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 acetone
  - **Sample solution:** Shake a portion of Capsule contents, nominally equivalent to 50 mg of indomethacin, with 10 mL of acetone 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° 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), Thin-Layer Chromatography.)

**Mode:** LC

**Detector:** UV 240 nm

**Column:** 3.9-mm x 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:** NMT 2.0 for the indomethacin peak, Standard solution A
  - **Capacity factor, k':** NLT 4.0 for the indomethacin peak, Standard solution A; and 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
- \(C_S\) = concentration of USP Indomethacin RS in Standard solution A (mg/mL)
- \(C_U\) = nominal concentration of indomethacin in the Sample solution (mg/mL)
- **Acceptance criteria:** 90.0%–110.0%

**PERFORMANCE TESTS**

- **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 Spectrophotometry and Light-Scattering (851).)
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 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 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
Apparatus, Sample solution, Standard solution, and Analysis: Proceed as directed in Test 1.
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 Acceptance Table 2.

Test 4: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 4.
Apparatus 1: 73 rpm
Times: 1, 2, 4, 12, and 24 h
Mobile phase: Acetonitrile and 0.1% phosphoric acid (60:40)

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Time Point (i)</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>
<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>

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 RS in Medium from the Standard stock solution, where L is the label claim, in mg
Sample solution: Pass a portion of the solution under test 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 x 100-mm; 3.5-µm packing L1
Column temperature: 40°
Flow rate: 1.2 mL/min
Injection volume: 10 µL
System suitability
Sample: Standard solution
Suitability requirements
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):

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

\( r_0 \) = peak response of indomethacin from the Sample solution
\( r_i \) = peak response of indomethacin from the Standard solution
\( C_i \) = 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:

\[
\text{Result}_1 = C_i \times V_i \times (1/L) \times 100
\]

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

\[
\text{Result}_3 = \left[ C_i \times (V - (V_i - V_j)) + [C_{i-1} + C_{i-2} + \ldots + C_{i}] \times (1/L) \times 100
\]

\( C_i \) = concentration of indomethacin in the portion of sample withdrawn at timepoint i (mg/mL)
\( V_i \) = volume of the Medium, 900 mL
\( V_j \) = label claim of indomethacin (mg/Capsule)

Tolerances: See Table 4.

Table 4

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Time Point (i)</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>
<tr>
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<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 (C_{19}H_{16}ClNO_{4}) dissolved at the times specified conform to 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**

(See Spectrophotometry and Light-Scattering (851).)

**Mode:** UV

**Analytical wavelength:** 318 nm

**Cell:** 1 cm

**Blank:** Methanol and Solution A (1:1)

**Analysis**

**Samples:** Standard solution and Sample solution

Calculate the percentage of indomethacin (C_{19}H_{16}ClNO_{4}) in the Capsule taken:

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

- \(A_U\) = 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)

- \(C_U\) = 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 (C_{7}H_{5}ClO_{2}) 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 the Standard solution
- \(C_S\) = concentration of 4-chlorobenzoic acid in Standard solution B (mg/mL)
- \(C_U\) = 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