Indomethacin Extended-Release Capsules

DEFINITION

Indomethacin Extended-Release Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of indomethacin ($C_{19}H_{16}ClNO_4$).

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: 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 R_F 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 actonitrile 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 stock 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: 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:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

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

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 *Spectrophotometry and Light-Scattering* ⟨851⟩.)

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

Table 1

Time (h)	Amount Dissolved
1	10%–25%
2	20%–40%
4	35%–55%
6	45%–65%
12	60%–80%
24	NLT 80%

The percentages of the labeled amount of indomethacin ($C_{19}H_{16}ClNO_4$) 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 2

Time (h)	Amount Dissolved
1	12%–32%
2	27%–52%
4	50%–80%
12	NLT 80%

The percentages of the labeled amount of indomethacin ($C_{19}H_{16}ClNO_4$) 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*.
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 3

Time (h)	Amount Dissolved
1	15%–40%
2	35%–55%
4	55%–75%
6	65%–85%
12	NLT 75%
24	NLT 85%

The percentages of the labeled amount of indomethacin ($C_{19}H_{16}ClNO_4$) 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*.
Medium: pH 6.2 phosphate buffer (see *Reagents, Indicators, and Solutions*); 900 mL
Apparatus 1: 75 rpm
Times: 1, 2, 4, 12, and 24 h
Mobile phase: Acetonitrile and 0.1% phosphoric acid (60:40)

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 × 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_i) of indomethacin ($C_{19}H_{16}ClNO_4$) in the sample withdrawn from the vessel at each time point (i):

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

r_U = peak response of indomethacin from the *Sample solution*
r_S = peak response of indomethacin from the *Standard solution*
C_S = concentration of USP Indomethacin RS in the *Standard solution*

Calculate the percentages of the labeled amount (Q_{ti}) of indomethacin ($C_{19}H_{16}ClNO_4$) dissolved at each time point i:

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$

$$\text{Result}_2 = \{[C_2 \times (V - V_S)] + [C_1 \times V_S]\} \times (1/L) \times 100$$

$$\text{Result}_i = \{[C_i \times (V - ([i - 1] \times V_S))] + [(C_{[i-1]} + C_{[i-2]} + \ldots + C_1) \times V_S]\} \times (1/L) \times 100$$

C_i = concentration of indomethacin in the portion of sample withdrawn at timepoint i (mg/mL)
V = volume of the *Medium*, 900 mL
L = label claim of indomethacin (mg/Capsule)
V_S = volume of the *Sample solution* withdrawn from the *Medium* (mL)

Tolerances: See *Table 4*.

Table 4

Time (h)	Time Point (i)	Amount Dissolved
1	1	10%–30%
2	2	20%–40%
4	3	35%–55%
12	4	60%–80%
24	5	NLT 75%

The percentages of the labeled amount of indomethacin ($C_{19}H_{16}ClNO_4$) dissolved at the times specified conform to *Acceptance Table 2*. ● (RB1-Jan-2012)

- **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:

$$\text{Result} = (A_U/A_S) \times (C_S/C_U) \times 100$$

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**

Mobile phase, Diluent, Standard solution A, Standard solution B, Sample solution, Chromatographic system, and **System suitability:** Proceed as directed in the *Assay*.

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 ($C_7H_5ClO_2$) in the portion of Capsules taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

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