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Misoprostol Dispersion

DEFINITION

Misoprostol Dispersion is a mixture of Misoprostol and Hypromellose. It contains NLT 95.0% and NMT 104.0% of the labeled amount of misoprostol ($C_{22}H_{38}O_5$).

IDENTIFICATION

• **A. Ultraviolet Absorption**

Perform both *Procedure 1* and *Procedure 2*.

Procedure 1

Medium: Methanol and water (4:1)

Sample solution: Nominally 16 µg/mL of misoprostol in *Medium* prepared as follows. Dissolve the amount of Misoprostol Dispersion, equivalent to 400 µg of misoprostol, in 25 mL of *Medium*.

Blank: Prepare a solution of hypromellose in *Medium* having the same concentration as in the *Sample solution*.

Analysis: Determine UV absorption spectrum of *Sample solution* against the *Blank* from 330–230 nm.

Acceptance criteria 1: It exhibits no maximum near 280 nm.

Procedure 2

Medium: Methanol and 1 N potassium hydroxide (4:1)

Sample solution: Add 10 mL of *Medium* to 10 mL of the *Sample solution* prepared from *Procedure 1*. Allow to stand for 30 min at room temperature.

Blank: Add 10 mL of *Medium* to 10 mL of the *Blank* prepared from *Procedure 1*. Allow to stand for 30 min at room temperature.

Analysis: Determine UV absorption spectrum of *Sample solution* against the *Blank* from 330–230 nm.

Acceptance criteria 2: It exhibits a maximum near 280 nm.

• **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**

[Note—During addition of water to a solution of misoprostol in isopropyl alcohol, an exothermic reaction takes place. After each addition of water, invert the flask to mix isopropyl alcohol and water. Allow the solution to cool to room temperature before the final dilution.]

Buffer: 1.36 g/L of monobasic potassium phosphate in water, adjusted with phosphoric acid to a pH of 3.0 ± 0.1

Mobile phase: Isopropyl alcohol and *Buffer* (27:73)

Standard stock solution: 0.5 mg/mL of USP Misoprostol RS in isopropyl alcohol. [Note—This solution is stable up to 28 days when stored at 5 ± 3°.]

Standard solution: 0.1 mg/mL of USP Misoprostol RS in water from *Standard stock solution*. [Note—This solution is stable up to 7 days when stored at 5 ± 3°.]

Sample solution: Nominally 0.1 mg/mL of misoprostol prepared as follows. Place an amount of Misoprostol Dispersion, equivalent to about 10 mg of misoprostol, into a 100-mL volumetric flask, and add 25 mL of isopropyl alcohol. Shake to disperse the solid, place the solution in an ice bath, swirl, and allow to cool for 10 min. Carefully add about 70 mL of water, previously chilled in a refrigerator, remove from the ice bath, and shake. Sonicate as necessary at a temperature not exceeding 20°. Equilibrate to room temperature, dilute with water to volume, and immediately cool the solution to 5°. [Note—This solution is stable up to 7 days when stored at 5 ± 3°.]

Chromatographic system

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

Mode: LC

Detector: UV 205 nm

Column: 4.6-mm × 15-cm; 5-µm packing L7

Temperatures

Column: 50 ± 2°; the *Mobile phase* must be preheated prior to introduction on the column.

Autosampler: 5 ± 3°

Flow rate: 1.5 mL/min

Injection volume: 100 µL

System suitability

Sample: *Standard solution*

[NOTE—USP Misoprostol RS contains 12-epimisoprostol as a minor component. The relative retention times for 12-epimisoprostol and misoprostol are 0.84 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 2.7 between 12-epimisoprostol and misoprostol

Relative standard deviation: NMT 1.0%

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 Misoprostol Dispersion 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: 95.0%–104.0%

IMPURITIES

• **ORGANIC IMPURITIES**

[NOTE—During the addition of water to a solution of misoprostol in isopropyl alcohol, an exothermic reaction takes place. After each addition of water, invert the flask to mix isopropyl alcohol and water. Allow the solution to cool to room temperature before the final dilution.]

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

Diluent: Isopropyl alcohol and water (27:73)

Blank: Prepare a solution of hypromellose in the *Diluent* having the same concentration as in the *Sample solution*.

Diluted standard solution: 0.5 µg/mL of USP Misoprostol RS in *Diluent* from *Standard solution*

Sensitivity solution: 0.1 µg/mL of USP Misoprostol RS in *Diluent* from *Diluted standard solution*

System suitability

Samples: *Standard solution* and *Sensitivity solution*

Suitability requirements

Resolution: NLT 2.7 between 12-epimisoprostol and misoprostol, *Standard solution*

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

Analysis

Samples: *Sample solution*, *Blank*, and *Diluted standard solution*

Calculate the percentage of any individual impurity in the portion of Misoprostol Dispersion taken:

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

r_U = peak response of any individual impurity from the *Sample solution*

r_S = peak response of misoprostol from the *Diluted standard solution*

C_S = concentration of USP Misoprostol RS in the *Diluted standard solution* (µg/mL)

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

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

Acceptance criteria: See *Table 1*. Disregard a peak from the *Diluent*, eluting at about 4 min, and any other peak observed in the *Blank*.

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
12-Epimisoprostol	0.84	—	—[a]
8-Epimisoprostol[b]	0.90	0.90	0.50
Misoprostol	1.0	—	—
B-Type misoprostol[c]	1.6	0.78	0.30
A-Type misoprostol[d]	1.9	2.6	0.50
Any other individual impurity	—	1.0	0.1
Total impurities	—	—	1.8

[a] This is a process impurity in the manufacturing of misoprostol. It is controlled in the misoprostol, which is the starting material for the Misoprostol Dispersion. This impurity is included in the table for identification only, and it is not to be reported or included in the total impurities for the Misoprostol Dispersion.

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

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

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

SPECIFIC TESTS

• **Water Determination,** *Method Ic*⟨921⟩

Sample: 300 mg

Analysis: Perform the test immediately after opening the sample container. Use the evaporation technique in which water is released and evaporated from the *Sample* by heating it in an external oven at 105° and transferring it to the reaction cell with the aid of an inert gas.

Acceptance criteria: NMT 1.0%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight containers, protected from light, and store in a refrigerator.

• **Labeling:** The label states that this article is not intended for direct administration to humans or animals. Label it to indicate the nominal concentration or percentage of misoprostol in the Misoprostol Dispersion.

• **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 DISPERSION	Documentary Standards Support	SM32020 Small Molecules 3
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM32020 Small Molecules 3

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