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 ($C_{14}H_{10}Cl_2NNaO_2$) and NLT 90.0% and NMT 110.0% of the labeled amount of misoprostol ($C_{22}H_{38}O_5$).

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 *Diluent*, shake for 30 min, dilute with *Diluent* 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°). Use the supernatant.

Blank: *Diluent*

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

• **B.**

Misoprostol: The retention time of the misoprostol peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay* for *Misoprostol*.

Diclofenac sodium: The retention time of the diclofenac peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay* for *Diclofenac Sodium*.

ASSAY

Change to read:

• **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.• (IRA 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°). 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°

Column: 35°

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 ($C_{22}H_{38}O_5$) in the portion of Tablets 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 USP Misoprostol RS in the *Standard solution* (mg/mL)

C_U = 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

[1] A suitable filter is available as GD/X Syringe Filter, Whatman, www.whatman.com, catalog no. 6874-2504.

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 diclofenac sodium ($C_{14}H_{10}Cl_2NNaO_2$) in the portion of Tablets 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 USP Diclofenac Sodium RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of diclofenac sodium in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- **DISSOLUTION** ⟨**711**⟩

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 ($C_{22}H_{38}O_5$) dissolved:

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

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 for misoprostol (mg/Tablet)
V = volume of *Medium*, 500 mL

Tolerances: NLT 75% (*Q*) of the labeled amount of misoprostol ($C_{22}H_{38}O_5$) 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

Times: 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.

System suitability
Sample: *Acid stage standard solution*
Suitability requirements
Tailing factor: NMT 2
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Acid stage standard solution* and *Acid stage sample solution*
Calculate the percentage of the labeled amount of diclofenac sodium ($C_{14}H_{10}Cl_2NNaO_2$) dissolved during the *Acid stage*:

$$\text{Result} = (r_U/r_S) \times (C_S/L) \times V \times D \times 100$$

r_U = peak response from the *Acid stage sample solution*
r_S = peak response from the *Acid stage standard solution*
C_S = concentration of USP Diclofenac Sodium RS in the *Acid stage standard solution* (mg/mL)
L = label claim for diclofenac sodium (mg/Tablet)
V = volume of *Acid stage medium*, 750 mL
D = dilution factor for the *Acid stage sample solution*, 1.1

Tolerances: NMT 10% of the labeled amount of diclofenac sodium ($C_{14}H_{10}Cl_2NNaO_2$) is dissolved.
The percentage of the labeled amount of diclofenac sodium dissolved at the time specified conforms to *Dissolution* ⟨711⟩, *Acceptance Table 3*.

Buffer stage
Buffer 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 *Buffer stage medium* to volume.
Buffer stage sample solution: Pass a portion of the solution under test through a suitable filter of 10-µm pore size.
System suitability
Sample: *Buffer stage* •*standard*• (IRA 1-Mar-2018) solution
Suitability requirements
Tailing factor: NMT 2
Relative standard deviation: NMT 2.0%
Analysis
Samples: •*Acid stage sample solution*,• (IRA 1-Mar-2018) *Buffer stage standard solution*, and *Buffer stage sample solution*
Calculate the percentage of the labeled amount of diclofenac sodium ($C_{14}H_{10}Cl_2NNaO_2$) dissolved during the *Buffer stage*:

$$\text{Result} = (r_U/r_S) \times (C_S/L) \times (V - V_S) \times 100$$

r_U = peak response from the *Buffer stage sample solution*
r_S = peak response from the *Buffer stage standard solution*
C_S = concentration of USP Diclofenac Sodium RS in the *Buffer stage standard solution* (mg/mL)
L = label claim for 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 ($C_{14}H_{10}Cl_2NNaO_2$) 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

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°). 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°
Column: 35°
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:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

r_U = peak response at 200 nm of any impurity from the *Sample solution*
r_S = peak response at 200 nm of misoprostol from the *Standard solution*
C_S = concentration of USP Misoprostol RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of misoprostol in the *Sample solution* (mg/mL)
F = relative response factor (see *Table 1*)

Calculate the percentage of B-type misoprostol in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

r_U = peak response at 280 nm of B-type misoprostol from the *Sample solution*
r_S = peak response at 200 nm of misoprostol from the *Standard solution*
C_S = concentration of USP Misoprostol RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of misoprostol in the *Sample solution* (mg/mL)
F = relative response factor (see *Table 1*)

Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
8-Epimisoprostol[a]	0.87	0.93	2.0[b]
Misoprostol	1.0	1.0	—
B-Type misoprostol[c]	1.5	4.8[d]	•0.7• (IRA 1-Mar-2018)
A-Type misoprostol[e]	1.7	1.6	•3.5• (IRA 1-Mar-2018)
Any other individual impurity	—	1.0	0.6
•Total misoprostol-related impurities	—	—	6.2• (IRA 1-Mar-2018)

[a] Methyl(1*S**,2*R**,3*R**)-3-hydroxy-2-[(*E*)-4-hydroxy-4-methyl-1-octenyl]-5-oxocyclopentaneheptanoate.

[b] 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.

[c] (*E*)-Methyl 7-[2-(4-hydroxy-4-methyloct-1-enyl)-5-oxocyclopent-1-enyl]heptanoate.

[d] Impurity peak response determined at 280 nm, quantitated against the misoprostol peak response determined at 200 nm.

[e] Methyl 7-[(1*R**,2*S**)-2-[(*E*)-4-hydroxy-4-methyloct-1-enyl]-5-oxo-cyclopent-3-enyl]heptanoate.

Change to read:

• **ORGANIC IMPURITIES: DICLOFENAC SODIUM**

Mobile phase, Diluent, System suitability solution, Sample solution, and **Chromatographic system:** Proceed as directed in the *Assay* for *Diclofenac Sodium*.

Standard solution: 0.004 mg/mL of USP Diclofenac Related Compound A RS in *Diluent*

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 5.0%, *Standard solution*

Analysis

Samples: *Sample solution* and *Standard solution*

Calculate the percentage of diclofenac related compound A and any other individual impurity in the portion of Tablets 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 USP Diclofenac Related Compound A RS in the *Standard solution* (mg/mL)
C_U = 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%• (IRA 1-Mar-2018)

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.
$C_{14}H_9Cl_2NO$ 278.14
USP Misoprostol RS