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Dimethyl Fumarate Delayed-Release Capsules

DEFINITION

Dimethyl Fumarate Delayed-Release Capsules contain an amount of Dimethyl Fumarate equivalent to NLT 90.0% and NMT 110.0% of the labeled amount of dimethyl fumarate ($C_6H_8O_4$).

IDENTIFICATION

- **A.** The UV spectrum of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.
- **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

Change to read:

- **Procedure**

Dilute phosphoric acid: Dilute 11.5 mL of phosphoric acid with 88.5 mL of water.

Dilute sodium hydroxide solution: 10% sodium hydroxide in water (w/v)

Buffer A: 1.38 g/L of sodium phosphate, monobasic in water; adjusted with either *Dilute sodium hydroxide solution* or *Dilute phosphoric acid* to a pH of 2.5

Buffer B: 6.9 g/L of sodium phosphate, monobasic in water; adjusted with either *Dilute sodium hydroxide solution* or *Dilute phosphoric acid* to a pH of 3.15

Solution A: *Buffer A*

Solution B: Methanol

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	75	25
9	75	25
10	45	55
12	45	55
13	75	25
17	75	25

Diluent: Methanol and *Buffer B* (40:60)

System suitability stock solution: 0.48 mg/mL each of USP Dimethyl Fumarate RS, USP Dimethyl Fumarate Related Compound A RS, and USP Fumaric Acid RS in *Diluent* prepared as follows. Transfer appropriate quantities of USP Dimethyl Fumarate RS, USP Dimethyl Fumarate Related Compound A RS, and USP Fumaric Acid RS into a suitable volumetric flask and add 80% of the flask volume of *Diluent*. Sonicate to completely dissolve and dilute with *Diluent* to volume.

System suitability solution: 4.8 µg/mL each of USP Dimethyl Fumarate RS, USP Dimethyl Fumarate Related Compound A RS, and USP Fumaric Acid RS from the *System suitability stock solution* in *Diluent*

Standard solution: 0.96 mg/mL of USP Dimethyl Fumarate RS prepared as follows. Transfer an appropriate quantity of USP Dimethyl Fumarate RS into a suitable volumetric flask, add 60% of the flask volume of methanol, and sonicate to completely dissolve. Add about 30% of the flask volume of *Buffer B* and allow the solution to cool to room temperature. Dilute with *Buffer B* to volume.

Sample solution: Nominally 0.96 mg/mL of dimethyl fumarate prepared as follows. Transfer an appropriate quantity, equivalent to 5 Capsules, of micro-tablets from the content of 10 Capsules into a suitable volumetric flask and add about 60% of the flask volume of methanol. Sonicate with occasional swirling to disintegrate the micro-tablets. An additional two cycles of the sonication step may be added to ensure all micro-tablets are disintegrated. [Note—A sonication time of about 15 min for each cycle may be suitable.] Add about 30% of

the flask volume of *Buffer B* and allow the solution to cool to room temperature. Dilute with *Buffer B* to volume. Pass the solution through a suitable filter of 0.7-µm pore size, discarding the first few milliliters. Further dilute ▲with *Diluent*▲ (IRA 1-Jan-2025) to the final concentration.

Chromatographic system

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

Mode: LC

Detector: UV 223 nm. For *Identification A*, use a diode array detector in the range of 200–300 nm.

Column: 4.6-mm × 10-cm; 5-µm packing L1

Temperatures

Autosampler: 5°

Column: 30°

Flow rate: 1.5 mL/min

Injection volume: 5 µL

System suitability

Samples: *System suitability solution* and *Standard solution*

[NOTE—See *Table 2* for the relative retention times.]

Suitability requirements

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

Tailing factor: 0.8–1.5, *Standard solution*

Relative standard deviation: NMT 1.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of dimethyl fumarate ($C_6H_8O_4$) in the portion of Capsules taken:

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

r_U = peak response of 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* (mg/mL)

C_U = nominal concentration of dimethyl fumarate in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

• **DISSOLUTION ⟨711⟩**

Acid stage

Acid stage medium: 0.1 N hydrochloric acid in water; 500 mL

Apparatus 2: 100 rpm

Time: 120 min

At the end of 120 min, pour the *Acid stage medium* through a suitable strainer into a suitable container and carefully transfer the micro-tablets in the strainer to a dissolution vessel containing the *Buffer stage medium*.

Buffer stage

Buffer stage medium: pH 6.8 buffer (4.8 g/L of citric acid and 21.9 g/L of sodium phosphate dibasic anhydrous prepared as follows. Transfer suitable quantities of citric acid and sodium phosphate dibasic anhydrous to an appropriate container and dissolve with 98% of the final volume of water. Adjust with *Dilute sodium hydroxide solution* or *Dilute phosphoric acid* (prepare as directed in the *Assay*) to a pH of 6.8, and dilute with water to the final volume); 500 mL.

Apparatus 2: 100 rpm

Time: 30 min

Buffer A and **Buffer B:** Prepare as directed in the *Assay*.

Mobile phase: Methanol and *Buffer A* (40:60)

Acid stage diluent: Methanol and *Buffer B* (50:50)

Buffer stage diluent: *Acid stage diluent* and *Dilute phosphoric acid* (90:10)

Acid stage standard stock solution 1: 600 µg/mL of USP Dimethyl Fumarate RS prepared as follows. Transfer an appropriate quantity of USP Dimethyl Fumarate RS into a suitable volumetric flask. Add 10% of the flask volume of methanol and sonicate for approximately 10 min to dissolve, dilute with *Acid stage medium* to volume.

Acid stage standard stock solution 2: 60 µg/mL of USP Dimethyl Fumarate RS from *Acid stage standard stock solution 1* in *Acid stage medium*

Acid stage standard solution: 3.0 µg/mL of USP Dimethyl Fumarate RS prepared as follows. Transfer 5 mL of *Acid stage standard stock solution 2* to a 100-mL volumetric flask and add 50 mL of *Acid stage diluent*, then dilute with *Acid stage medium* to volume.

Acid stage sample solution

For Capsules labeled to contain 120 mg: Transfer 5 mL of a filtered portion of the solution under test to a 10-mL volumetric flask, and dilute with *Acid stage diluent* to volume.

For Capsules labeled to contain 240 mg: Transfer 2.5 mL of a filtered portion of the solution under test to a 10-mL volumetric flask, add 2.5 mL of *Acid stage medium*, and dilute with *Acid stage diluent* to volume.

Buffer stage standard stock solution 1: 1.32 mg/mL of USP Dimethyl Fumarate RS prepared as follows. Transfer an appropriate quantity of USP Dimethyl Fumarate RS into a suitable volumetric flask. Add 10% of the flask volume of methanol, sonicate for about 10 min, and dilute with *Buffer stage medium* to volume.

Buffer stage standard stock solution 2: 0.26 mg/mL of USP Dimethyl Fumarate RS from *Buffer stage standard stock solution 1* in *Buffer stage medium*

Buffer stage standard solution: 0.11 mg/mL of USP Dimethyl Fumarate RS prepared as follows. Transfer 4 mL of *Buffer stage standard stock solution 2* into a 10-mL volumetric flask, add 1 mL of *Buffer stage medium*, and dilute with *Buffer stage diluent* to volume.

Buffer stage sample solution

For Capsules labeled to contain 120 mg: Transfer 5 mL of a filtered portion of the solution under test to a 10-mL volumetric flask, and dilute with *Buffer stage diluent* to volume.

For Capsules labeled to contain 240 mg: Transfer 2.5 mL of a filtered portion of the solution under test to a 10-mL volumetric flask, add 2.5 mL of *Buffer stage medium*, and dilute with *Buffer stage diluent* to volume.

Chromatographic system

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

Mode: LC

Detector: UV 223 nm

Column: 4.6-mm × 10-cm; 5-µm packing L1

Temperatures

Autosampler: 5°

Column: 30°

Flow rate: 1.2 mL/min

Injection volume: 5 µL

Run time: NLT 2.2 times the retention time of dimethyl fumarate

System suitability

Samples: *Acid stage standard solution* and *Buffer stage standard solution*

Suitability requirements

Tailing factor: 0.8–1.5, *Acid stage standard solution* and *Buffer stage standard solution*

Relative standard deviation: NMT 1.5%, *Buffer stage standard solution*

Analysis

Samples: *Acid stage standard solution*, *Acid stage sample solution*, *Buffer stage standard solution*, and *Buffer stage sample solution*

Calculate the percentage of the labeled amount of dimethyl fumarate ($C_6H_8O_4$) dissolved in the *Acid stage medium*:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times D \times (1/L) \times 100$$

r_U = peak response of dimethyl fumarate from the *Acid stage sample solution*

r_S = peak response of dimethyl fumarate from the *Acid stage standard solution*

C_S = concentration of USP Dimethyl Fumarate RS in the *Acid stage standard solution* (mg/mL)

V = volume of *Acid stage medium*, 500 mL

D = dilution factor, if needed

L = label claim (mg/Capsule)

Calculate the percentage of the labeled amount of dimethyl fumarate ($C_6H_8O_4$) dissolved in the *Buffer stage medium*:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times D \times (1/L) \times 100 + Q_A$$

r_U = peak response of dimethyl fumarate from the *Buffer stage sample solution*

r_S = peak response of dimethyl fumarate from the *Buffer stage standard solution*

C_S = concentration of USP Dimethyl Fumarate RS in the *Buffer stage standard solution* (mg/mL)

V = volume of *Buffer stage medium*, 500 mL

D = dilution factor, if needed

L = label claim (mg/Capsule)

Q_A = percentage of dimethyl fumarate dissolved in the *Acid stage*

Tolerances

Acid stage: NMT 10% of the labeled amount of dimethyl fumarate ($C_6H_8O_4$) is dissolved.

Buffer stage: NLT 80% (*Q*) of the labeled amount of dimethyl fumarate ($C_6H_8O_4$) is dissolved.

The percentages of the labeled amount of dimethyl fumarate ($C_6H_8O_4$) dissolved at the times specified conform to *Dissolution ⟨711⟩, Delayed-Release Dosage Forms*.

• **Uniformity of Dosage Units ⟨905⟩:** Meet the requirements

IMPURITIES

Change to read:

• **Organic Impurities**

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

Sensitivity solution: ▲0.96▲ (IRA 1-Jan-2025) µg/mL of USP Dimethyl Fumarate RS from the *Standard solution* in *Diluent*

System suitability

Samples: *System suitability solution*, *Standard solution*, and *Sensitivity solution*

▲[Note—The relative retention times in *Table 2* are provided as information that could aid in peak assignment.]

Table 2▲ (IRA 1-Jan-2025)

Name	Relative Retention Time
Fumaric acid	0.20
Dimethyl fumarate related compound A	0.40
Dimethyl fumarate	1.0

Suitability requirements

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

Tailing factor: 0.8–1.5, *Standard solution*

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

Analysis

Sample: *Sample solution*

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

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

r_U = peak response of any degradation product

r_S = sum of all peak responses

Acceptance criteria: See *Table 3*.▲ Use an appropriate reporting threshold. (See *User-Determined Reporting Thresholds ⟨477⟩*.)

[Note—A reporting threshold of 0.1% may be suitable when the maximum daily dose is ≤1 g.]

▲ (IRA 1-Jan-2025)

Table 3

Name	Acceptance Criteria, NMT (%)
Fumaric acid	0.7
Dimethyl fumarate related compound A	1.0
▲▲ (IRA 1-Jan-2025)	▲▲ (IRA 1-Jan-2025)

Name	Acceptance Criteria, NMT (%)
Any unspecified degradation product	0.2
Total degradation products	2.0

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight containers and protect from light. Store at controlled room temperature.

• **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

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

Topic/Question	Contact	Expert Committee
DIMETHYL FUMARATE DELAYED-RELEASE CAPSULES	Documentary Standards Support	SM42020 Small Molecules 4

Chromatographic Database Information: Chromatographic Database

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