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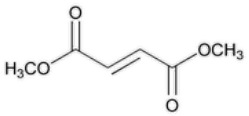
Add the following:

▲Dimethyl Fumarate



$C_6H_8O_4$ 144.13

2-Butenedioic acid, (2*E*)-, dimethyl ester;

Dimethyl (2*E*)-but-2-enedioate;

Dimethyl fumarate CAS RN®: 624-49-7; UNII: FO2303MNI2.

DEFINITION

Dimethyl Fumarate contains NLT 98.0% and NMT 102.0% of dimethyl fumarate ($C_6H_8O_4$).

IDENTIFICATION

• **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197A or 197K

• **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**

Solution A: 0.1% phosphoric acid in water, prepared by diluting 1.2 mL of phosphoric acid with water to 1000 mL

Mobile phase: Acetonitrile and *Solution A* (30:70)

Buffer: 2.72 g/L of potassium phosphate, monobasic in water prepared as follows. Dissolve 2.72 g of potassium phosphate, monobasic in 800 mL of water in a 1-L volumetric flask. Adjust with 25% phosphoric acid to a pH of 3.0 and dilute with water to volume.

Diluent: Acetonitrile and *Buffer* (30:70)

Impurity standard stock solution 1: 0.5 mg/mL of USP Fumaric Acid RS in *Diluent*. Sonicate to completely dissolve.

Impurity standard stock solution 2: 0.5 mg/mL of USP Dimethyl Fumarate Related Compound A RS in *Diluent*. Sonicate to completely dissolve.

Standard solution: 300 µg/mL of USP Dimethyl Fumarate RS, 1.5 µg/mL of USP Fumaric Acid RS, and 0.9 µg/mL of USP Dimethyl Fumarate Related Compound A RS in *Diluent* prepared as follows. Transfer an appropriate quantity of USP Dimethyl Fumarate RS to a suitable volumetric flask and dissolve in 80% of the flask volume of *Diluent*. Sonicate to completely dissolve. Transfer appropriate volumes of *Impurity standard stock solution 1* and *Impurity standard stock solution 2* to the flask and dilute with *Diluent* to volume.

Sample solution: 300 µg/mL of Dimethyl Fumarate in *Diluent*. Sonicate to completely dissolve.

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 4.0-mm × 25-cm; 4-µm packing L1

Temperatures

Autosampler: 5°

Column: 35°

Flow rate: 1 mL/min

Injection volume: 5 µL

Run time: NLT 3.7 times the retention time of dimethyl fumarate

System suitability

Sample: *Standard solution*

[NOTE—See *Table 1* for the relative retention times.]

Suitability requirements

Resolution: NLT 6.0 between fumaric acid and dimethyl fumarate related compound A

Tailing factor: 0.8–1.5 for dimethyl fumarate

Relative standard deviation: NMT 0.73% for dimethyl fumarate

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of dimethyl fumarate ($C_6H_8O_4$) in the portion of Dimethyl Fumarate taken:

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

r_U = peak response of dimethyl fumarate from the *Sample solution*

r_S = peak response of dimethyl fumarate from the *Standard solution*

C_S = concentration of USP Dimethyl Fumarate RS in the *Standard solution* (µg/mL)

C_U = concentration of Dimethyl Fumarate in the *Sample solution* (µg/mL)

Acceptance criteria: 98.0%–102.0%

IMPURITIES

- **RESIDUE ON IGNITION ⟨281⟩:** NMT 0.1%
- **ORGANIC IMPURITIES**

Solution A, Mobile phase, Buffer, Diluent, Impurity standard stock solution 1, Impurity standard stock solution 2, Standard solution, Sample solution, and **Chromatographic system:** Proceed as directed in the *Assay*.

Sensitivity solution: 0.15 µg/mL of USP Dimethyl Fumarate RS from the *Standard solution* in *Diluent*

System suitability

Samples: *Standard solution* and *Sensitivity solution*

[NOTE—See *Table 1* for the relative retention times.]

Suitability requirements

Resolution: NLT 6.0 between fumaric acid and dimethyl fumarate related compound A, *Standard solution*

Tailing factor: 0.8–1.5 for fumaric acid, dimethyl fumarate related compound A, and dimethyl fumarate, *Standard solution*

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

Analysis

Sample: *Sample solution*

Calculate the percentage of any individual impurity in the portion of Dimethyl Fumarate taken:

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

r_U = peak response of any individual impurity

r_S = sum of all peak responses

Acceptance criteria: See *Table 1*. The reporting threshold is 0.05%.

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Fumaric acid	0.32	0.5
Dimethyl fumarate related compound A	0.47	0.3
Dimethyl fumarate	1.0	—
Any unspecified impurity	—	0.10

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Total impurities	—	0.8

SPECIFIC TESTS

• **Chloride and Sulfate** ⟨221⟩, *Sulfate*: NMT 0.03%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight containers.

• **USP Reference Standards** ⟨11⟩

USP Dimethyl Fumarate RS

USP Dimethyl Fumarate Related Compound A RS

(*E*)-4-Methoxy-4-oxobut-2-enoic acid.

$C_5H_6O_4$ 130.10

USP Fumaric Acid RS

Fumaric acid.

$C_4H_4O_4$ 116.07▲ (USP 1-Dec-2023)

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

Topic/Question	Contact	Expert Committee
DIMETHYL FUMARATE	Documentary Standards Support	SM42020 Small Molecules 4

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. 47(5)

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