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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

Change to read:

• **A.** ▲Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:⟨197K⟩.▲ (USP 1-May-2020)

Standard: ▲▲ (USP 1-May-2020) Prepare a solution of 5 mg/mL of USP Indomethacin RS in acetone. ▲Transfer 5 mL of this solution to a stoppered flask, add 20 mL of water, 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.▲ (USP 1-May-2020)

Sample: ▲▲ (USP 1-May-2020) Shake a portion of Capsule contents, nominally equivalent to 50 mg of indomethacin, with 10 mL of acetone for about 2 min, and filter. ▲Transfer 5 mL of the filtrate to a stoppered flask, add 20 mL of water, 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.▲ (USP 1-May-2020)

Acceptance criteria: ▲ The IR absorption spectrum of the *Sample* exhibits maxima only at the same wavelengths as that of the *Standard*.▲ (USP 1-May-2020)

Change to read:

• **B.** ▲The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.▲ (USP 1-May-2020)

Delete the following:

▲• **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.▲ (USP 1-May-2020)

ASSAY

Change to read:

• **Procedure**

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

Diluent: Phosphoric acid and water (1:99)

▲**Standard solution:** ▲ (USP 1-May-2020) 0.8 mg/mL of USP Indomethacin RS, prepared as follows. Transfer a suitable quantity of USP Indomethacin RS to a suitable volumetric flask, dissolve with 60% of the flask volume of acetonitrile, and dilute with *Diluent* to volume. ▲▲ (USP 1-May-2020)

Sample solution: ▲Nominally 0.75 mg/mL of indomethacin prepared as follows.▲ (USP 1-May-2020) 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 ▲supernatant.▲ (USP 1-May-2020)

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 240 nm

Column: 3.9-mm × 30-cm; ▲10-µm▲ (USP 1-May-2020) packing L1

Flow rate: 2 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution* ▲▲ (USP 1-May-2020)

Suitability requirements

▲▲ (USP 1-May-2020)

Tailing factor: NMT 2.0 ▲▲ (USP 1-May-2020)

Relative standard deviation: NMT 2.0% ▲▲ (USP 1-May-2020)

Analysis

Samples: ▲*Standard solution*▲ (USP 1-May-2020) and *Sample solution*

Calculate the percentage of ▲the labeled amount of▲ (USP 1-May-2020) indomethacin ($C_{19}H_{16}ClNO_4$) in the portion of Capsules taken:

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

r_U = peak response ▲of indomethacin▲ (USP 1-May-2020) from the *Sample solution*

r_S = peak response ▲of indomethacin from the *Standard solution*▲ (USP 1-May-2020)

C_S = concentration of USP Indomethacin RS in ▲the *Standard solution*▲ (USP 1-May-2020) (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

▲▲ (USP 1-May-2020)

Medium: pH 6.2 phosphate buffer (see *Reagents and Reference Tables, Solutions, Buffer Solutions*); 750 mL

Apparatus 1: 75 rpm

Times: 1, 2, 4, 6, 12, and 24 h

Standard solution: USP Indomethacin RS at a known concentration in *Medium*

Sample solution: ▲Pass a portion of the solution under test through a suitable filter. Dilute with *Medium*, if necessary.▲ (USP 1-May-2020)

Instrumental conditions

(See *Ultraviolet-Visible Spectroscopy ⟨857⟩*.)

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%

Time (h)	Amount Dissolved
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 *Dissolution ⟨711⟩, Acceptance Table 2*.

Test 2: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.

Medium: pH 6.2 phosphate buffer (see *Reagents and Reference Tables, Solutions, Buffer Solutions*); 900 mL

▲**Apparatus 1:** 75 rpm▲ (USP 1-May-2020)

Standard solution, Sample solution, and **Analysis:** Proceed as directed in *Test 1*.

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 *Dissolution ⟨711⟩, 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 and Reference Tables, Solutions, Buffer Solutions*); 750 mL

▲**Apparatus 1:** 75 rpm▲ (USP 1-May-2020)

Standard solution, Sample 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 *Dissolution ⟨711⟩, 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 and Reference Tables, Solutions, Buffer 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▲ (USP 1-May-2020) 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* ▲(mg/mL)▲ (USP 1-May-2020)

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 time point *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%

Time (h)	Time Point (*i*)	Amount Dissolved
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 *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 and Reference Tables, 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 from the *Standard stock solution* diluted in *Medium*. Pass through a suitable filter of 0.45-µm pore size.

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. Dilute with *Medium*, if necessary.

Instrumental conditions

(See *Ultraviolet-Visible Spectroscopy ⟨857⟩*.)

Mode: UV

Analytical wavelength: 318 nm

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 1.0%

Analysis: Replace the volume of medium withdrawn for analysis with an equal volume of fresh *Medium* after each sampling.

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*):

$$C_i = (A_U/A_S) \times C_S \times D$$

A_U = absorbance of the *Sample solution* at time point (*i*)

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 ($C_{19}H_{16}ClNO_4$) dissolved at each time point (*i*):

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

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

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

C_i = concentration of indomethacin in the portion of sample withdrawn at time point (*i*) (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 5

Time (h)	Amount Dissolved (%)
1	10–25
2	20–40
4	35–55
6	45–65
12	65–85
24	NLT 80

The percentages of the labeled amount of indomethacin ($C_{19}H_{16}ClNO_4$) dissolved at the times specified conform to *Dissolution ⟨711⟩, Acceptance Table 2*.

Change to read:

• **Uniformity of Dosage Units ⟨905⟩:** ▲Meets the requirements▲ (USP 1-May-2020)

Procedure 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).

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

Standard solution: 25 µg/mL of USP Indomethacin RS in *Diluent*

Sample solution: Nominally 25 µg/mL of indomethacin in *Diluent*, prepared as follows. Transfer the contents of 1 Capsule to a 200-mL volumetric flask, and add 100 mL of *Diluent*. Sonicate until the contents are dispersed, dilute with *Diluent* to volume, and centrifuge. Dilute a portion of the clear solution with *Diluent* to obtain the above concentration.

Instrumental conditions

(See *Ultraviolet-Visible Spectroscopy ⟨857⟩*.)

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 the labeled amount▲ (USP 1-May-2020) 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)

▲▲ (USP 1-May-2020)

IMPURITIES

Delete the following:

▲• **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%▲ (USP 1-May-2020)

Add the following:

▲• **Organic Impurities**

Solution A: Dilute 1 mL of phosphoric acid with water to 1000 mL.

Solution B: Acetonitrile

Mobile phase: See *Table 6*.

Table 6

Time (min)	Solution A (%)	Solution B (%)
0	80	20
40	30	70
45	30	70
50	80	20
60	80	20

Diluent: Acetonitrile and water (60:40)

Sensitivity solution: 0.4 µg/mL of USP Indomethacin RS in *Diluent*. Sonicate to dissolve if needed.

Standard solution: 0.8 µg/mL of USP Indomethacin RS, 1.1 µg/mL of USP Indomethacin Related Compound A RS, and 3.3 µg/mL of USP Indomethacin Related Compound B RS in *Diluent*. Sonicate to dissolve if needed.

Sample solution: Nominally 750 µg/mL of indomethacin in *Diluent*, prepared as follows. Transfer a suitable quantity of the contents of Capsules (NLT 20), equivalent to about 75 mg of indomethacin, to a 100-mL volumetric flask. Add about 60 mL of *Diluent*, shake gently for 5 min, then sonicate for about 10 min with intermittent shaking. Dilute with *Diluent* to volume. Pass through a suitable filter of 0.45-µm pore size.

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

[Note—Rinsing with 2 mL of methanol and water (80:20) may be used before and after injection.]

Mode: LC

Detector: UV 230 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Temperatures

Autosampler: 6°

Column: 40°

Flow rate: 1 mL/min

Injection volume: 10 µL

System suitability

Samples: *Sensitivity solution* and *Standard solution*

Suitability requirements

Relative standard deviation: NMT 5.0% for indomethacin, indomethacin related compound A, and indomethacin related compound B, *Standard solution*

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentages of indomethacin related compound A and indomethacin related compound B in the portion of Capsules taken:

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

r_U = peak response of indomethacin related compound A or indomethacin related compound B from the *Sample solution*

r_S = peak response of indomethacin related compound A or indomethacin related compound B from the *Standard solution*

C_S = concentration of the corresponding USP Reference Standard in the *Standard solution* (µg/mL)

C_U = nominal concentration of indomethacin in the *Sample solution* (µg/mL)

Calculate the percentage of any unspecified degradation product in the portion of Capsules taken:

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

r_U = peak response of any unspecified degradation product 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* (µg/mL)

C_U = nominal concentration of indomethacin in the *Sample solution* (µg/mL)

Acceptance criteria: See *Table 7*.

Table 7

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Indomethacin related compound A	0.38	0.15
Indomethacin related compound B	0.59	0.44
Indomethacin benzamide impurity[a,b]	0.86	—
Indomethacin	1.0	—
Indomethacin dibenzylate impurity[a,c]	1.07	—
Indomethacin diamide impurity[a,d]	1.34	—
Any unspecified degradation product	—	0.2
Total degradation products	—	1.2▲ (USP 1-May-2020)

[a] Process impurity listed for peak identification only, and not to be reported or to be included in the total degradation products.

[b] 4-Chloro-*N*-(4-methoxyphenyl)benzamide.

[c] 1-(4-Chlorobenzoyl)-1-(4-methoxyphenyl)-2-(4-chlorobenzoyl)hydrazide.

[d] 4-Chloro-*N*'-(2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)acetyl)-*N*-(4-methoxyphenyl)benzohydrazide.

ADDITIONAL REQUIREMENTS

Change to read:

• **Packaging and Storage:** Preserve in well-closed containers. ▲Store at controlled room temperature.▲ (USP 1-May-2020)

Change to read:

• **Labeling:**▲ When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.▲ (USP 1-May-2020)

Change to read:

• **USP Reference Standards** ⟨11⟩

▲ USP Indomethacin RS

USP Indomethacin Related Compound A RS

2-(5-Methoxy-2-methyl-1*H*-indol-3-yl)acetic acid.

$C_{12}H_{13}NO_3$ 219.24

USP Indomethacin Related Compound B RS

4-Chlorobenzoic acid.

$C_7H_5ClO_2$ 156.57▲ (USP 1-May-2020)

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
INDOMETHACIN EXTENDED-RELEASE CAPSULES	Documentary Standards Support	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

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