Indomethacin Extended-Release Capsules

Type of Posting: Revision Bulletin
Posting Date: 17–Nov–2017
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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 Indomethacin Extended-Release Capsules. The purpose for the revision is to add Dissolution Test 5 to accommodate the FDA approved drug product with different dissolution conditions and tolerances than the existing dissolution tests.

Additionally, minor editorial changes have been made to update the monograph to current USP style.

The Indomethacin Extended-Release Capsules Revision Bulletin supersedes the currently official monograph. The Revision Bulletin will be incorporated in the Second Supplement to USP 41–NF 36.

Should you have any questions, please contact Wei Yang, Scientific Liaison (301-816-8338 or wiy@usp.org).
Indomethacin Extended-Release Capsules

DEFINITION
Indomethacin Extended-Release Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of indomethacin (C19H16ClNO4).

IDENTIFICATION
• A.
  Standard solution: 5 mg/mL of USP Indomethacin RS in acetonitrile
  Sample solution: Shake a portion of Capsule contents, nominally equivalent to 50 mg of indomethacin, with 10 mL of acetonitrile for about 2 min, and filter.

  Analysis
  Samples: Standard solution and Sample solution
  Transfer 5 mL of each of the Samples to individual stoppered flasks, add 20 mL of water to each flask, and shake for 2 min until a precipitate forms and crystallizes. Filter and collect the crystals. Dry the crystals in air, then dry at a pressure below 5 mm of mercury at 100°C for 2 h.

  Acceptance criteria: The IR absorption spectrum of a potassium bromide dispersion of the dried crystals from the Sample solution so obtained exhibits maxima only at the same wavelengths as that of a similar preparation from the Standard solution.

• B.
  Standard solution: 1 mg/mL of USP Indomethacin RS in methanol
  Sample solution: Shake a portion of Capsule contents, nominally equivalent to 25 mg of indomethacin, with 25 mL of methanol, and filter.

Chromatographic system
(See Chromatography (621), General Procedures, Thin-Layer Chromatography.)

  Mode: TLC
  Adsorbent: 0.25-mm layer of chromatographic silica gel mixture
  Application volume: 2 μL
  Developing solvent system: Chloroform and methanol (4:1)

  Analysis
  Samples: Standard solution and Sample solution
  Dry the spots with the aid of a current of air. Develop the chromatogram in the Developing solvent system until the solvent front has moved three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, allow it to dry, and locate the spots under short-wavelength UV light.

  Acceptance criteria: The intensity and Rf value of the principal spot of the Sample solution correspond to those of the Standard solution.

• C.
  Sample solution: Equivalent to 1 mg/mL of indomethacin in sodium hydroxide solution (0.4 mg/mL) from powdered Capsule contents

  Analysis: Shake the Sample solution for 5 min, and filter. To 1 mL of the clear filtrate add 1 mL of 1 mg/mL sodium nitrite solution, mix, and allow to stand for 5 min. Add 0.5 mL of sulfuric acid.

  Acceptance criteria: A golden yellow color develops.

ASSAY

  PROCEDURE
  Mobile phase: Methanol, water, and phosphoric acid (600: 400: 0.8)

  Diluent: Phosphoric acid and water (1:99)
  Standard solution A: 0.8 mg/mL of USP Indomethacin RS, prepared by dissolving 60% of the flask volume in acetonitrile and diluting with Diluent to volume
  Standard stock solution B: 0.18 mg/mL of 4-chlorobenzoic acid in acetonitrile
  Standard solution B: 0.0036 mg/mL of 4-chlorobenzoic acid in Diluent, from Standard solution B

  Sample solution: Weigh and finely powder the contents of NLT 20 Capsules. Transfer a portion of the powder, nominally equivalent to 75 mg of indomethacin, to a 100-mL volumetric flask, add 40 mL of Diluent, and shake for 1 h. Sonicate for 15 min, add 40 mL of acetonitrile, sonicate for 15 min, and dilute with acetonitrile to volume. Centrifuge a portion of this solution, and use the filtrate.

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

  Mode: LC
  Detector: UV 240 nm
  Column: 3.9-mm × 30-cm; packing L1
  Flow rate: 2 mL/min
  Injection volume: 20 μL

System suitability
Samples: Standard solution A and Standard solution B

  Suitability requirements
  Column efficiency: NLT 1000 theoretical plates from the indomethacin peak, Standard solution A
  Tailing factor, Rt: NLT 4.0 for the indomethacin peak, Standard solution A

  Capacity factor, k′: NLT 0.9 for the 4-chlorobenzoic acid peak, Standard solution B
  Relative standard deviation: NMT 2.0%, Standard solution A

  Analysis
  Samples: Standard solution A, Standard solution B, and Sample solution

  Calculate the percentage of indomethacin in the portion of Capsules taken:

  \[
  \text{Result} = \left( \frac{R_U}{R_S} \right) \times \left( \frac{C_S}{C_U} \right) \times 100
  \]

  \(R_U\) = peak response from the Sample solution
  \(R_S\) = peak response from Standard solution A
  \(C_U\) = concentration of USP Indomethacin RS in Standard solution A (mg/mL)
  \(C_S\) = nominal concentration of indomethacin in the Sample solution (mg/mL)

  Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

Dissolution (711)

  Test 1: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 1.
  Medium: pH 6.2 phosphate buffer (see Reagents, Indicators, and Solutions); 750 mL
  Apparatus 1: 75 rpm
  Times: 1, 2, 4, 6, 12, and 24 h
  Sample solution: Sample per Dissolution (711). Dilute with Medium as necessary, filtered.
  Standard solution: USP Indomethacin RS at a known concentration in Medium

  Instrumental conditions
  (See Ultraviolet-Visible Spectroscopy (857).)
Indomethacin

Mode: UV
Analytical wavelength: 318 nm
Analysis Samples: Standard solution and Sample solution
Tolerances: See Table 1.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10%–25%</td>
</tr>
<tr>
<td>2</td>
<td>20%–40%</td>
</tr>
<tr>
<td>4</td>
<td>35%–55%</td>
</tr>
<tr>
<td>6</td>
<td>45%–65%</td>
</tr>
<tr>
<td>12</td>
<td>60%–80%</td>
</tr>
<tr>
<td>24</td>
<td>NLT 80%</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of indomethacin (C₁₉H₁₆ClNO₄) 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.
Apparatus, Sample solution, Standard solution, and Analysis: Proceed as directed in Test 1.
Medium: pH 6.2 phosphate buffer (see Reagents, Indicators, and Solutions); 900 mL
Tolerances: See Table 2.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12%–32%</td>
</tr>
<tr>
<td>2</td>
<td>27%–52%</td>
</tr>
<tr>
<td>4</td>
<td>50%–80%</td>
</tr>
<tr>
<td>12</td>
<td>NLT 80%</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of indomethacin (C₁₉H₁₆ClNO₄) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.

Test 3: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 3.
Apparatus, Sample solution, Standard solution, and Analysis: Proceed as directed in Test 1.
Medium: pH 6.8 phosphate buffer (see Reagents, Indicators, and Solutions); 750 mL
Tolerances: See Table 3.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15%–40%</td>
</tr>
<tr>
<td>2</td>
<td>35%–55%</td>
</tr>
<tr>
<td>4</td>
<td>55%–75%</td>
</tr>
<tr>
<td>6</td>
<td>65%–85%</td>
</tr>
<tr>
<td>12</td>
<td>NLT 75%</td>
</tr>
<tr>
<td>24</td>
<td>NLT 85%</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of indomethacin (C₁₉H₁₆ClNO₄) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.

Test 4: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 4.
Apparatus, Sample solution, Standard solution, and Analysis: Proceed as directed in Test 1.
Medium: pH 6.2 phosphate buffer (see Reagents, Indicators, and Solutions); 900 mL

brane at each time point (h) specified conform to USP

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Time Point (t)</th>
<th>Amount Dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>10%–30%</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>20%–40%</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>35%–55%</td>
</tr>
</tbody>
</table>

Apparatus 1: 75 rpm
Times: 1, 2, 4, 12, and 24 h
Mobile phase: Acetonitrile and 0.1% phosphoric acid

Standard stock solution: 0.4 mg/mL of USP Indomethacin RS in solution prepared as follows. Transfer a suitable amount of USP Indomethacin RS into a suitable volumetric flask. Add 10% of the flask volume of acetonitrile, and sonicate to promote dissolution, if necessary. Dilute with Medium to volume.

Standard solution: (L/900) mg/mL of USP Indomethacin in Medium from the Standard stock solution, where L is the label claim, in mg

Sample solution: Pass a portion of the solution through a suitable filter. Dilute with Medium, if necessary.

Chromatographic system (See Chromatography (621), System Suitability.)
Mode: LC
Detector: UV 235 nm
Column: 4.6-mm × 100-mm; 3.5-µm packing L1
Column temperature: 40°C
Flow rate: 1.2 mL/min
Injection volume: 10 µL

Tolerances: NMT 3%
Relative standard deviation: NMT 3%

Analysis Samples: Standard solution and Sample solution
Calculate the concentration (C) of indomethacin (C₁₉H₁₆ClNO₄) in the sample withdrawn from the vessel at each time point (i):

\[
\text{Result} = \left( \frac{r_i}{r_S} \right) \times C_i
\]

\[ r_i \] is the peak response of indomethacin from the Sample solution
\[ r_S \] is the peak response of indomethacin from the Standard solution

\[ C_i \] is the concentration of USP Indomethacin RS in the Standard solution

Calculate the percentages of the labeled amount (Q_i) of indomethacin (C₁₉H₁₆ClNO₄) dissolved at each time point (i):

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

\[ V \] = volume of the Medium, 900 mL
\[ L \] = label claim of indomethacin (mg/Capsule)
\[ V_i \] = volume of the Sample solution withdrawn from the Medium (mL)

Tolerances: See Table 4.
Indomethacin

Table 4 (Continued)

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Time Point (L)</th>
<th>Amount Dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>4</td>
<td>60%-80%</td>
</tr>
<tr>
<td>24</td>
<td>5</td>
<td>NLT 75%</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of indomethacin (C19H16ClNO4) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.

**Test 5**: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 5.

- **Medium**: pH 6.2 phosphate buffer (see Reagents, Indicators, and Solutions—Buffer Solutions); 750 mL
- **Apparatus 1**: 75 rpm
- **Times**: 1, 2, 4, 6, 12, and 24 h
- **Standard stock solution**: 0.5 mg/mL of USP Indomethacin RS in methanol. Sonicate, if needed, to dissolve.
- **Standard solution**: 0.025 mg/mL of USP Indomethacin RS in methanol. Sonicate, if needed, to dissolve.
- **Sample solution**: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size.

**System suitability**

- **Suitability requirements**
  - **Relative standard deviation**: NMT 1.0%
  - **Analysis**: Replace the volume of medium withdrawn for analysis with equal volume of fresh Medium after each sampling.

**Sample**

- **Sample**: Standard solution and Sample solution
- **Calculate the concentration (C) of indomethacin (C19H16ClNO4) in the sample withdrawn from the vessel at each time point (t):**

  \[ C = \left( \frac{A_s}{A_o} \right) \times C_s \times D \]

- \( A_o \) = absorbance of the Sample solution at time point (t)
- \( A_s \) = absorbance of the Standard solution
- \( C_s \) = concentration of USP Indomethacin RS in the Standard solution (mg/mL)
- \( D \) = dilution factor for the Sample solution

**Calculate the percentage of the labeled amount of indomethacin (C19H16ClNO4) dissolved at each time point (t):**

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

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

\[ \text{Result}_3 = \left[ \left( C \times V \right) + \left[ \left( C_{11} \times V_{11} \right) + \left( C_{12} \times V_{12} \right) + \ldots + \left( C_i \times V_i \right) \right] \right] \times \left( \frac{1}{L} \right) \times 100 \]

- \( C \) = concentration of indomethacin in the portion of sample withdrawn at time point (t) (mg/mL)
- \( V \) = volume of Medium, 750 mL
- \( L \) = label claim (mg/Capsule)
- \( V_s \) = volume of the Sample solution withdrawn at each time point (mL)

**Tolerances:** See Table 5.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10-25</td>
</tr>
<tr>
<td>2</td>
<td>20-40</td>
</tr>
<tr>
<td>4</td>
<td>35-55</td>
</tr>
<tr>
<td>6</td>
<td>45-65</td>
</tr>
<tr>
<td>12</td>
<td>65-85</td>
</tr>
<tr>
<td>24</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of indomethacin (C19H16ClNO4) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.

**Uniformity of Dosage Units (905)**

**Analysis for content uniformity**

- **Solution A**: Dissolve 17.42 g of dibasic potassium phosphate in 800 mL of water, adjusting with phosphoric acid to a pH of 7.5, and diluting with water to 1000 mL (pH 7.5 phosphate buffer).
- **Standard solution**: 25 µg/mL of USP Indomethacin RS in a mixture of methanol and Solution A (1:1)
- **Sample solution**: 25 µg/mL of indomethacin in a mixture of methanol and Solution A (1:1). Prepare as follows. Transfer the contents of 1 Capsule to a 200-mL volumetric flask, and add 100 mL of a mixture of methanol and Solution A (1:1). Sonicate until the contents are dispersed, dilute with the methanol and Solution A mixture (1:1) to volume, and centrifuge. Dilute a portion of the clear solution with the methanol and Solution A mixture (1:1) to obtain the above concentration.

**Instrumental conditions**

- **Analytical wavelength**: 318 nm
- **Cell**: 1 cm
- **Mode**: UV

**Analysis**

- **Samples**: Standard solution and Sample solution
- **Calculate the percentage of indomethacin (C19H16ClNO4) in the Capsule taken:**

  \[ \text{Result} = \left( \frac{A_o}{A_s} \right) \times \left( \frac{C_s}{C_o} \right) \times 100 \]

  - \( A_o \) = absorbance of the Sample solution
  - \( A_s \) = absorbance of the Standard solution
  - \( C_s \) = concentration of USP Indomethacin RS in the Standard solution (µg/mL)
  - \( C_o \) = nominal concentration of indomethacin in the Sample solution (µg/mL)

**Acceptance criteria**: Meet the requirements

**Impurities**

**Limit of 4-Chlorobenzoic Acid**


**Analysis**

- **Samples**: Standard solution B and Sample solution
- Using the peak responses measured and recorded in the Assay, calculate the percentage of 4-chlorobenzoic acid (C7H7ClO2) in the portion of Capsules taken:

  \[ \text{Result} = \left( \frac{r_o}{r_s} \right) \times \left( \frac{C_i}{C_i} \right) \times 100 \]

  - \( r_o \) = peak response from the Sample solution
4 Indomethacin

\[ r_\text{s} = \text{peak response from the Standard solution} \]
\[ C_\text{s} = \text{concentration of 4-chlorobenzoic acid in Standard solution B (mg/mL)} \]
\[ C_\text{o} = \text{measured concentration of indomethacin in the Sample solution as determined from the Assay (mg/mL)} \]

Acceptance criteria: NMT 0.44%

**ADDITIONAL REQUIREMENTS**

- **Packaging and Storage:** Preserve in well-closed containers.
- **Labeling:** The labeling indicates the Dissolution Test with which the product complies.
- **USP Reference Standards (11)**
  - USP Indomethacin RS

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