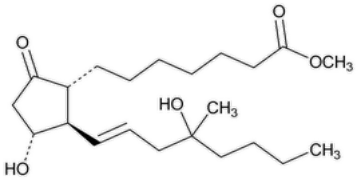
Status: Currently Official on 15-Feb-2025
Official Date: Official as of 01-May-2020
Document Type: USP Monographs
DocId: GUID-57AE12DF-9974-4E28-AC51-C68F7FCAB190_2_en-US
DOI: https://doi.org/10.31003/USPNF_M54300_02_01
DOI Ref: 4c0d7

Misoprostol



$C_{22}H_{38}O_5$ 382.53

Prost-13-en-1-oic acid, 11,16-dihydroxy-16-methyl-9-oxo-, methyl ester, (1*R**,2*R**,3*R**,*E*)-;

(±)-Methyl (1*R*,2*R*,3*R*)-3-hydroxy-2-[(*E*)-(4*RS*)-4-hydroxy-4-methyl-1-octenyl]-5-oxocyclopentaneheptanoate CAS RN®: 59122-46-2; UNII: 0E43V0BB57.

DEFINITION

Misoprostol contains NLT 97.0% and NMT 102.0% of $C_{22}H_{38}O_5$, calculated on the anhydrous basis.

IDENTIFICATION

Change to read:

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

Sample solution: 30 mg/mL

Medium: Chloroform

• **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

• **Procedure**

Mobile phase: 2,2,4-Trimethylpentane, dioxane, and acetonitrile (78:21.5:0.5)

Standard solution: 5.0 mg/mL of USP Misoprostol RS in *Mobile phase*

Sample solution: 5.0 mg/mL of Misoprostol in *Mobile phase*

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 25-cm; 5-µm packing L3

Flow rate: 2 mL/min

Injection size: 20 µL

System suitability

Sample: *Standard solution*

[Note—Identify the impurities based on the retention times shown in *Impurity Table 1*.]

Suitability requirements

Resolution: NLT 1.2, between the second diastereomer peak for 12-epimisoprostol and the Misoprostol peak

Relative standard deviation: NMT 1.0%, for three replicate injections

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of $C_{22}H_{38}O_5$ in the portion of Misoprostol taken:

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

r_U = peak response of the *Sample solution*

r_S = peak response of the *Standard solution*

C_S = concentration of the *Standard solution* (mg/mL)

C_U = concentration of the *Sample solution* (mg/mL)

Acceptance criteria: 97.0%–102.0% on the anhydrous basis

IMPURITIES

Organic Impurities

- **Procedure 1**

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

Analysis

Samples: *Standard solution* and *Sample solution*

Record the chromatogram for at least 3 times the retention time of the Misoprostol peak, and measure the peak responses. Identify the impurities based on the retention times shown in *Impurity Table 1*.

Calculate the percentage of each impurity in the portion of Misoprostol taken:

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

r_U = peak response of each impurity from the *Sample solution*

r_S = peak response of the *Standard solution*

C_S = concentration of USP Misoprostol RS in the *Standard solution* (mg/mL)

C_U = concentration of Misoprostol in the *Sample solution* (mg/mL)

F = relative response factor (see *Impurity Table 1*)

Acceptance criteria

Individual impurities: See *Impurity Table 1*.

Total impurities: NMT 1.5%

Impurity Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
A-Type misoprostol[a]	0.22	7.8	0.1
B-Type misoprostol[b]	0.33	0.80	0.1
Norprostol[c]	0.51	8.4	0.1
8-Epimisoprostol[d]	0.71	1.05	0.3
12-Epimisoprostol[e]	0.86 and 0.92[f]	1.08	1.0[f]
Misoprostol	1.0	—	—
Any other individual impurity	—	1.0	0.1

[a] Methyl 7-{(1*R**,2*S**)-2-[(*E*)-4-hydroxy-4-methyloct-1-enyl]-5-oxocyclopent-3-enyl}heptanoate.

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

[c] Methyl 7-(3-hydroxy-5-oxocyclopent-1-enyl)heptanoate.

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

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

[f] 12-Epimisoprostol consists of two diastereomers that are separated under these conditions; integrate both peaks together for the impurity calculations.

- **Procedure 2: Content of Diastereomers**

Mobile phase: Hexane, ethanol, and isopropyl alcohol (94:4:2)

Sample solution: 1.0 mg/mL of Misoprostol in *Mobile phase*

Chromatographic system

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

Mode: LC

Detector: UV 205 nm

Column: 4.6-mm × 25-cm; 5-µm packing L3

Column temperature: 40°

Flow rate: 1 mL/min

Injection size: 20 µL

System suitability

Sample: *Sample solution*

[NOTE—Identify the components based on their relative retention times which are about 0.92 for the first diastereomer peak and 1.0 for the second diastereomer peak.]

Suitability requirements

Resolution: NLT 2.0, between the two diastereomer peaks

Relative standard deviation: NMT 2.0% from the area of the first diastereomer peak

Analysis

Sample: *Sample solution*

Calculate the fraction of the first diastereomer in the portion of Misoprostol taken:

$$\text{Result} = r_1/(r_1 + r_2)$$

r_1 = peak response for the first diastereomer

r_2 = peak response for the second diastereomer

Acceptance criteria

Fraction of the first diastereomer: 0.51–0.56

SPECIFIC TESTS

• **WATER DETERMINATION,** *Method Ic*⟨921⟩**:** NMT 0.5%

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in tight containers, and store in a freezer.

• **USP REFERENCE STANDARDS** ⟨11⟩

USP Misoprostol RS

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

Topic/Question	Contact	Expert Committee
MISOPROSTOL	Documentary Standards Support	SM32020 Small Molecules 3

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. PF 35(3)

Current DocID: GUID-57AE12DF-9974-4E28-AC51-C68F7FCAB190_2_en-US

DOI: https://doi.org/10.31003/USPNF_M54300_02_01

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