. Transfer 10.0 mL of the Sample stock solution into a 20-mL volumetric flask, and dilute with Diluent to volume. Pass a portion of the solution through a PTFE with GMF filter of 0.45-µm pore size, discarding the first few milliliters of the filtrate.

Chromatographic system
(See Chromatography (621), System Suitability.)
Mode: LC
Detector: UV 254 nm
Column: 4.6-mm × 25-cm; 5-µm packing L7
Flow rate: 1.0 mL/min
Injection volume: 10 µL
System suitability
Samples: System suitability solution and Standard solution

NOTE—The relative retention times for diethyl phthalate, diclofenac related compound A, and diclofenac are about 0.6, 0.7, and 1.0, respectively.

Suitability requirements
Resolution: NLT 2.2 between the diethyl phthalate and diclofenac related compound A peaks; NLT 6.5 between the diclofenac related compound A and diclofenac peaks, System suitability solution
Tailing factor: NMT 2, Standard solution
Relative standard deviation: NMT 2.0%, Standard solution

Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of the labeled amount of misoprostol (C₂₂H₃₈O₅) dissolved:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_s}{C_U} \right) \times 100
\]

\[r_U = \text{peak response from the Sample solution}\]
\[r_S = \text{peak response from the Standard solution}\]
\[C_s = \text{concentration of USP Misoprostol RS in the Standard solution (mg/mL)}\]
\[C_U = \text{nominal concentration of misoprostol in the Sample solution (mg/mL)}\]

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- Dissolution

Misoprostol
Medium: Water; 500 mL, deaerated
Apparatus 2: 50 rpm
Time: 20 min
Buffer: Prepare as directed in the Assay for Misoprostol.
Mobile phase: Acetonitrile and Buffer (42:58)
Standard stock solution: Transfer 4 mg of USP Misoprostol RS into a 100-mL volumetric flask, add 20 mL of acetonitrile, and shake for about 15 min. If the outer misoprostol layers of the Tablets contain hypromellose, add a suitable amount of hypromellose to the flask to achieve the same final concentration of hypromellose in the Standard solution as expected in the Sample solution. Add 20 mL of water, and sonicate for about 2 min. Add water up to the neck of the flask, and allow the solution to cool to room temperature before the final dilution to volume.

Standard solution: About 0.0004 mg/mL of USP Misoprostol RS prepared as follows. Dilute 2.0 mL of the Standard stock solution with Medium to 200 mL.

Sample solution: Pass a portion of the solution under test through a suitable filter of 10-µm pore size.

Chromatographic system: Proceed as directed in the Assay for Misoprostol, except for Injection volume.

Injection volume: 200 µL

System suitability
Sample: Standard solution
Suitability requirements
Tailing factor: NMT 2
Relative standard deviation: NMT 5.0%

Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of the labeled amount of misoprostol (C₂₂H₃₈O₅) dissolved:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_s}{C_U} \right) \times V \times 100
\]

\[r_U = \text{peak response from the Sample solution}\]
\[r_S = \text{peak response from the Standard solution}\]
\[C_s = \text{concentration of USP Misoprostol RS in the Standard solution (mg/mL)}\]
\[L = \text{label claim for misoprostol (mg/Tablet)}\]
\[V = \text{volume of Medium, 500 mL}\]

Tolerances: NLT 75% (Q) of the labeled amount of misoprostol (C₂₂H₃₈O₅) is dissolved.

Diclofenac sodium
Proceed as directed in Dissolution (711), Procedure, Apparatus 1 and Apparatus 2, Delayed-Release Dosage Forms, Method A Procedure.

Acid stage medium: 0.1 N hydrochloric acid; 750 mL, deaerated
Buffer stage medium: After 2 h, add 250 mL of 0.2 M tribasic sodium phosphate to the Acid stage medium and, if needed, adjust with either 2 N hydrochloric acid or 2 N sodium hydroxide to a pH of 6.8.
Apparatus 2: 100 rpm
Time: 2 h for Acid stage; 45 min for Buffer stage
Buffer: 0.025 M monobasic potassium phosphate buffer with a pH of 3.0 prepared as follows. Adjust a solution containing 3.4 g/L of monobasic potassium phosphate in water with phosphoric acid to a pH of 3.0.

Mobile phase: Acetonitrile and Buffer (60:40)

Standard stock solution: 0.68 mg/mL of USP Diclofenac Sodium RS, first dissolved in 0.1 N sodium hydroxide using about 10% of the final volume, and then diluted with water to volume

Chromatographic system
(See Chromatography (621), System Suitability.)
Mode: LC
Detector: UV 276 nm
Column: 4.6-mm × 15-cm; 5-µm packing L7
Flow rate: 1.0 mL/min
Injection volume: 10 µL

Acid stage
Acid stage standard solution: 13.6 µg/mL of USP Diclofenac Sodium RS prepared as follows. Transfer 2.0 mL of the Standard stock solution to a 100-mL volumetric flask, and dilute with a mixture of 0.1 N hydrochloric acid and 5 N sodium hydroxide (900:20) to volume.

Acid stage sample solution: Run the test in Acid stage medium for 2 h. Withdraw a 10-mL aliquot, transfer it to a flask containing 1.0 mL of 1 N sodium hydroxide, and mix well. Pass a portion of this solution through a suitable filter of 10-µm pore size.

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Interim Revision Announcement
Official March 1, 2018
UNIFORMITY OF DOSAGE UNITS

• Official March 1, 2018

Diclofenac

Interim Revision Announcement

Meet the requirements for diclofenac sodium and misoprostol

IMPURITIES

Change to read:

• ORGANIC IMPURITIES: MISOPROSTOL

Buffer: Prepare as directed in the Assay for Misoprostol.
Solvent mixture: Acetonitrile and methanol (26:28)
Mobile phase: Solvent mixture and Buffer (58:42)
Diluent: Acetonitrile and water (50:50)
Standard stock solution: Use the Standard solution prepared as directed in the Assay for Misoprostol.

Standard solution: 0.001 mg/mL of USP Misoprostol RS prepared as follows. Transfer 5 mL of the Standard stock solution to a 50-mL volumetric flask, and dilute with Diluent to volume.

Sample solution: Nominally 0.1 mg/mL of misoprostol prepared as follows. Using a quantity of Tablets equivalent to 2 mg of misoprostol, place 1 Tablet at a time on its edge inside a well-folded piece of weighing paper. Tap very carefully the edge of the Tablet with a pestle to separate the Tablet into the outer and inner layers. Remove the inner core containing diclofenac sodium. Fold back the outer layers of the Tablets containing misoprostol, and gently grind them. Transfer the ground outer layers into a 20-mL volumetric flask containing a magnetic stir bar, add 10 mL of acetonitrile, and stir the flask for 2 h. Allow the sample to stand for 10 min, transfer a portion of the solution into a glass centrifuge tube, and centrifuge for 10 min under refrigerated conditions (10°C). Transfer 2.5 mL of the supernatant into a 5-mL volumetric flask, and dilute with water to volume.

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

Mode: LC
Detector: UV 200 and 280 nm
Column: 4.6-mm × 25-cm; 5-µm packing L7
Temperatures
Autosampler: 10°C
Column: 35°C
Flow rate: 0.6 mL/min
Injection volume: 100 µL
Run time: About 2.5 times the retention time of the misoprostol peak

System suitability
Sample: Standard solution at 200 nm
Suitability requirements
Tailing factor: NMT 2
Relative standard deviation: NMT 5.0%

Analysis
Samples: Standard solution and Sample solution

Calculate the percentage of 8-epimisoprostol, A-type misoprostol, and any other individual impurity in the portion of Tablets taken:

Result = \( \frac{r_U}{r_S} \times \left( \frac{C_S}{L} \right) \times \left( V - V_S \right) \times 100 \)

where:

- \( r_U \) = peak response from the Sample solution
- \( r_S \) = peak response from the Standard solution
- \( C_S \) = concentration of USP Misoprostol RS in the Standard solution (mg/mL)
- \( L \) = label claim of diclofenac sodium (mg/Tablet)
- \( V \) = volume of Buffer stage medium, 1000 mL
- \( V_S \) = volume of the Acid stage sample solution, 10 mL

Tolerances: NLT 75% (Q) of the labeled amount of diclofenac sodium (C₁₄H₁₀Cl₂NNaO₂) is dissolved. The percentage of the labeled amount of diclofenac sodium dissolved at the time specified conforms to Dissolution (711), Acceptance Table 4.

- UNIFORMITY OF DOSAGE UNITS (905), Content Uniformity: Meet the requirements for diclofenac sodium and misoprostol

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Diclofenac

\[ r_0 = \text{peak response at } 280 \text{ nm of B-type misoprostol from the Sample solution} \]
\[ r_s = \text{peak response at } 200 \text{ nm of misoprostol from the Standard solution} \]
\[ C_s = \text{concentration of USP Misoprostol RS in the Standard solution (mg/mL)} \]
\[ C_u = \text{nominal concentration of misoprostol in the Sample solution (mg/mL)} \]
\[ F_r = \text{relative response factor (see Table 1)} \]

Acceptance criteria: See Table 1.

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Relative Response Factor</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8-Epimisoprostol</td>
<td>0.87</td>
<td>0.93</td>
<td>2.0</td>
</tr>
<tr>
<td>Misoprostol</td>
<td>1.0</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>B-Type misoprostol</td>
<td>1.5</td>
<td>4.8</td>
<td>0.7 (IRA 1-Mar-2018)</td>
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<tr>
<td>A-Type misoprostol</td>
<td>1.7</td>
<td>1.6</td>
<td>3.5 (IRA 1-Mar-2018)</td>
</tr>
<tr>
<td>Any other individual impurity</td>
<td>—</td>
<td>1.0</td>
<td>0.6</td>
</tr>
<tr>
<td>*Total misoprostol-related impurities</td>
<td>—</td>
<td>—</td>
<td>6.2 (IRA 1-Mar-2018)</td>
</tr>
</tbody>
</table>

*Methyl(13S,28S,30S)-3-hydroxy-2-[[\(E\)]-4-hydroxy-4-methyl-1-octenyl]-5-oxocyclopentaneheptanoate.
*12-Epimisoprostol, which is a process impurity controlled in the drug substance, and 8-epimisoprostol are not separated by this method and should be integrated together to determine conformance.
*[(\(E\))-Methyl 7-[[1R,2S]-2-[[\(E\)]-4-hydroxy-4-methylcyclopentyl]heptanoate.
*Impurity peak response determined at 280 nm, quantitated against the misoprostol peak response determined at 200 nm.
*Methyl 7-[[1R,2S]-2-[[\(E\)]-4-hydroxy-4-methylcyclopentyl]heptanoate.

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

\[ r_0 = \text{peak response from the Sample solution} \]
\[ r_s = \text{peak response from the Standard solution} \]
\[ C_s = \text{concentration of USP Diclofenac Related Compound A RS in the Standard solution (mg/mL)} \]
\[ C_u = \text{nominal concentration of diclofenac sodium in the Sample solution (mg/mL)} \]

Acceptance criteria:
- Diclofenac related compound A: NMT 0.5%
- Any other individual impurity: NMT 0.2%
- *Total diclofenac-related impurities: NMT 1.0%

**ADDITIONAL REQUIREMENTS**
- **PACKAGING AND STORAGE:** Preserve in tight containers. Store at controlled room temperature.
- **USP REFERENCE STANDARDS (11)**
  - USP Diclofenac Sodium RS
  - USP Diclofenac Related Compound A RS
  - N-(2,6-Dichlorophenyl)indolin-2-one.
  - C₁₃H₁₇ClNO₂ 278.14
  - USP Misoprostol RS